

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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201023

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA	201023
Submission Date:	March 31, 2010
Brand Name:	JEVTANA [®]
Generic Name:	Cabazitaxel
Formulation/Strength:	Single Use Vial 60 mg/1.5 mL and Diluent
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ORM Division:	Division of Drug Oncology Products
Sponsor:	Sanofi-aventis US LLC
Submission Type; Code:	Original NDA; 000
Dosing Regimen:	Cabazitaxel 25 mg/m ² administered every three weeks as a one-hour IV infusion in combination with oral prednisone 10 mg administered daily throughout cabazitaxel treatment
Indication:	Metastatic hormone refractory prostate cancer previously treated with a docetaxel-containing regimen

Table of contents

1	Executive Summary	5
1.1	Recommendations	6
1.2	Post-Marketing Requirements	6
1.3	Clinical Pharmacology Summary	7
2	Question Based Review	9
2.1	General Attributes	9
2.2	General Clinical Pharmacology	10
2.3	Intrinsic Factors	29
2.4	Extrinsic Factors	35
2.5	General Biopharmaceutics	40
2.6	Analytical Section	41
3	Detailed Labeling Recommendations	45
4	Pharmacometric Review	51

List of Tables

Table 1. Instantaneous solubility of cabazitaxel at 25°C in various solvent	9
Table 2. Clinical trials supporting the dosing regimen.....	11
Table 3. Pharmacokinetic parameters of cabazitaxel after a 1-hour IV infusion at the first available cycle (mainly cycle 1)	19
Table 4. C _{max} and AUC of cabazitaxel at the first available cycle following one-hour infusion at 25 mg/m ²	20
Table 5. Pharmacokinetics of cabazitaxel in 4 patients treated with 25 mg/m ² [¹⁴ C]-cabazitaxel as a 1-hour IV infusion.....	22
Table 6. Predicted <i>in vivo</i> intrinsic and metabolic clearance values of cabazitaxel (XRP6258) in human	23
Table 7. <i>In vitro</i> intrinsic clearance and fraction (mean ±SD) metabolized by CYP3A and overall CYP enzymes of XRP6258 in fresh human hepatocytes (n = 3).....	23
Table 8. <i>In vitro</i> enzyme kinetics of cabazitaxel (RPR116258) metabolism in human liver microsomes	24
Table 9. Pharmacokinetic parameters of cabazitaxel in patients treated at 10 to 30 mg/m ² according to gender, age, race, tumor type, creatinine clearance, transaminase ratio, and alkaline phosphatase ratio	30
Table 10. The proposed dose modifications for adverse reactions in patients treated with cabazitaxel	31
Table 11. C _{max} and AUC of cabazitaxel at the first available cycle following 1-hour infusion at 25 mg/m ²	36
Table 12. K _i and I/K _i of cabazitaxel on CYPs	36
Table 13. The potential of cabazitaxel (XRP6258) to induce CYP1A1/2, CYP2C9 and CYP3A4/5 enzyme activities (expressed as % of control) in fresh human hepatocytes following 72 hours treatment with cabazitaxel (0 to 10 μM) or reference inducers .	37
Table 14. Bidirectional transport of cabazitaxel (XRP6258) using Caco-2 cells.....	38
Table 15. Composition of to-be-marketed cabazitaxel concentrate for solution for injection, 60 mg/1.5 mL.....	41
Table 16. Summary of bioanalytical studies associated with clinical pharmacology studies and efficacy/safety clinical studies.....	42

List of Figures

- Figure 1: Exposure-response relationship of cabazitaxel (CBZ) for overall survival (left panel) in comparison with the same relationship excluding four patients with neutropenia related deaths on CBZ/PRED arm from the dataset (right panel). Small black, green and red vertical ticks on the plots are censored observations. MTX/PRED (Mitoxantrone/Prednisone) is the comparator arm. 13
- Figure 2: Exposure-response relationship of cabazitaxel (CBZ) for time to tumor progression. Small black, green and red vertical ticks on the plots are censored observation. MTX/PRED (Mitoxantrone/Prednisone) is the comparator arm. 14
- Figure 3: The probability of patients with \geq grade 3 neutropenia-AUC relationship. Solid black symbols represent the observed proportion of patients experiencing \geq grade 3 neutropenia in each AUC quartile. The vertical black bars represent the 95% confidence interval. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval of the prediction. The exposure range in each AUC quartile is denoted by the horizontal black line along with the number of subjects with adverse events/total number of subjects in each quartile. The horizontal dotted red and blue line represents the % of \geq grade 3 neutropenic events observed in the CBZ/PRED and MTX/PRED arm of the pivotal trial (EFC 6193), respectively. 15
- Figure 4: The median time course of neutrophils among patients in cabazitaxel arm who never received G-CSF during the pivotal trial (EFC6193). The two black dashed lines represents cutoff for neutropenia ($<1.5 \times 10^9/L$) and \geq grade 3 neutropenia ($<1.0 \times 10^9/L$). 16
- Figure 5: The median time course of neutrophils among patients who received G-CSF at some point during the pivotal trial (EFC6193). The two black dashed lines represents cutoff for neutropenia ($<1.5 \times 10^9/L$) and \geq grade 3 neutropenia ($<1.0 \times 10^9/L$). 17
- Figure 6: The time-concentration profiles of cabazitaxel in patients (n=13) with advanced tumors when a dose of 25 mg/m^2 was administered via a one-hour intravenous infusion. 20
- Figure 7: Mass balance of total radioactivity after a single 1-hour IV infusion of [^{14}C]-cabazitaxel in 4 patients with advanced solid tumors (mean \pm SD). 22
- Figure 8: The metabolites formed by heterologously expressed human cytochrome P450 and FMO isoenzymes that metabolize cabazitaxel (RPR 116258) at $1 \text{ }\mu\text{M}$ (left bar) and $10 \text{ }\mu\text{M}$ (right bar) *in vitro*. 24
- Figure 9: Effect of chemical inhibitors of cytochrome P450 isoenzymes on the metabolism of cabazitaxel (RPR 116258) at $10 \text{ }\mu\text{M}$ in human liver microsomes. 25
- Figure 10: Proposed metabolic pathways of [^{14}C]-cabazitaxel in humans 26
- Figure 11: Cabazitaxel $\text{AUC}_{0-48\text{hr}}$ in the first cycle increased with dose with a slope of 0.73 (0.31, 1.15) from 10 to 30 mg/m^2 of cabazitaxel every three weeks administered via 1-hour intravenous infusion. 28

Figure 12: Cycle-independent clearance of cabazitaxel in humans with pooled pharmacokinetic data from studies TED6188 and TED6190	28
Figure 13: Dose normalized AUC_{0-t} versus cycle in breast cancer patients following weekly administration of cabazitaxel (1-hour IV infusions on Days 1, 8, 15, and 22 every 5 weeks)	29
Figure 14: The effect of body surface area (BSA) on the plasma clearance (L/Hr) in the first treatment cycle estimated by population pharmacokinetic analysis.....	31
Figure 15: The effect of tumor type (left) or trial (right) on the plasma clearance (CL) (L/h/m ²)	32
Figure 16: The effect of sex on the BSA-normalized plasma CL (L/h/m ²) estimated by population PK analysis.	32
Figure 17: The effect of age on the BSA-normalized individual plasma clearance (CL) (L/h/m ²) predicted by population pharmacokinetic analysis. Each red dot represents a patient.	33
Figure 18: The effect of renal function on clearance of cabazitaxel as depicted creatinine clearance (CRCL) vs BSA normalized clearance (CL) relationship. Each red dot represents a patient. Three vertical lines represents cut off for mild, moderate and severe renal impairment.....	34
Figure 19: The effect of race/ethnicity on the BSA-normalized individual plasma CL (L/h/m ²) predicted by population pharmacokinetic analysis. Each red dot represents a patient.	34
Figure 20: The effect of co-administration of prednisone/prednisolone on pharmacokinetics of cabazitaxel. Each red dot represents a patient.	38

1 EXECUTIVE SUMMARY

Cabazitaxel is a new molecular entity in the taxane class. In the current original NDA submission, the applicant seeks approval of cabazitaxel in combination with prednisone for the treatment of metastatic hormone refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.

In a Phase 3 trial supporting the efficacy and safety of cabazitaxel, mHRPC patients were randomized to receive either cabazitaxel 25 mg/m² (n=378) or mitoxantrone 12 mg/m² (n=377), both of which were administered via intravenous infusion every three weeks (Q3W) in combination with 10 mg daily oral prednisone. Overall survival was significantly improved in cabazitaxel arm (median: 15.1 months) compared to mitoxantrone arm (median: 12.7 months), with a hazard ratio of 0.70 (95% CI: 0.59, 0.83). Neutropenia, febrile neutropenia, diarrhea, infection, and renal failure are the most prominent toxicities for cabazitaxel treatment.

Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment pharmacokinetic (PK) model with α -, β -, and γ - half-lives of 4 minutes, 2 hours, and 95 hours, respectively. Cabazitaxel demonstrates no major deviation from dose proportionality between 10 mg/m² and 30 mg/m². No accumulation or changes in the pharmacokinetics were observed for up to three treatment cycles. Mean human plasma protein binding was 92%. Based on the population PK analysis, steady-state volume of distribution and plasma clearance of cabazitaxel were 4,864 L and 48.5 L/h (i.e., 2,643 L/m² and 26.4 L/h/m² for a patient with a median BSA of 1.84 m²), respectively.

Cabazitaxel was extensively metabolized by hepatic cytochrome P450 (CYP) 3A4/5 (80% to 90%) and to a lesser extent by CYP2C8. Cabazitaxel is primarily excreted into feces as metabolites (76% of the administered dose), with a low urinary excretion (3.7% of the administered dose, with 2.3% excreted as unchanged drug). At clinically relevant concentrations *in vitro*, cabazitaxel does not inhibit CYPs or transporters including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug-resistance protein (MRP). Based on *in vitro* studies, the potential for cabazitaxel to inhibit or induce major CYPs is low. Furthermore, cabazitaxel is a substrate of P-gp, but not a substrate of MRP1, MRP2, or BCRP.

Body surface area (BSA) and tumor type were identified as significant covariates on the plasma clearance of cabazitaxel. The BSA effect was accounted for by a BSA-based dosing regimen. Plasma clearance of cabazitaxel is 60% lower in patients with breast cancer compared to other tumor types. However, as 34 out of 37 breast cancer patients came from a single trial (ARD6191), it is difficult to distinguish if this is a trial effect or true tumor type effect.

A conclusive exposure-response relationship could not be identified for overall survival possibly due to limited PK data (N=67) at one dose level (25 mg/m²) collected in the pivotal trial. The shallow slope of the exposure-response relationship for \geq Grade 3 neutropenia suggested that dose reduction from 25 to 20 mg/m² will reduce the risk of having \geq grade 3 neutropenia by 5% when no prophylactic G-CSF was used.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed NDA 20-1023. This NDA is acceptable from a clinical pharmacology perspective provided that the applicant agrees to the labeling language and the post-marketing requirements listed below.

1.2 POST-MARKETING REQUIREMENTS

1. Complete and submit the final report of trial TES10884, along with a thorough review of cardiac safety data, for the potential of cabazitaxel on QTc interval prolongation in patients.
2. Conduct and submit the final report of trial POP6972 to determine the pharmacokinetics and safety of cabazitaxel in patients with hepatic impairment.
3. Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inducer (e.g., rifampin) on the pharmacokinetics of cabazitaxel in humans.
4. Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of cabazitaxel in humans.

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1.3 CLINICAL PHARMACOLOGY SUMMARY

Cabazitaxel is a new molecular entity in taxane class. In the current original NDA submission, the applicant seeks approval of cabazitaxel for the treatment of metastatic hormone refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.

A Phase 3 trial (EFC6193) was conducted to support the efficacy and safety of cabazitaxel. mHRPC patients were randomized to receive either cabazitaxel 25 mg/m² (n=378) or mitoxantrone 12 mg/m² (n=377), both of which were administered via intravenous infusion every three weeks (Q3W) in combination with 10 mg daily oral prednisone. Overall survival was significantly improved in cabazitaxel arm (median: 15.1 months) compared to mitoxantrone arm (median: 12.7 months), with a hazard ratio of 0.70 (95% CI: 0.59, 0.83). Neutropenia, febrile neutropenia, diarrhea, and renal failure are the most prominent toxicities for cabazitaxel treatment.

The dosage selection of 25 mg/m² Q3W based on efficacy and safety during Phase 1, 2 and 3 trials appears acceptable. In Phase 1 trials in patients with advanced solid tumors, the maximum tolerated dose (MTD) was independently determined as 30 mg/m² (TED6188) and 25 mg/m² (TED6190) via a one-hour IV infusion Q3W. The dose limiting toxicities (DLTs) were Grade 4 neutropenia, febrile neutropenia, and Grade 3 diarrhea or infection. Therefore, the recommended dose for the Phase 2 trial (RP2D) were determined as 25 mg/m² and 20 mg/m², respectively. Subsequently, an initial dose level of 20 mg/m² Q3W was tested in a Phase 2 trial (ARD6191) in advanced breast cancer and intra-patient dose escalation to 25 mg/m² was allowed if no Grade > 2 toxicity was observed in Cycle 1. Of 71 patients, 21 patients could be escalated to 25 mg/m² Q3W in Cycle 2. The applicant then chose 25 mg/m² Q3W for the pivotal Phase 3 trial in mHRPC patients. However, conclusive exposure-response relationship could not be identified for overall survival with limited PK data (N=67) collected in pivotal trial at one dose level (25 mg/m²). Shallow slope of the exposure-response relationship for ≥ Grade 3 neutropenia suggested that dose reduction from 25 to 20 mg/m² will reduce the risk of ≥ Grade 3 neutropenia by 5% when no prophylactic G-CSF was used. The median neutrophil count data (Day 1, 8 and 15 of the treatment cycle) for patients who did not use G-CSF in the trial showed that dose reduction alone provides modest increase in neutrophil counts. This is in accordance with a reduction of ≥ grade 3 neutropenia risk by 5% when reducing the dose from 25 to 20 mg/m² as demonstrated by exposure-safety analysis. The neutrophil count data from patients who used G-CSF in the trial showed that use of G-CSF or G-CSF in combination with dose reduction is a reasonable option for management of neutropenia. Thus, the proposed dose modification scheme for treating ≥ grade 3 neutropenia appears reasonable from a clinical management perspective.

Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment PK model with α-, β-, and γ- half-lives of 4 minutes, 2 hours, and 95 hours, respectively. Cabazitaxel demonstrates no major deviation from the dose proportionality between 10 mg/m² and 30 mg/m². No accumulation or changes in the pharmacokinetics of cabazitaxel were observed for up to three treatment cycles at 25 mg/m² Q3W. Mean human plasma protein binding is 92%. Based on the population PK analysis, steady-state volume of distribution and plasma clearance of cabazitaxel are 4,864 L and 48.5 L/h (i.e., 2,643 L/m² and 26.4 L/h/m² for a patient with a median BSA of 1.84 m²), respectively.

Cabazitaxel is extensively metabolized by cytochrome P450 (CYP) 3A4/5 (80% to 90%) and to

a lesser extent by CYP2C8. Cabazitaxel is excreted mainly into feces (76% of the administered dose) as approximately 20 metabolites, with a low urinary excretion (3.7% of the administered dose with 2.3% excreted as unchanged drug). *In vitro*, the potential for cabazitaxel is low to inhibit or induce major CYP isoenzymes or transporters including P-gp, BCRP, and MRP at clinically relevant concentration. In addition, cabazitaxel is a substrate of P-gp, but not a substrate of MRP1, MRP2, or BCRP.

Population PK analysis identified body surface area (BSA) and tumor types as significant covariates on the clearance of cabazitaxel. BSA is positively correlated with clearance, which justifies the BSA-based dosing regimen. Plasma clearance is 60% lower in patients with breast cancer compared to other tumor types. However, since 34 out of 37 breast cancer patients came from a single trial (ARD6191), it is difficult to distinguish if this is a trial variation or a true tumor type effect. In addition, no significant effect of gender, age, race (Caucasians vs non-Caucasians), mild or moderate renal impairment on the PK of cabazitaxel was observed in patients. The concomitant use of weak CYP3A inducers prednisone or prednisolone did not affect the pharmacokinetics of cabazitaxel.

The following issues should be addressed as post-marketing requirements: QTc risk evaluation; the effect of a strong CYP3A4 inhibitor, a strong CYP3A4 inducer; and hepatic impairment on the pharmacokinetics of cabazitaxel.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

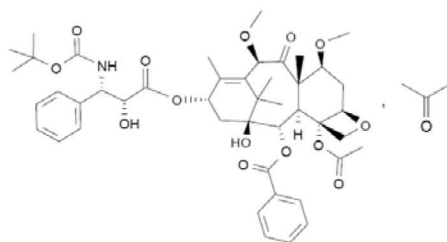
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Cabazitaxel is white to almost white power. JEV TANA (cabazitaxel) Injection is supplied as a kit consisting of the following:

- Concentrate (60 mg/1.5 mL): contains 60 mg cabazitaxel in 1.5 mL polysorbate-80
- Diluent: contains (b) (4) of 13% (w/w) ethanol in water for injection.

Physico-chemical properties

1. Structural formula:



2. Established name: Cabazitaxel, RPR116258, XRP6258
3. Molecular Weight: 894.01 (for the acetone solvate); 835.93 (for the solvent free)
4. Molecular Formula: $C_{45}H_{57}NO_{14}$, C_3H_6O
5. Partition coefficient (log P): 3.88 ± 0.03 , at 24°C, pH 7 in presence of 0.15 M potassium chloride (KCl)
6. Chemical Name (CAS): (2 α ,5 β ,7 β ,10 β ,13 α)-4-acetoxy-13-({(2R,3S)-3-[(tert-butoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl} oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate – propan-2-one(1:1).
7. Solubility

Table 1. Instantaneous solubility of cabazitaxel at 25°C in various solvent

Solvent	Solubility (according to Ph. Eur./USP terminology) ^a	Approximate volume of solvent in mL per g of solute ^a
Water	Practically insoluble	(b) (4)
Methanol	Soluble	
Ethanol	Soluble	
Dichloromethane	Freely soluble	
Acetone	Freely soluble	
Acetonitrile	Slightly soluble	
Ethyl acetate	Slightly soluble	
Cyclohexane	Practically insoluble	
Heptane	Practically insoluble	

^a Ph. Eur. and USP General Notices

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

Cabazitaxel is an antineoplastic agent in the taxane class. Cabazitaxel binds to tubulin and promotes the assembly of tubulin into microtubules while simultaneously inhibiting their disassembly. This leads to the stabilization of microtubules, which results in the inhibition of mitotic and interphase cellular functions. Cabazitaxel demonstrated a broad spectrum of antitumor activity, including activity in docetaxel-insensitive tumor models.

The proposed indication of cabazitaxel in combination with prednisone is for treatment of patients with mHRPC previously treated with a docetaxel-containing regimen.

2.1.3 What are the proposed dosage and route of administration?

The proposed dose of cabazitaxel is 25 mg/m² administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout cabazitaxel treatment.

The following premedications should be administered intravenously 30 minutes before each dose of JEV TANA:

- Antihistamine (dexchloropheniramine 5.0 mg, diphenhydramine 25 mg or equivalent antihistamine)
- Corticosteroid (dexamethasone 8 mg or equivalent steroid)
- H2 antagonist (ranitidine or equivalent H2 antagonist)
- Antiemetic prophylaxis (oral or IV) is recommended as needed

Furthermore, patients treated with JEV TANA may receive prophylactic G-CSF to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection).

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?

Seven clinical trials were submitted to support the clinical pharmacology of cabazitaxel. These studies included three Phase 1 dose finding trials (TED6188, TED6189, TED6190) in patients with solid tumors, one mass balance trial (BEX6702), two Phase 2 trials (ARD6191, ECD 6945) in patients with metastatic breast cancer, and one Phase 3 trial (EFC6193) in mHRPC patients previously treated with a docetaxel-containing regimen.

Extensive blood sampling was performed in Q3W studies TED6188, TED6190, BEX6702 and weekly regimen TED6189 (one-hour IV infusion on Days 1, 8, 15, and 22 every five weeks). Sparse sampling was implemented in 34 patients in Trial ARD6191 (Cycle 1, Day 1) and in 67 patients in Trial EFC6193 (Cycle 1).

The applicant performed a population PK analysis with pooled data to assess the effects of intrinsic and extrinsic factors. PK/PD relations were also investigated using PK parameters of cabazitaxel as prognostic factors for efficacy and safety endpoints (e.g., overall survival and neutropenia) respectively.

Table 2. Clinical trials supporting the dosing regimen

	Study identifier Location	Study design Objectives	Dosage regimen and route of administration	Number of patients
Dose-finding, safety, pharmacokinetics, efficacy	[TED6188] 5.3.3.2	Multicenter, open-label, nonrandomized study IV dose escalation: To determine the maximum tolerated dose and dose-limiting toxicity of cabazitaxel when administered IV on Day 1 of a 3-week cycle Additional objectives: safety profile, establish recommended dose and time intervals, determine PK profile, and evaluate antitumor activity	- cabazitaxel 10, 20, 25, and 30 mg/m ² (Day 1) - every 3 weeks - IV (1 hour)	21
Dose-finding (IV) & oral bioavailability, safety, PK, efficacy	[TED6189] 5.3.3.2	Multicenter, open-label, nonrandomized study IV dose escalation: To determine the maximum-tolerated dose and dose-limiting toxicity when cabazitaxel was administered weekly on Days 1, 8, 15, and 22 of a 5-week cycle Oral bioavailability: 1 oral admin on Day 1 of Cycle 1 in a subset of randomized patients followed by 3 weekly 1-hour IV infusions Additional objectives: safety profile, establish recommended dose and time intervals, determine PK profile, and evaluate antitumor activity	IV dose escalation: - cabazitaxel 1.5, 3, 6, 8.4, 10, and 12 mg/m ² (Days 1, 8, 15, and 22) - the first 4 weeks of a 5-week cycle - IV (1 hour) Oral bioavailability: - cabazitaxel 8.4 mg/m ² (Day 1 Cycle 1) - followed by 3 weekly IV infusions (also 8.4 mg/m ²) for the first cycle only - oral and IV	IV dose escalation: 31 Oral bioavailability: 11
Dose-finding (IV) & oral bioavailability, safety, PK, efficacy	[TED6190] 5.3.3.2	Single-center, open-label, nonrandomized study IV dose escalation: To determine the maximum-tolerated dose and dose-limiting toxicity when cabazitaxel was administered IV on Day 1 of a 3-week cycle Oral bioavailability: 1 oral admin for Cycle 1 followed by infusions every 3 weeks for subsequent cycles Additional objectives: safety profile, establish recommended dose and time intervals, determine PK profile, and evaluate antitumor activity	IV dose escalation: - cabazitaxel 10, 15, 20, and 25 mg/m ² (Day 1) - every 3 weeks - IV (1 hour) Oral bioavailability: - cabazitaxel 20 mg/m ² (Day 1/Cycle 1 only) - followed by infusions every 3 weeks (also 20 mg/m ²) - oral (Cycle 1) and IV (1 hour) (subsequent cycles)	IV dose escalation: 25 Oral bioavailability: 11
PK (excretion balance), metabolism, safety	[BEX6702] 5.3.3.2	Open-label, nonrandomized, single-radiolabeled IV Excretion balance and systemic exposure of radioactivity, PK parameters, Safety profile	- [¹⁴ C]-cabazitaxel 25 mg/m ² (Day 1/Cycle 1) - thereafter, nonradiolabeled cabazitaxel every 3 weeks - IV (1 hour)	4
Efficacy, safety, PK	[EFC6193] 5.3.5.1	Multicenter, multinational, randomized, open-label, comparative study Efficacy (overall survival) of patients treated with cabazitaxel in combination with prednisone versus mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with docetaxel-containing regimen Additional efficacy objectives: progression-free survival (PFS), overall response rate (ORR), prostate-specific antigen (PSA) response, PSA progression, pain response, and pain progression Safety: to assess the overall safety of cabazitaxel in combination with prednisone PK: to assess the PK of cabazitaxel and its metabolite, RPR123142, and assess the effect of prednisone on the PK of cabazitaxel	- cabazitaxel 25 mg/m ² (Day 1) - every 3 weeks - IV (1 hour) and 10-mg prednisone/ prednisolone orally given daily	742 treated 67 PK analysis
Efficacy, safety, PK	[ARD6191] 5.3.5.4	Multicenter, multinational, nonrandomized, open-label study with 2 strata based on pretreatment exposures Efficacy (objective response) of cabazitaxel when administered once every 3 weeks to patients with metastatic breast cancer. Additional efficacy objectives: duration of response, duration of stable disease, time to progression, and survival Safety: to confirm safety profile of cabazitaxel at 20 mg/m ² and to evaluate clinical benefit PK: to assess PK in this patient population	- cabazitaxel 15, 20, and 25 mg/m ² (Day 1) - every 3 weeks - IV (1 hour) Or - cabazitaxel 10 mg/m ² (Days 1, 8, 15, and 22) - the first 4 weeks of a 5-week cycle - IV (1 hour)	71 treated 34 PK analysis
Dose-finding, efficacy, safety, PK	[TCD6945] 5.3.5.4	Dose-escalating, multicenter, single-arm, open-label study Determination of maximum administered dose and maximum tolerated dose of cabazitaxel in combination with capecitabine for the treatment of metastatic breast cancer Efficacy: antitumor activity as assessed by objective response rate, time to progression, and duration of response Safety: assess safety of cabazitaxel in combination with capecitabine PK of cabazitaxel and its metabolite, RPR123142, and of capecitabine and its metabolite, 5-FU, and PK drug-drug interactions	- cabazitaxel 20 or 25 mg/m ² (Day 1) - every 3 weeks - IV (1 hour) with escalating doses of capecitabine twice daily (825 or 1000 mg/m ²) for the first 2 weeks in each 3-week cycle	33 treated 32 PK analysis

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?

The primary efficacy endpoint was overall survival in the pivotal Phase 3 trial EFC6193. As overall survival is an unambiguous endpoint, improvement in overall survival is generally considered as the gold standard for drug approval in oncology. Overall survival was defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, the survival time was censored at the last date patient was known to be alive or at the cut-off date, whichever had come first.

Being the main secondary efficacy endpoint, progression free survival was defined as the first occurrence of any of the following events: tumor progression per Response Evaluation Criteria In Solid Tumors [RECIST], prostate specific antigen [PSA] progression, pain progression, or death due to any cause.

Because a large proportion of patients with mHRPC have nonmeasurable disease (45% of patients in Phase 3 trial EFC6193), secondary endpoints such as PFS, tumor response rate, and tumor progression have inherent limitations in assessment of disease in these patients due to inter-observer bias and variability. PSA response and PSA progression, although objective endpoints for assessment of treatment effect in this patient population, have not been fully validated as surrogates for overall 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?

Yes. Cabazitaxel was the primary moiety in plasma appropriately identified and measured during clinical studies using validated LC-MS/MS methods.

Cabazitaxel is the major circulating compound in plasma (70%) with no other relevant circulating metabolites. In addition, cabazitaxel was equally distributed between plasma and blood cells, with a blood to plasma ratio of 0.90 to 0.99 (Studies PKFAC 9901 and DMPK/FR 2238). Therefore, plasma was an appropriate matrix for monitoring the PK of cabazitaxel.

Also see Sections 2.2.5.2, 2.2.5.4, and 2.6.

2.2.4 Exposure-response

Conclusive exposure-response relationships could not be identified for overall survival or time to tumor progression possibly due to limited PK data (N=67) in pivotal trial at one dose level (25 mg/m²). Shallow slope of the exposure-neutropenia (\geq Grade 3) relationship suggested that dose reduction from 25 to 20 mg/m² will reduce the risk of having \geq Grade 3 neutropenia by 5% when no prophylactic G-CSF was used.

2.2.4.1 Is there evidence of an exposure-response relationship for efficacy?

There were insufficient exposure data collected in the pivotal trial to support evidence of exposure-response for efficacy endpoint of overall survival and time to tumor progression.

- Only 67 patients (18% of the total enrolled in the cabazitaxel arm) were included in the exposure-efficacy analysis.

- Data from only one dose level (25 mg/m²) was available so the range of exposures might not be wide enough to explore exposure-efficacy relationship.

Exploratory exposure-efficacy analysis was conducted using data from the pivotal trial (EFC6193) following 25 mg/m² dose of cabazitaxel. Overall survival and time to tumor progression were the response variables utilized in the analysis. Due to few patients with PK data from only one dose level (N=67), exposure data were divided by median into two groups: AUC < 907 ng•hr/mL (N=35) and AUC > 907 ng•hr/mL (N=32). The left panel below (Figure 1) suggests that patients with higher exposures had lower overall survival. This relationship is, however, confounded by four deaths related to neutropenic complications within 30 days of dosing. The analysis was repeated without these four patients (three in higher and one in lower exposure groups). Results suggested that the separation between the two survival curves disappeared (right panel in Figure 1).

The exposure-response analysis for time to tumor progression showed numerically higher (not statistically significant) median time to progression for the higher exposure group (Figure 2).

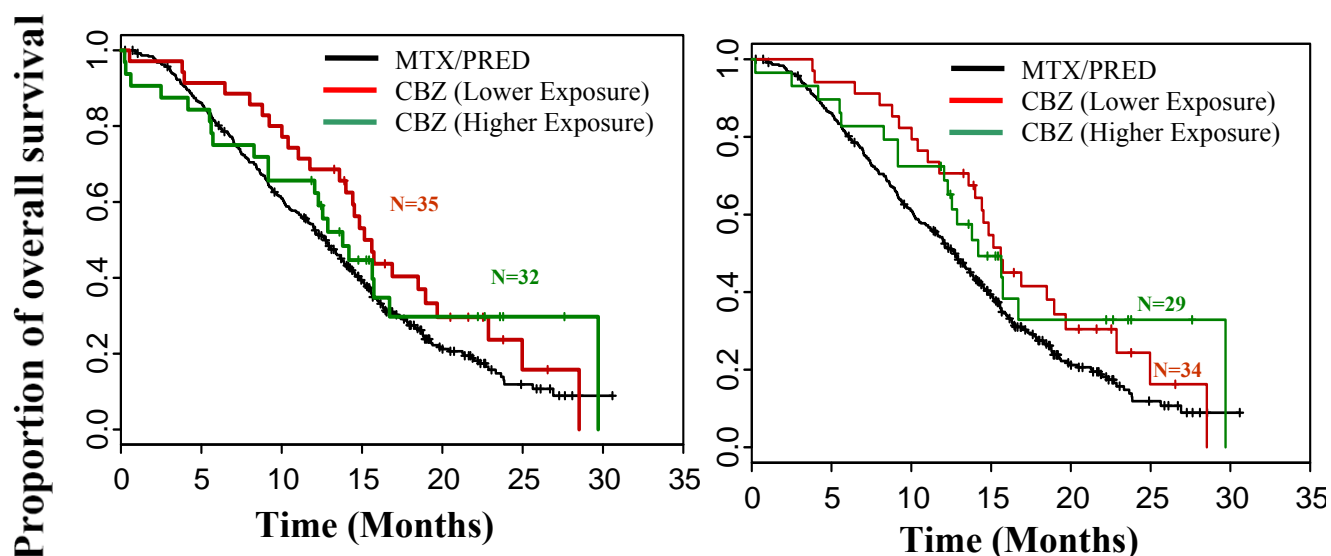


Figure 1: Exposure-response relationship of cabazitaxel (CBZ) for overall survival (left panel) in comparison with the same relationship excluding four patients with neutropenia related deaths on CBZ/PRED arm from the dataset (right panel). Small black, green and red vertical ticks on the plots are censored observations. MTX/PRED (Mitoxantrone/Prednisone) is the comparator arm.

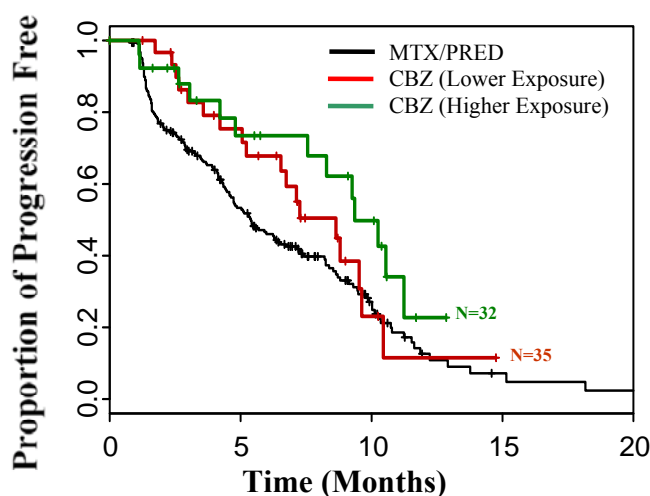


Figure 2: Exposure-response relationship of cabazitaxel (CBZ) for time to tumor progression. Small black, green and red vertical ticks on the plots are censored observation. MTX/PRED (Mitoxantrone/Prednisone) is the comparator arm.

2.2.4.2 Is there an evidence of exposure-response for safety?

Yes, there is evidence of exposure-response relationship for \geq grade 3 neutropenia in patients with advanced solid tumors. Univariate logistic regression models were used to explore the relationship between exposure (AUC) and \geq grade 3 neutropenia at the end of first cycle. Safety data from only Cycle 1 was taken to avoid the confounding effect of prophylactic G-CSF which was allowed later in the trial to treat \geq grade 3 neutropenia. Data from two Phase 1 trials (TED6188 and TED6190) and the pivotal trial (EFC6193) were combined to explore the exposure-safety analysis. AUC was found to be a predictor of \geq grade 3 neutropenia with a P value <0.05 . Adverse reactions such as \geq grade 3 diarrhea, febrile neutropenia and renal failure were not explored for the exposure-safety relationship due to limited events of adverse reactions in these categories.

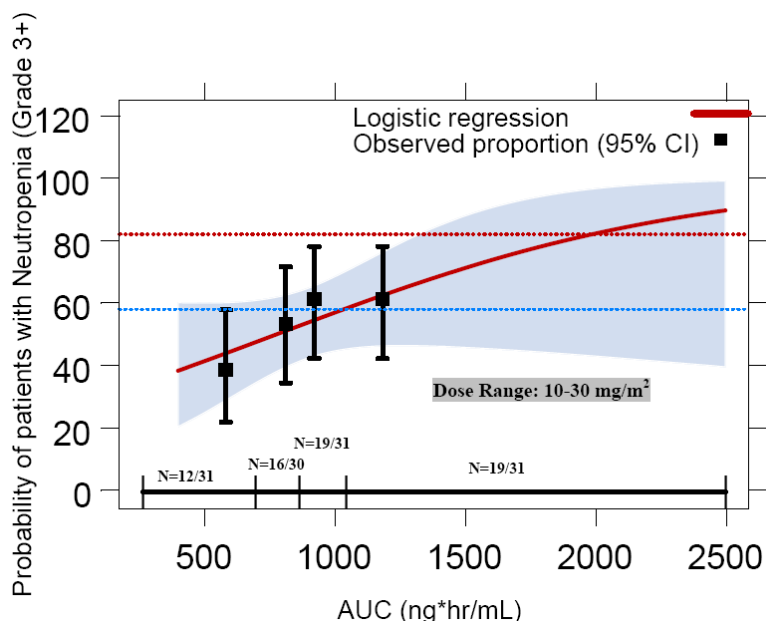


Figure 3: The probability of patients with \geq grade 3 neutropenia-AUC relationship. Solid black symbols represent the observed proportion of patients experiencing \geq grade 3 neutropenia in each AUC quartile. The vertical black bars represent the 95% confidence interval. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval of the prediction. The exposure range in each AUC quartile is denoted by the horizontal black line along with the number of subjects with adverse events/total number of subjects in each quartile. The horizontal dotted red and blue line represents the % of \geq grade 3 neutropenic events observed in the CBZ/PRED and MTX/PRED arm of the pivotal trial (EFC 6193), respectively.

2.2.4.3 Is the proposed dose reduction from 25 to 20 mg/m² adequate to reduce the risk of neutropenia (Grade \geq 3) based on exposure-safety relationship?

The dose reduction from 25 to 20 mg/m² (without G-CSF use) will not cause significant reduction in \geq grade 3 neutropenic events because slope of the exposure-safety relationship in patients with advanced solid tumors was shallow (See Pharmacometrics Review, Table 8). The logistic regression model suggests that decreasing the dose from 25 to 20 mg/m² would reduce the probability of patients experiencing neutropenia \geq grade 3 from 54% to 49%. This dose reduction can not be justified from an exposure-safety relationship.

The applicant provided data for the neutrophil count at different days within a treatment cycle for patients in the cabazitaxel arm who never received G-CSF in the pivotal trial (EFC6193). Median neutrophil count in the patients who never received G-CSF decreased from Day 1 to Day 15 within the cycle (solid blue line in Figure 4). Solid red line and orange line represents the neutrophil counts in a subset of patients before and under dose reduction, respectively. The data suggest that dose reduction alone only provides modest benefit and neutrophil count still remain below the baseline and near neutropenic levels. This observation is in accordance with modest reduction in \geq grade 3 neutropenia with dose reduction from 25-20 mg/m².

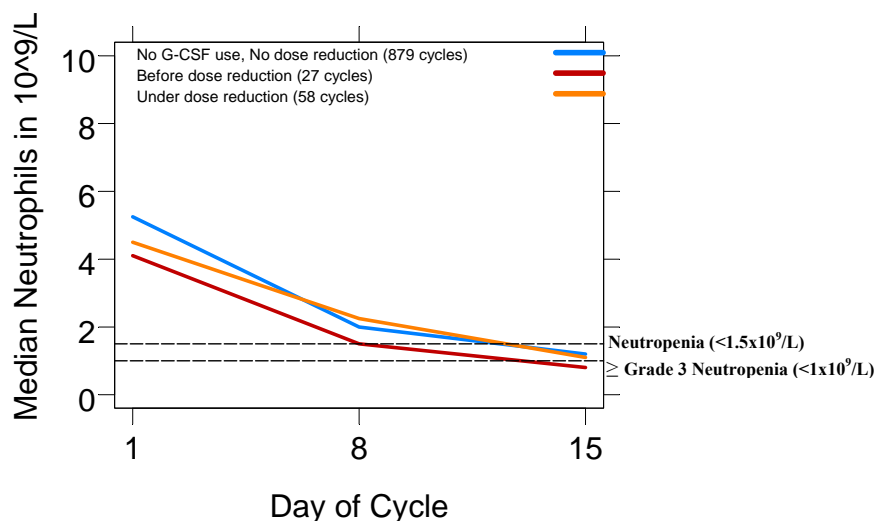


Figure 4: The median time course of neutrophils among patients in cabazitaxel arm who never received G-CSF during the pivotal trial (EFC6193). The two black dashed lines represents cutoff for neutropenia ($<1.5 \times 10^9/\text{L}$) and \geq grade 3 neutropenia ($<1.0 \times 10^9/\text{L}$).

Note: This figure was reproduced from the figure submitted by the applicant.

The dose modification scheme for neutropenia as proposed by the applicant first involves the use of appropriate medications (including G-CSF) to treat neutropenia. Then the dose will be delayed until neutrophil count is $\geq 1500 \text{ cells}/\text{mm}^3$. Subsequently, dose will be reduced (with concurrent use of G-CSF) if the patient doesn't respond to G-CSF therapy. The applicant also provided data for the neutrophil count at different days within a cycle for the patients in the cabazitaxel arm who did receive G-CSF at some point in the pivotal trial. Figure 5 shows that the use of G-CSF was able to bring the neutrophil counts back to baseline and the median neutrophil count at Day 8 was above $1.0 \times 10^9/\text{L}$. Use of combination of G-CSF and dose reduction seems to keep the median neutrophil levels at Day 8 above when compared to patients with G-CSF alone. However, the median neutrophil count at Day 15 (orange line) was lower than neutrophil count for patients on G-CSF alone (red line). This analysis has some limitations as the patients in these two groups (red and orange line) may not be the same and only 92 cycles contribute to the data for the G-CSF use with dose reduction (orange line).

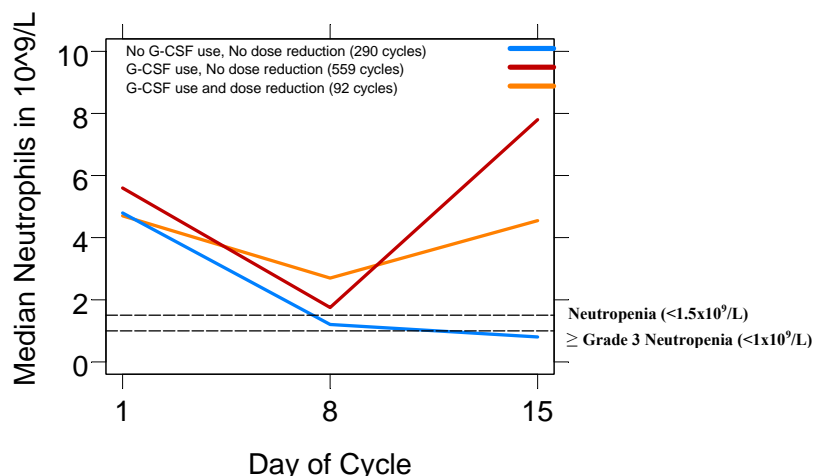


Figure 5: The median time course of neutrophils among patients who received G-CSF at some point during the pivotal trial (EFC6193). The two black dashed lines represents cutoff for neutropenia ($<1.5 \times 10^9/\text{L}$) and \geq grade 3 neutropenia ($<1.0 \times 10^9/\text{L}$).

Note: Reproduced from the figure submitted by the applicant.

It is noted that the proposed dose reduction scheme was applied in 9.7% of the cycles and in 14% (N=54) of patients in the CBZ/PRED arm in the pivotal trial and the \geq grade 3 neutropenia was manageable with G-CSF use. The proposed dose modification scheme (use of G-CSF or dose reduction in combination with G-CSF) seems to be reasonable from a clinical management perspective. Patients who develop \geq grade 3 neutropenia despite appropriate medication including G-CSF, and have to be continued on CBZ/PRED therapy, dose reduction in combination with G-CSF use is a reasonable option.

Please see Pharmacometrics review by Dr. Mehrotra for more information.

2.2.4.4 Does this drug prolong the QT or QTc interval?

The effect of cabazitaxel on cardiac repolarization has not been evaluated. A PMR will be issued to require the applicant to complete and submit the final report of ongoing trial TES10884, along with a thorough review of all available cardiac safety data, for the potential of cabazitaxel on QTc interval prolongation in patients.

2.2.4.5 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 selection of $25 \text{ mg}/\text{m}^2$ Q3W based on efficacy and safety during Phase 1, 2 and 3 trials appears acceptable because this dosing regimen demonstrated improved overall survival and the major TEAE neutropenia is manageable by prophylactic use of G-CSF. A conclusive exposure-response relationship could not be identified for overall survival possibly due to limited PK data (N=67) at one dose level ($25 \text{ mg}/\text{m}^2$) collected in the pivotal trial. The shallow slope of the exposure-response relationship for \geq Grade 3 neutropenia suggested that dose reduction from 25 to $20 \text{ mg}/\text{m}^2$ will reduce the risk of having \geq grade 3 neutropenia by 5% when no prophylactic G-CSF was used..

The recommended phase 2 dose (RP2D) was determined independently as 25 mg/m² in Trial TED6188 and 20 mg/m² in Trial TED6190, with corresponding MTDs of 30 mg/m² and 25 mg/m². The DLTs were Grade 4 neutropenia, febrile neutropenia, and Grade 3 diarrhea or infection. Subsequently, an initial dose level of 20 mg/m² Q3W was tested in a Phase 2 trial (ARD6191) in advanced breast cancer, and intra-patient dose escalation to 25 mg/m² was allowed if no Grade > 2 toxicity was observed in Cycle 1. The dose could be escalated to 25 mg/m² Q3W in 21 of 71 patients in cycle 2. A decrease of 60% in the plasma clearance was noted in this trial by the population PK analysis, but whether tumor type or trial variation cause this effect is unclear. The applicant then chose 25 mg/m² dose for the pivotal Phase 3 trial.

In the pivotal Phase 3 trial, a total of 755 patients were randomized to receive either cabazitaxel 25 mg/m² via a one-hour intravenous (IV) infusion every three weeks (Q3W) for a maximum of 10 cycles with prednisone 10 mg orally daily (n = 378), or to receive mitoxantrone 12 mg/m² via IV infusion Q3W for 10 cycles with prednisone 10 mg orally daily (n = 377) for a maximum of 10 cycles. Patients receiving cabazitaxel (n = 378) demonstrated statistically significant longer overall survival compared to those receiving mitoxantrone (n=377) (p < 0.0001). The median survival for patients in the cabazitaxel arm was 15.1 months in comparison to 12.7 months in the mitoxantrone arm. The hazard ratio was 0.70 (95% CI: 0.59, 0.83) in favor of cabazitaxel corresponding to a 30% reduction in risk of death.

Cabazitaxel demonstrated more prominent toxicities than mitoxantrone. Treatment emergent adverse events (TEAEs) Grade ≥ 3 occurred in 57.4% of patients in the cabazitaxel group and 39.4% of patients in the mitoxantrone group. The incidence of TEAEs leading to death were 4.9% in the cabazitaxel group and 1.9% in the mitoxantrone group. Most frequent hematological AEs on cabazitaxel group were neutropenia based on laboratory assessments (81.7% versus 58%, with clinical neutropenia requiring intervention reported in 21.3% versus 7% of patients), and its clinical consequences of infections (10.2% versus 5.1%) and febrile neutropenia (7.5% versus 1.3%). The applicant proposed that deaths by the cabazitaxel treatment due to neutropenia and its clinical consequences and dehydration are potentially manageable by patient education, close monitoring for development of neutropenia, prompt administration of corrective therapy such as hydration, use of antibiotics, and/or G-CSF use as per American Society of Clinical Oncology (ASCO) guidelines.

The following unresolved dosing and administration issues should be addressed as PMRs:

- dose adjustment in patients with hepatic impairment
- dose adjustment based on drug interactions of cabazitaxel with strong CYP3A inhibitors, and with strong CYP3A inducers

Also see section 2.2.1.

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 pharmacokinetics of cabazitaxel in patients after a one-hour IV infusion has the following features (as summarized in Table 3):

- Based on the population pharmacokinetic analysis, after an intravenous dose of cabazitaxel 25 mg/m² every three weeks, the mean C_{max} in patients with metastatic

prostate cancer was 226 ng/mL (CV 107%) and was reached at the end of the one-hour infusion (T_{max}). The mean AUC in patients with metastatic prostate cancer was 991 ng•h/mL (CV 34%).

- Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment PK model with α -, β -, and γ - half-lives of 4 minutes, 2 hours, and 95 hours, respectively (Figure 6). No major deviation from the dose proportionality was observed between 10 to 30 mg/m². No difference in exposure was observed following three consecutive cycles every three weeks, indicative of time-independent PK. No accumulation was observed under the proposed 25 mg/m² Q3W dosing regimen.
- The mean human plasma protein binding of cabazitaxel was 92%, independent of concentration up to 50,000 ng/mL. Steady-state volume of distribution of cabazitaxel is 4,864 L (CV 93%) (i.e., 2,643 L/m² for a patient with a median BSA of 1.84 m²).
- Based on the population pharmacokinetic analysis, cabazitaxel has a plasma clearance of 48.5 L/h (CV 39%; 26.4 L/h/m² for a patient with a median BSA of 1.84 m²) in patients with metastatic prostate cancer, which is consistent with other advanced solid tumors except for breast cancer (Table 9). The plasma clearance of cabazitaxel was 60% lower in breast cancer patients compared to other tumor types. However, as 34 out of 37 breast cancer patients came from a single trial (ARD6191), it is difficult to distinguish if this is a trial effect or a true tumor type effect.
- BSA is positively correlated with plasma clearance of cabazitaxel, which justified the adjustment of dose to BSA.

Table 3. Pharmacokinetic parameters of cabazitaxel after a 1-hour IV infusion at the first available cycle (mainly cycle 1)

Study	Type of study, regimen	Dose (mg/m ²)	Number of patients with PK	$t_{1/2\gamma}$ (h)	CL (L/h/m ²)	V_{ss} (L/m ²)
Individual modeling						
TED6188	Monotherapy, once every 3 weeks	10-30	19	62.0 (44%)	44.7 (30%)	2484 (41%)
TED6190	Monotherapy, once every 3 weeks	10-25	23	76.6 (60%)	27.5 (35%)	2013 (75%)
	Monotherapy (IV arm of the bioavailability arm)	20	7	96.8 (29%)	26.1 (46%)	2559 (47%)
BEX6702	Monotherapy, once every 3 weeks	25	4	155 (51%)	28.6 (52%)	4200 (55%)
Noncompartmental analysis						
TCD6945	Combination with capecitabine Cabazitaxel : once every 3 weeks, Capecitabine : twice daily for 14 days, every 3 weeks	20-25	11	79.1 (59%)	33.6 (52%)	2332 (69%)
Population PK analysis (POH0124)						
POH0124	TED60188, TED6189 (TED6190, ARD6191 and EFC6193)	10-30	-	95.1*	26.4*	2640*
TED6188	Monotherapy, once every 3 weeks	10-30	21	108 (55%)	34.5 (25%)	3660 (52%)
TED6189	Monotherapy, once every 3 weeks or 4 weekly administration, every 5 weeks (Cycle 1, Day 1) (Cycle 1, Day 1)	10-12	13	130 (72%)	25.5 (36%)	3160 (66%)
TED6190	Monotherapy, once every 3 weeks included IV arm of the bioavailability arm	10-25	35	103 (51%)	24.2 (36%)	2710 (84%)
ARD6191	Monotherapy, once every 3 weeks or 4 weekly administration, every 5 weeks (Cycle 1, Day 1)	10-20	34	210 (56%)	12.1 (26%)	3270 (64%)
EFC6193	Combination with prednisone/prednisolone.	25	67	120 (50%)	27.0 (24%)	3700 (64%)
Overall		10-30	170	134 (63%)	24.2 (40%)	3360 (66%)

* population PK estimates for a patient with a median BSA of 1.84 m²

Source: NDA submission 2.7.2 Summary of Clinical Pharmacology Studies

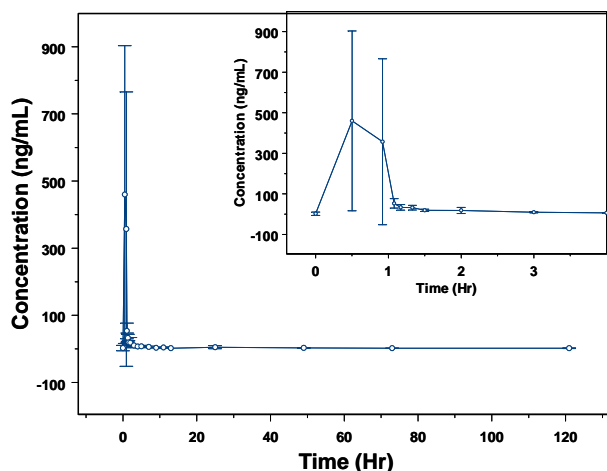


Figure 6: The time-concentration profiles of cabazitaxel in patients (n=13) with advanced tumors when a dose of 25 mg/m² was administered via a one-hour intravenous infusion.

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 cabazitaxel were conducted in cancer patients.

2.2.5.3 What are the characteristics of drug absorption?

Absorption is not pertinent for the current application, as cabazitaxel is administered via intravenous infusion.

Based on the population pharmacokinetic analysis, after an intravenous dose of cabazitaxel 25 mg/m² every 3 weeks, the mean C_{max} in patients with metastatic prostate cancer was 226 ng/mL (CV 107%) and was reached at the end of the one-hour infusion (T_{max}). The mean AUC in patients with metastatic prostate cancer was 991 ng·h/mL (CV 34%).

Table 4. C_{max} and AUC of cabazitaxel at the first available cycle following one-hour infusion at 25 mg/m²

Study	Number of patient	Observed C _{max} * (ng/mL)	AUC** (ng.h/mL)
TED6189	7	242 (65%)	678 (41%)
TED6190	5	535 (57%)	1038 (29%)
BEX6702	4	200 (58%)	1130 (69%)
EFC6193	67	250 ^a (170%)	991 (34%)

* Generally corresponding to 5 min before the end of infusion in TED6189, TED6190 and BEX6702 and within 15 minutes before the end of infusion in EFC6193; ** individual modeling for TED6189, TED6190 and BEX6702 and population PK analysis for EFC6193; a: n=29.

Source: NDA submission Table 16 in Section 3.2.2 in Summary of Clinical Pharmacology

Reviewer's note: The absolute bioavailability of oral cabazitaxel has been evaluated at 8.4 mg/m² in 9 patients (Trial TED6189) and at 20 mg/m² in 8 patients (Trial TED6190). The absolute bioavailability of oral cabazitaxel was low (mean: 5.8% to 7.4%), and highly variable (CV%: 98%-103%).

2.2.5.4 What are the characteristics of drug distribution?

Plasma Protein Binding

In vitro, cabazitaxel was highly bound to human plasma proteins with a mean of 89% and 92% in studies PKFAC 9902 and LPR0995, respectively, in a concentration-independent manner up to 50,000 ng/mL.

The mean *ex-vivo* plasma protein binding was 92% in Trial TED6188. The plasma protein binding was not saturable in the concentration range of 66 to 722 ng/mL. Cabazitaxel showed a high binding to human serum albumin (82%) and lipoproteins (88% for HDL, 70% for LDL, and 56% for VLDL) and a low binding to α -1 glycoprotein acid (18%) (Study PKFAC9902).

Blood to Plasma Ratio

Cabazitaxel was equally distributed between plasma and blood cells as suggested in the following studies:

- *In vitro* mean blood to plasma ratio for cabazitaxel was 0.90 and 0.99 in studies PKFAC 9901 and DMPK/FR 2238, respectively.
- In the mass balance trial BEX6702, the mean value of the radioactivity blood to plasma ratio was 1.1 at the middle and end of infusion following a one-hour IV administration of [¹⁴C]-cabazitaxel, where unchanged drug was the major component circulating in plasma (86%).

P-Glycoprotein

In vitro studies suggested that cabazitaxel is a substrate for P-glycoprotein. See section 2.4.2.4.

Volume of Distribution

The population analysis predicted a mean V_{ss} of 4,864 L (2,643 L/m² for a patient with a median BSA of 1.84 m²), which was comparable to the V_{ss} observed in patients with advanced solid tumors from the Phase 1 monotherapy studies (2,710 to 3,660 L/m²) (Table 3).

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

Mass balance trial suggested that hepatic excretion is the major route of elimination for cabazitaxel.

Four patients with advanced solid tumors received a single 1-hour IV infusion of [¹⁴C]-cabazitaxel at 25 mg/m² (50 μ Ci) in the human mass balance trial BEX6702. [¹⁴C]-cabazitaxel and its related metabolites were mainly excreted in the feces (mean: 76% of the administered dose), whereas the urinary route contributed markedly less (mean 3.7% of the administered dose) over two weeks post-dose. The mean recovery was 79.7% of the dose within two weeks with individual values ranging from 72.6% to 91.2% (Figure 7). No unchanged compound was

excreted in feces and on average 2.3% of the dose was excreted as parent drug in urine, revealing an extensive metabolism of cabazitaxel in humans.

Also see section 2.2.5.6 and 2.2.5.7.

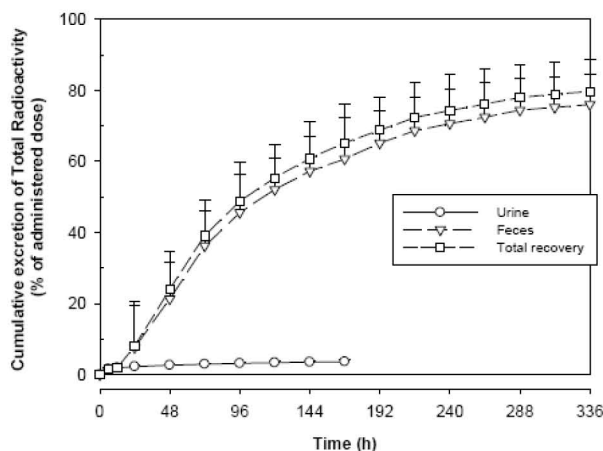


Figure 7: Mass balance of total radioactivity after a single 1-hour IV infusion of [¹⁴C]-cabazitaxel in 4 patients with advanced solid tumors (mean ±SD).

Source: Figure 6 of trial report of BEX6702

Table 5. Pharmacokinetics of cabazitaxel in 4 patients treated with 25 mg/m² [¹⁴C]-cabazitaxel as a 1-hour IV infusion

Dose (mg/m ²)	Patients Treated/with PK	C _{max} (ng/mL)	t _{last} (h)	AUC _(0-t) (ng.h/mL)	AUC (ng.h/mL)	t _{1/2λ} (h)	CL (L/h/m ²)	V _{ss} (L/m ²)
Blood radioactivity								
25	4/4	234 (65%)	8 ⁽¹⁾ [1.25-73h]	1180 (143%)	NC	ND	-	-
Plasma radioactivity								
25	4/4	242 (65%)	9 ⁽¹⁾ [3-25h]	495 (89%)	729 ⁽²⁾ (95%)	10.3 ⁽³⁾ [6.2-14.3]	-	-
Cabazitaxel								
25	4/4	200 (58%)	-	-	1130 (69%)	155 (51%)	28.6 (52%)	4200 (55%)

PK parameters estimated by noncompartmental analysis for radioactivity data and by a 3-compartment open model with first order elimination rate for cabazitaxel

(1): median [min-max]; (2): n=3 out of 4; (3): n=2 out of 4 and interval for t_{1/2} calculation [min-max], underestimated due to the high LLOQ; (d) third half-life

Abbreviations: NC: not calculated extrapolated AUC being superior to 30%, AUC could not be calculated as well as t_{1/2z}; ND: t_{1/2z} not determined due to the few concentrations above the LOQ.

Note : parameters were expressed as mean (CV%).

Source: Trial BEX6702

2.2.5.6 What are the characteristics of drug metabolism?

The metabolism of cabazitaxel was studied both *in vitro* and *in vivo*, as summarized below:

In vitro

Cabazitaxel was rapidly and extensively metabolized to numerous metabolites. CYP3A4/5 and CYP2C8 are involved in the human cabazitaxel biotransformation, with CYP3A4/5 contributing to 80% to 90% of the overall hepatic clearance and CYP2C8 contributing to a portion of the remainder of clearance.

In study MIH0350 to determine the *in vitro* intrinsic clearance of cabazitaxel using fresh human hepatocytes in primary culture, the *in vitro* intrinsic clearance of cabazitaxel showed slight saturation. The predicted *in vivo* metabolic hepatic clearance in man ranged from 64 L/h to 55 L/h (Table 6). Approximately 80% to 90% of the overall hepatic clearance was attributed to CYP3A (Table 7).

Table 6. Predicted *in vivo* intrinsic and metabolic clearance values of cabazitaxel (XRP6258) in human

XRP6258 initial concentration	CL _{int, in vivo} (L/h)	CL _{hep, in vivo} (L/h)	% hepatic blood flow
0.1 μM	238.7	63.8	73
1 μM	243.3	64.1	74
5 μM	152.4	55.4	64

Note:

1. *In vitro* intrinsic clearance (CL_{int, in vitro}) was calculated according to the following equation:

$$CL_{int, in vitro} = k \times V$$

Where: CL_{int, in vitro} is the *in vitro* intrinsic clearance expressed in mL/h/10⁶ hepatocytes, *k* is the elimination rate constant expressed in h⁻¹. *V* is the incubation volume expressed in mL normalized to 10⁶ hepatocytes.

2. The *in vivo* intrinsic clearance in man (CL_{int, in vivo}) expressed in L/h, was calculated from CL_{int, in vitro} by direct scale up using literature values for cell density and liver weight according to the following equation:

$$CL_{int, in vivo} (L/h) = CL_{int, in vitro} (mL/h/10^6 \text{ cells}) \times 178$$

3. The predicted *in vivo* hepatic clearance (CL_{hep}), expressed in L/h, was determined from CL_{int, in vivo} using the well-stirred model as follows (3):

$$CL_{hep} = \frac{CL_{int, in vivo} \times Qh}{Qh + CL_{int, in vivo}}$$

Source: Study MIH0350 report

Table 7. *In vitro* intrinsic clearance and fraction (mean ±SD) metabolized by CYP3A and overall CYP enzymes of XRP6258 in fresh human hepatocytes (n = 3)

XRP6258	CL _{int, in vitro} (mL/h/10 ⁶ cells)	fm CYP3A	fm CYP enzymes
0.1 μM	1.341 ± 0.747	92 ± 2	97 ± 2
1 μM	1.367 ± 0.863	89 ± 3	99
5 μM	0.856 ± 0.645	81 ± 5	100

Note:

The fraction metabolized by CYP3A and overall CYP enzymes was determined by the equation:

$$fm = 1 - \frac{CL'_{int, in vitro}}{CL_{int, in vitro}}$$

where CL' _{int, in vitro} and CL _{int, in vitro} are the *in vitro* clearance in the presence and absence of inhibitor (ketoconazole for CYP3A or aminobenzotriazole for CYPs), respectively.

Source: Study MIH0350 report

Study DMPK/FR 2266 indicated that CYPs but not flavin mono-oxygenases were responsible for the biotransformation of cabazitaxel in human liver microsomes. The biotransformation of

cabazitaxel was characterized as a low K_m and a high V_{max} , with 55.8%, 37.2% and 15.9% conversion to RPR 123142, RPR 112698 and RP 56976 (Table 8).

Table 8. *In vitro* enzyme kinetics of cabazitaxel (RPR116258) metabolism in human liver microsomes

	K_m	V_{max}	Metabolic clearance	
	μM	pmole/mg/min	$\mu l/mg/min$	% of RPR 116258
RPR 123142	2.1	428.6	204.1	55.8
RPR 112698	2.1	285.9	136.1	37.2
RP 56976*	0.8	46.4	58.0	15.9
RPR 116258	2.4	878.2	365.9	

*: estimations.

Source: Study DMPK/FR 2266

Using heterologously expressed human P450 and FMO isoenzymes, CYP3A4/5 and CYP2C8 were responsible for the biotransformation of cabazitaxel. CYP2C8 produced only RPR 112698, CYP3A5 produced RPR 112698 and RPR 123142, CYP3A4 produced RPR 112698, RPR 123142 and RP 56976 (Figure 8). The polymorphic CYP2A6, 2C9, 2C19 and 2D6 enzymes were not involved in the metabolism of cabazitaxel, nor were CYP1A1, 1A2, 1B1, 2B6, 2C18 and 2E1.

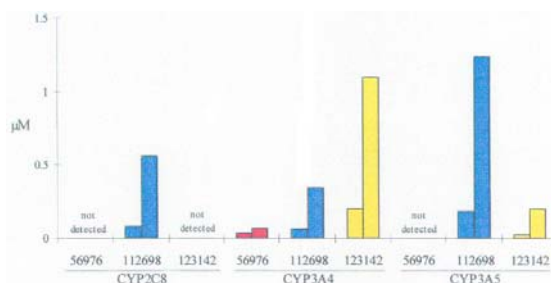


Figure 8: The metabolites formed by heterologously expressed human cytochrome P450 and FMO isoenzymes that metabolize cabazitaxel (RPR 116258) at 1 μM (left bar) and 10 μM (right bar) *in vitro*.

Source: Study DMPK/FR 2266

Using human microsomal fractions with a strong non-specific CYP inhibitor (benzylimidazole) and two strong specific CYP3A inhibitors (ketoconazole and TAO), CYP3A4/5 were found to be responsible for the human cabazitaxel biotransformation, with CYP3A contributing to 80% to 90% of the overall hepatic clearance and CYP2C8 contributing to some of the remainder (Figure 9). The other inhibitors, ANF, menthofuran, quercetin, quinidine, and DDC did not show significant inhibitory effect, which indicated that CYP1A2, CYP2A6, CYP2C8, CYP2D6 and CYP2E1, respectively, were not involved in the biotransformation of cabazitaxel at 10 μM in human liver microsomes. Quercetin did not inhibit RPR 112698 formation from RPR 116258 in human liver microsomes whereas yeast expressed CYP2C8 clearly produced it.

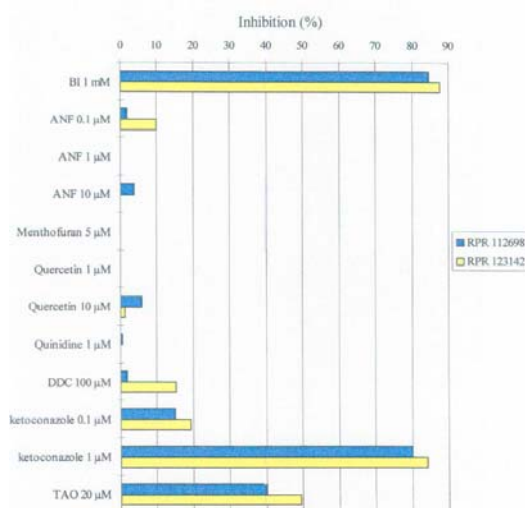


Figure 9: Effect of chemical inhibitors of cytochrome P450 isoenzymes on the metabolism of cabazitaxel (RPR 116258) at 10 μ M in human liver microsomes.

Source: Figure 15 of Study DMPK/FR 2266

In vivo

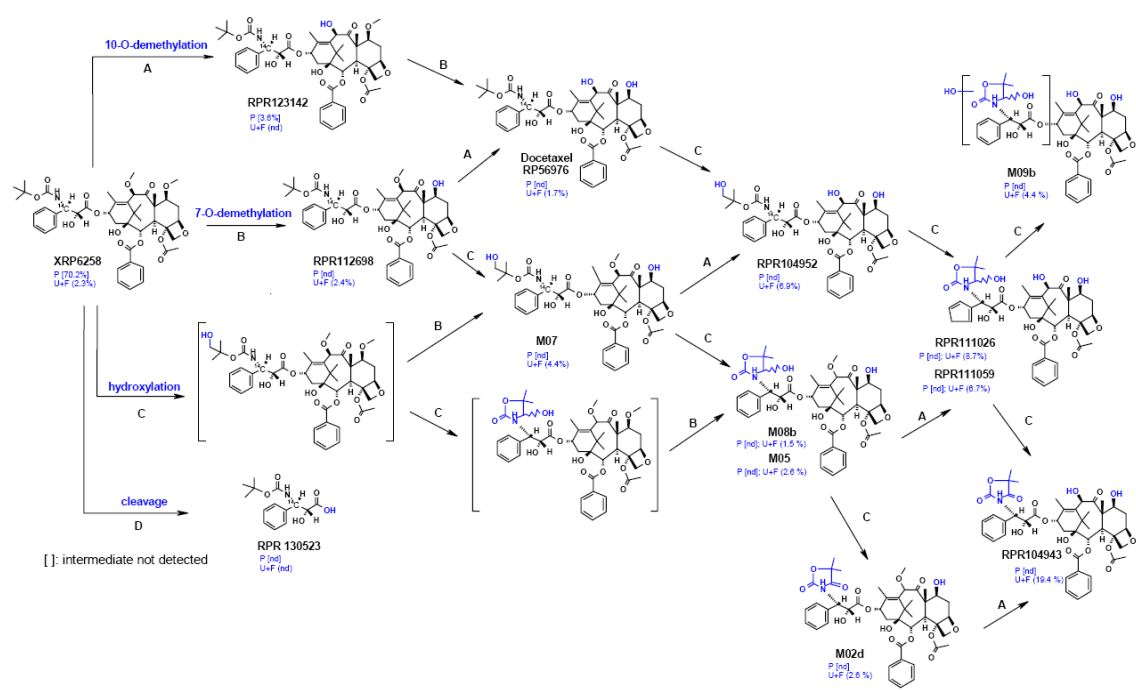
Cabazitaxel is extensively metabolized following a one-hour IV administration of 25 mg/m² [¹⁴C]-cabazitaxel in 4 patients with advanced tumors (Trial BEX6702 and Study MEH0033).

In plasma, the parent drug was the main circulating compound, representing an average 70.2% (range: 49.8% to 89.9%) of radioactivity AUC. Seven metabolites were detected in plasma, each accounting for less than 10% of parent drug AUC. The main metabolite was RPR123142, the 10-O-demethylated derivative on the taxane ring, accounting for 3.6% of radioactivity AUC and 5.1% of parent drug AUC. All the other circulating metabolites (docetaxel, RPR111026, RPR111059, M09b, RPR130523, and RPR112698) represented on average less than 2.3% of the radioactivity AUC. Cabazitaxel and RPR123142 were the only compounds quantifiable 6 to 24 hours after the end of infusion.

In excreta, the majority of the radioactivity was recovered in feces (62% to 77% of the administered dose within 7 to 10 days), while a further 3% to 4% of the administered dose was excreted in urine within three to four days. No unchanged compound was excreted in feces and on average 2.3% of the dose was excreted as parent drug in urine, revealing an extensive metabolism of cabazitaxel in humans. Among approximately 20 metabolites detected in excreta, main metabolites were combined mono- or di-O-demethyl derivatives on the taxane ring with hydroxyl- or cyclized derivatives on the lateral chain, such as RPR104943, oxazolidinedione derivative of docetaxel (19.4% of the dose), two isomers RPR111026 and PR111059, hydroxyoxazolidine derivatives of docetaxel (8.7% and 6.7% of the dose, respectively), and RPR104952, hydroxy-docetaxel (6.9% of the dose). Of note, these four metabolites have previously been found to be main metabolites of docetaxel, however, docetaxel itself was only detected at very low levels in plasma and feces.

Based on the identified metabolites, the following four metabolic pathways were proposed (Figure 10):

- Pathway A: 10-O-demethylation on the taxane ring leading to RPR123142, representing 16% of the administered dose
- Pathway B: 7-O-demethylation on the taxane ring leading to RPR112698, representing 24% of the administered dose
- Pathway C: hydroxylation on t-butyl moiety in the lateral chain followed by cyclization of the lateral chain giving rise to oxazolidine-type compounds, representing 21% of the administered dose
- Pathway D: cleavage of the parent drug giving rise to the loss of the taxane moiety, a minor pathway only detected at low levels in plasma and urine(<0.1% of the administered dose)



P=plasma, F=feeces, U=urine

Figure 10: Proposed metabolic pathways of [¹⁴C]-cabazitaxel in humans

Source: Study report BEX6702

2.2.5.7 What are the characteristics of drug elimination and excretion?

Elimination

Following a one-hour IV infusion at 25 mg/m² of [¹⁴C]-cabazitaxel, 80% of the dose was recovered in excreta over the two weeks post-dose. Radioactivity was largely excreted in the feces (76.0% of the administered dose) as numerous metabolites. The urinary route contributed markedly less to the overall excretion (3.7% of the administered dose with 2.3% excreted as unchanged drug).

Also see section 2.2.5.6.

Clearance

Based on the population PK analysis (Study POH0124) (Table 3), cabazitaxel exhibited a plasma clearance with a population value of 48.5 L/h (26.4 L/h/m² for a patient with a median BSA of 1.84 m²), which was comparable to those estimated in Phase 1 monotherapy studies TED6188, TED6189, and TED6190 (24.2 to 34.5 L/h/m²). It was noted that plasma clearance was 60% lower (12.1 L/h/m²) in patients with metastatic breast cancer from the Phase 2 monotherapy Trial ARD6191. However, this difference can not be discerned if this difference is due to an effect of tumor types or an effect of trial variation.

Also see section 2.2.5.1.

Half-lives

Following a one-hour IV infusion, the elimination profile of cabazitaxel was triphasic and characterized by rapid initial and intermediate phases with half-lives of 4 minutes and 2 hours, respectively, and by a long elimination half-life of 95 hours. The mean elimination half-life in the target population (120 hours) was comparable to those estimated in patients with advanced solid tumors from Phase 1 monotherapy trials TED6188, TED6189 and TED6190 (103 to 130 hours), while it was approximately twice as long (210 hours) in patients with metastatic breast cancer from the Phase 2 monotherapy trial (ARD6191) (Table 3).

Also see section 2.2.5.1.

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

No major deviation from dose proportionality was observed in the dose range from 10 to 30 mg/m² with a one-hour IV infusion Q3W schedule.

Using combined AUC_{0-48 hrs} in the first treatment cycle from 41 patients in studies TED6188 and TED6190), a power model was applied to test dose proportionality. The results suggested that the slope for the power model on logarithmic scale is 0.73 with a 90% confidence interval of (0.31, 1.15), which is overlapped with the confidence interval of (0.8, 1.25) for a conclusive dose proportionality. Therefore, though the AUC_{0-48 hrs} of cabazitaxel increased with BSA-normalized doses, it is inconclusive whether the AUC_{0-48hr} increases in a dose-proportional manner.

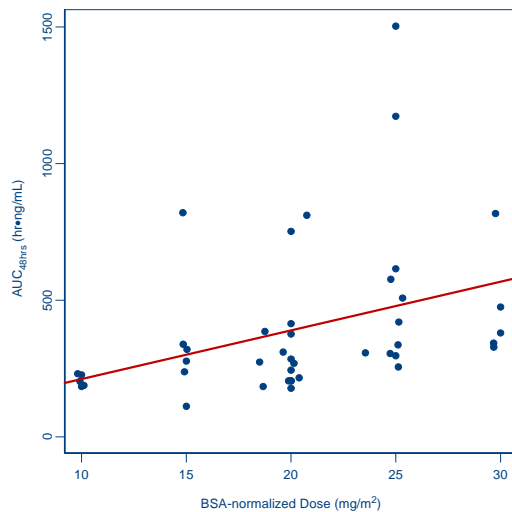


Figure 11: Cabazitaxel AUC_{0-48hr} in the first cycle increased with dose with a slope of 0.73 (0.31, 1.15) from 10 to 30 mg/m² of cabazitaxel every three weeks administered via 1-hour intravenous infusion.

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

Cycle Independence

After a one-hour IV infusion every three weeks (studies TED6188 and TED6190) at doses ranging from 10 to 30 mg/m², neither accumulation nor changes in the plasma clearance of cabazitaxel were observed up to 3 consecutive cycles.

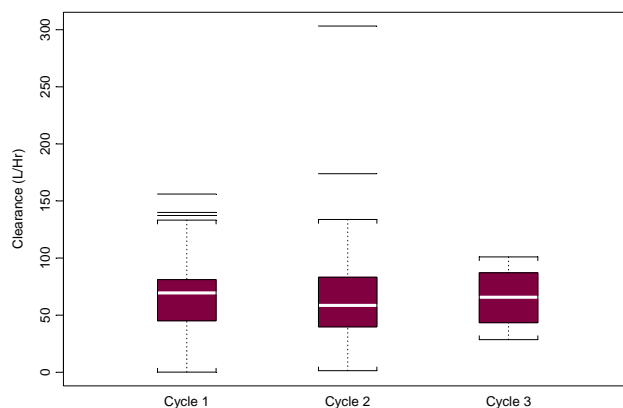


Figure 12: Cycle-independent clearance of cabazitaxel in humans with pooled pharmacokinetic data from studies TED6188 and TED6190

After weekly administration (one-hour IV infusions on Days 1, 8, 15, and 22 every five weeks in trial TED 6189 in metastatic breast cancer), no significant differences were observed in C_{max} and $AUC_{(0-t)}$ after the 1st and 4th administrations between Cycles 1 and 2 (Figure 13).

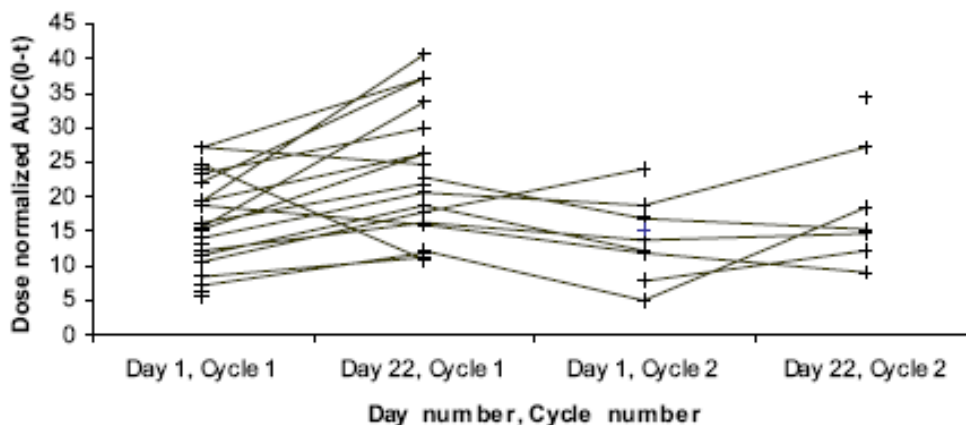


Figure 13: Dose normalized AUC_{0-t} versus cycle in breast cancer patients following weekly administration of cabazitaxel (1-hour IV infusions on Days 1, 8, 15, and 22 every 5 weeks)
Source: Trial TED6189

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?

Cabazitaxel has not been investigated in healthy volunteers.

The dose normalized $AUC_{(0-48hrs)}$, has an intra-patient variability of 23% in trial TED6188 and 27% in trial TED6190. Population PK analysis estimated an inter-patient variability of 48% for plasma CL and an inter-patient variability of 94% for V1 in the basic model. After including influential covariates (BSA and tumor type) in the final model, the inter-patient variability of plasma CL was decreased to 39%, while it remained unchanged for V1 (93% versus 94%). The inter-occasion (cycle to cycle variability) was 19% for plasma CL and 45% on the volume of the central compartment.

The unexplained variability may be attributed to the variation in treatment practices across the large number of clinical sites, concomitant medications, inaccuracy in dosing, PK sampling time, intrinsic factors in cancer patients, etc.

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?

No formal studies have been conducted to assess the effect of age, gender, race, BSA, renal or hepatic function on cabazitaxel PK.

BSA and tumor type were identified as significant covariates on the plasma CL of cabazitaxel in the population PK analysis. BSA is positively correlated with plasma clearance of cabazitaxel, which justifies the adjustment of dose to BSA. The plasma CL of cabazitaxel was approximately 60% lower in breast cancer patients compared to other tumor types. However, since 34 out of 37 breast cancer patients came from a single trial (ARD6191), it is difficult to distinguish if this is a trial effect or true tumor effect.

No impact of other intrinsic factors (age, race, renal function, or hepatic function) on the PK of cabazitaxel was identified by the population PK analysis.

Table 9. Pharmacokinetic parameters of cabazitaxel in patients treated at 10 to 30 mg/m² according to gender, age, race, tumor type, creatinine clearance, transaminase ratio, and alkaline phosphatase ratio

Group	N	CL (L/h)	CL (L/h/m ²)	V _{ss} (L)	V _{ss} (L/m ²)	t _{1/2γ} (h)
Male	110	53.5 (30%)	27.6 (29%)	6660 (69%)	3410 (65%)	113 (49%)
Female	60	30.3 (57%)	18.0 (54%)	5540 (72%)	3280 (69%)	173 (65%)
Caucasian	144	45.6 (44%)	24.2 (41%)	6610 (70%)	3530 (66%)	140 (64%)
Non Caucasian	26	46.3 (41%)	24.3 (39%)	4370 (54%)	2440 (52%)	102 (47%)
Age < 65	100	44.9 (47%)	24.1 (43%)	6070 (65%)	3290 (63%)	137 (65%)
65 ≤ Age < 75	57	46.1 (40%)	24.3 (37%)	6560 (80%)	3440 (75%)	131 (65%)
Age ≥ 75	13	44.5 (36%)	25.0 (31%)	6520 (59%)	3610 (53%)	123 (29%)
Breast Cancer	37	20.8 (28%)	12.4 (29%)	5630 (65%)	3330 (62%)	212 (55%)
Prostate Cancer	77	52.0 (29%)	26.6 (27%)	7050 (69%)	3570 (66%)	119 (50%)
GI Cancer	23	50.0 (44%)	27.7 (37%)	5300 (69%)	2980 (67%)	108 (57%)
Other Cancers	33	53.7 (31%)	29.5 (31%)	5820 (74%)	3200 (73%)	100 (49%)
CL _{CR} > 80 ml/min	96	48.3 (43%)	24.8 (41%)	6890 (72%)	3530 (69%)	138 (65%)
50 ≤ CL _{CR} ≤ 80 ml/min	59	42.7 (44%)	24.0 (41%)	5340 (57%)	3070 (58%)	126 (61%)
30 ≤ CL _{CR} < 50 ml/min	14	35.1 (37%)	20.7 (32%)	6050 (76%)	3540 (73%)	139 (58%)
CL _{CR} < 30 ml/min	1	49.3	29.2	3850	2280	79.3
ALTR < 1.5ULN	166	45.7 (43%)	24.4 (40%)	6260 (71%)	3340 (67%)	132 (62%)
ALTR ≥ 1.5ULN	4	28.7 (29%)	18.7 (29%)	6340 (43%)	4210 (48%)	208 (76%)
ASTR < 1.5ULN	151	46.1 (44%)	24.7 (40%)	6350 (70%)	3410 (66%)	134 (62%)
ASTR ≥ 1.5ULN	19	38.5 (41%)	20.6 (32%)	5640 (77%)	3040 (73%)	138 (73%)
ALPR ≤ 2.5ULN	152	44.9 (46%)	24.2 (42%)	6390 (71%)	3450 (66%)	139 (63%)
ALPR > 2.5ULN	18	48.3 (27%)	24.5 (23%)	5190 (63%)	2620 (62%)	93.4 (37%)

Abbreviations: ALPR: alkaline phosphatase ratio; ALTR: alanine amino transferase ratio; ASTR: aspartate amino transferase ratio

Source: Study report POH0124

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.

No dosage regimen adjustments were proposed for the special populations. The impact of BSA on the clearance has already been accounted for by the BSA-based dosing regimen. The dose adjustments were mainly based on the safety endpoints as described in the applicant's proposed label:

Table 10. The proposed dose modifications for adverse reactions in patients treated with cabazitaxel

(b) (4)

(b) (4)

2.3.2.1 Pediatric patients

Safety and effectiveness of cabazitaxel have not been established in pediatric patients. Prostate cancer is rare in pediatric patients. A full pediatric waiver has been granted by FDA.

2.3.2.2 Body Size

The population PK analysis identified BSA as a significant covariate. This effect of body size on plasma clearance has been taken into account by the adjustment of the dose to the BSA.

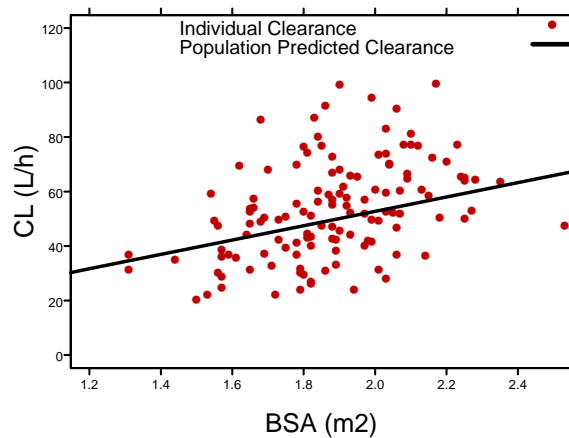


Figure 14: The effect of body surface area (BSA) on the plasma clearance (L/Hr) in the first treatment cycle estimated by population pharmacokinetic analysis.

2.3.2.3 Tumor Type

The population PK analysis identified tumor type as a significant covariate, with a 60% decrease in plasma clearance in patients with breast cancer (left panel, Figure 15). However, this tumor type effect may also be attributed to an inter-trial variation, as 34 out of 37 patients with breast cancer were from a single Phase 2 trial (right panel, Figure 15).

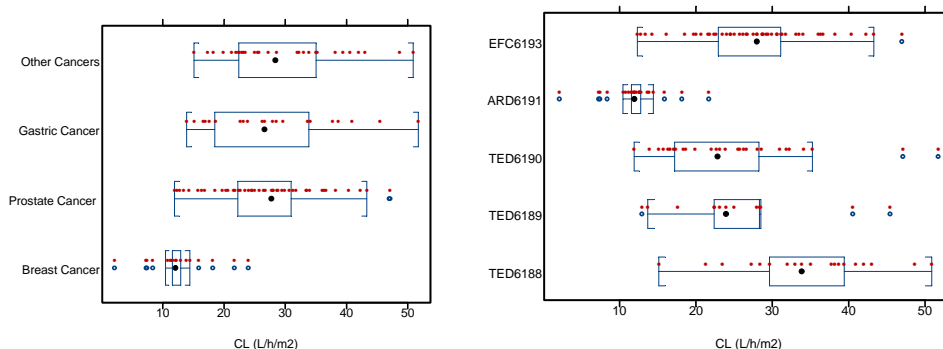


Figure 15: The effect of tumor type (left) or trial (right) on the plasma clearance (CL) (L/h/m²)

2.3.2.4 Sex

As prostate cancer only occurs in males, sex-based dose adjustment is not relevant.

Based on the population PK analysis, sex has no significant effect on the PK of cabazitaxel (Figure 16).

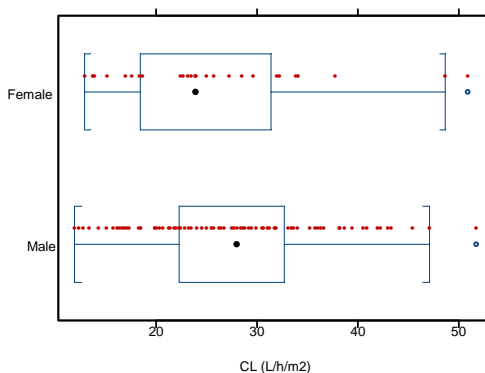


Figure 16: The effect of sex on the BSA-normalized plasma CL (L/h/m²) estimated by population PK analysis.

2.3.2.5 Elderly

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients < 65 years (n=100) and older (n=70) (Figure 17).

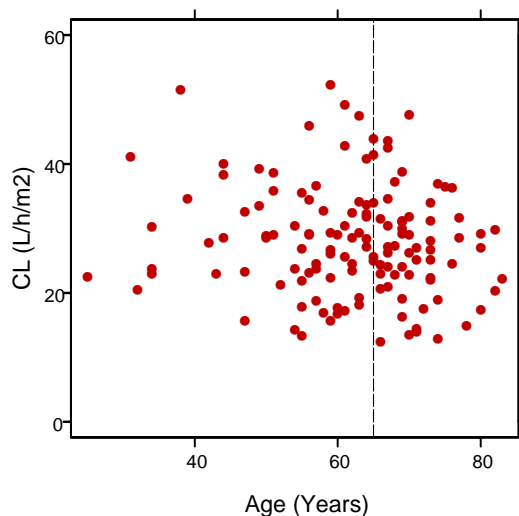


Figure 17: The effect of age on the BSA-normalized individual plasma clearance (CL) (L/h/m²) predicted by population pharmacokinetic analysis. Each red dot represents a patient.

2.3.2.6 Hepatic Impairment

No formal hepatic impairment trials have been conducted. As cabazitaxel is extensively metabolized by CYP 3A in liver, liver dysfunction is expected to increase the plasma concentrations of cabazitaxel. Patients with impaired hepatic function (total bilirubin \geq ULN, or AST and/or ALT $\geq 1.5 \times$ ULN) were excluded from the randomized clinical trial. Conducting a hepatic impairment trial will be a PMR to determine the dose regimen in patients with hepatic impairment.

Population PK analysis did not determine transaminases as significant covariates influencing cabazitaxel PK, possibly due to the fact that only a small number of patients had elevated transaminases, bilirubin, or alkaline phosphatase levels (eg, one patient with a bilirubin ratio $>$ ULN, four and 19 patients with ALT and AST ratios $> 1.5 \times$ ULN, respectively, and 18 patients with ALP ratio $> 2.5 \times$ ULN). Based on the limited number of patients with abnormal liver function at baseline, no dose adjustment can be recommended.

2.3.2.7 Renal Impairment

No formal trial has been conducted in patients with renal impairment. Population PK analysis suggested renal function measured by creatinine clearance has no significant correlation with the cabazitaxel clearance. As only 2.3% of the administered dose of cabazitaxel is eliminated renally, cabazitaxel PK was not changed in patients with mild renal impairment ($50 \text{ mL/min} \leq \text{CLCR} \leq 80 \text{ mL/min}$) and moderate ($30 \text{ mL/min} \leq \text{CLCR} \leq 50 \text{ mL/min}$). Patients with severe renal impairment ($\text{CLCR} < 30 \text{ mL/min}$) and end stage renal disease should be treated with caution and monitored carefully during treatment. Dose delay or reduction should be considered in the event of adverse drug reactions.

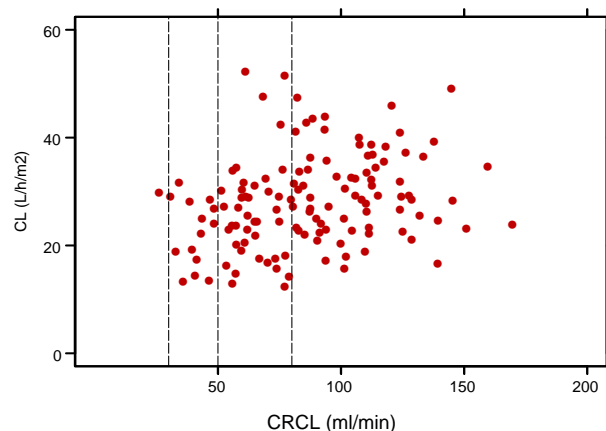


Figure 18: The effect of renal function on clearance of cabazitaxel as depicted creatinine clearance (CRCL) vs BSA normalized clearance (CL) relationship. Each red dot represents a patient. Three vertical lines represents cut off for mild, moderate and severe renal impairment.

2.3.2.8 Race/Ethnicity

The potential effects of race/ethnicity on cabazitaxel PK were not formally investigated. Population PK analysis did not identify race (non-Caucasian versus Caucasian) as a significant covariate influencing cabazitaxel pharmacokinetics. The model predicted a similar plasma CL value of cabazitaxel in Caucasian patients (24.2 L/h/m², N=144) and in non-Caucasian patients (24.3 L/h/m², N=26) (Table 8). Small changes in predicted CL in different races were observed: the predictive plasma CL values in non-Caucasian patients were 29.6 L/h/m² in oriental patients (N=9), 22.9 L/h/m² in black patients (N=4), 22.0 L/h/m² in Hispanic patients (N=7), and 19.8 L/h/m² in “other” patients (N=6).

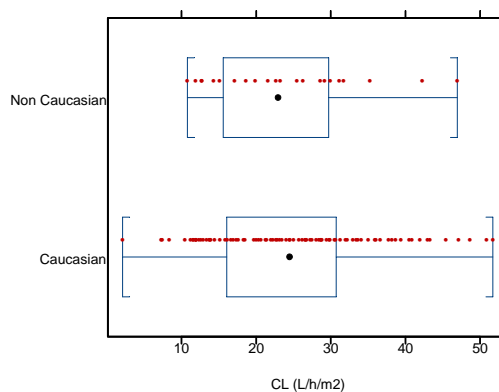


Figure 19: The effect of race/ethnicity on the BSA-normalized individual plasma CL (L/h/m²) predicted by population pharmacokinetic analysis. Each red dot represents a patient.

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

Cabazitaxel is pregnancy category D drug. Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats. It is not known whether this drug is excreted in human milk.

Within 2 hours of a single intravenous administration of cabazitaxel to lactating rats at a dose of 0.48 mg/m² (approximately 0.02 times the maximum recommended human dose), radioactivity related to cabazitaxel was detected in the stomachs of nursing pups. This was detectable for up to 24 hours post-dose. Approximately 1.5% of the dose delivered to the mother was calculated to be delivered in the maternal milk.

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?

No formal *in vivo* studies have been conducted to evaluate the effects of extrinsic factors such as drugs, herbal products, diet, smoking or alcohol use on the pharmacokinetics or pharmacodynamics of cabazitaxel.

2.4.2 Drug-drug interactions

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

Yes. As CYP3A4/5 are the major CYP isozymes responsible for the metabolism of cabazitaxel, inhibitors and inducers of CYP3A are expected to affect the pharmacokinetics of cabazitaxel.

Also see section 2.4.2.2, 2.4.2.3, and 2.4.2.4.

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

Cabazitaxel was extensively metabolized by liver to approximately 20 metabolites. Approximately 80% to 90% of the overall hepatic clearance is attributed to CYP3A4/5 (Table 6) and the remaining contribution could be attributed to CYP2C8 (Figure 8). Due to the minor contribution of CYP2C8 in the clearance of cabazitaxel, the genetic polymorphisms of CYP2C8 are not expected to significantly influence the metabolism of cabazitaxel in humans. However, the polymorphisms of CYP3A5 may affect the metabolism of cabazitaxel in humans.

Also see section 2.2.5.6.

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

***In-vitro* inhibition**

Cabazitaxel does not exhibit an *in vivo* potential to inhibit CYP3A4 at clinically relevant drug concentrations.

Based on the geometric mean of observed C_{max} values of 150 ng/mL [0.179 µmol/L] after the first administration in patients with mHRPC [Trial EFC6193]), the I/K_i ratio was lower than 0.1 for CYP2B6, 2C8, 2C9, 2D6, and 3A (Table 12). However, C_{max} of 150 ng/mL was likely underestimated as the samples for C_{max} were collected 5 minutes or 15 minutes early before the end of the infusion. Therefore, cabazitaxel may still have an *in vivo* potential to inhibit CYP3A4.

Table 11. C_{max} and AUC of cabazitaxel at the first available cycle following 1-hour infusion at 25 mg/m²

Study	Number of patient	Observed C _{max} [*] (ng/mL)	AUC ^{**} (ng.h/mL)
TED6189	7	242 (85%)	678 (41%)
TED6190	5	535 (57%)	1038 (29%)
BEX6702	4	200 (58%)	1130 (69%)
EFC6193	67	250 ^a (170%)	991 (34%)

^{*} Generally corresponding to 5 min before the end of infusion in TED6189, TED6190 and BEX6702 and within 15 minutes before the end of infusion in EFC6193; ^{**} individual modeling for TED6189, TED6190 and BEX6702 and population PK analysis for EFC6193; a: n=29.

Source: NDA submission Table 16 in Section 3.2.2 in Summary of Clinical Pharmacology

In order to further evaluate the inhibition potential of cabazitaxel on a sensitive CYP3A4 substrate *in vivo*, a computer program SimCYP[®] was applied to simulate the worst scenarios with midazolam as the CYP3A4 probe. The results suggested that the inhibition potential of cabazitaxel at 25 mg/m² on the sensitive CYP3A substrate midazolam is low. A post-marketing requirement for the effect of cabazitaxel on the pharmacokinetics of a sensitive CYP3A4 substrate is therefore not necessary.

In summary, the risk of interaction due to inhibition of CYP enzymes by cabazitaxel is low with CYP3A, CYP1A2, CYP2B6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 substrates in the clinical setting.

Table 12. K_i and I/K_i of cabazitaxel on CYPs

Isoenzyme	Cabazitaxel		
	Arithmetic Mean (Geometric Mean)	K _i	
	I (μmol/L) ^a	(μmol/L)	I/K _i
CYP2B6	0.299 (0.179)	130	0.0023 (0.0014)
CYP2C8	0.299 (0.179)	3.26	0.0917 (0.0549)
CYP2C9	0.299 (0.179)	79.1	0.0038 (0.0023)
CYP2D6	0.299 (0.179)	19.7	0.0152 (0.0091)
CYP3A (midazolam)	0.299 (0.179)	1.99	0.1503 (0.0899)
CYP3A (testosterone)	0.299 (0.179)	16.4	0.0182 (0.0109)

^a I = cabazitaxel arithmetic mean (geometric mean) C_{max} in patients with hormone refractory metastatic prostate cancers from EFC6193 [POH0124]

Source: NDA submission Section 3.4.1.1 in Summary of Clinical Pharmacology

***In vitro* induction**

Cabazitaxel did not induce CYP1A, CYP2C9, or CYP3A *in vitro*.

Study MIH0534 was conducted to evaluate the potential for cabazitaxel to induce CYP activity on primary cultures of human hepatocytes (N=3) at 0.1, 1, 5, and 10 μmol/L of cabazitaxel, using positive controls (omeprazole for CYP1A and rifampin for CYP2C9 and CYP3A). Cabazitaxel did not show potential to induce CYP1A, CYP2C9, or CYP3A isoenzymes at concentrations up to 10 μM. Based on the geometric mean of observed C_{max} values of 150 ng/mL [0.179 μmol/L]

after the first administration in patients with mHRPC [Trial EFC6193]), the potential of cabazitaxel to induce CYPs *in vivo* is low.

Table 13. The potential of cabazitaxel (XRP6258) to induce CYP1A1/2, CYP2C9 and CYP3A4/5 enzyme activities (expressed as % of control) in fresh human hepatocytes following 72 hours treatment with cabazitaxel (0 to 10 μ M) or reference inducers

Treatment	Concentration	Enzyme activity (% of control)					
		CYP1A1/2		CYP2C9		CYP3A4/5	
		Mean	SD	Mean	SD	Mean	SD
XRP6258	0 μ M	100	NA	100	NA	100	NA
	0.1 μ M	105	19	96	14	92	NA
	1 μ M	97	23	96	8	< 65	NA
	5 μ M	88	6	90	15	< 58	NA
	10 μ M	83	17	94	14	< 56	NA
DMSO	0.1 %	100	NA	100	NA	100	NA
Rifampicin	10 μ M	ND	ND	178	20	576	NA
Omeprazole	70 μ M	2479	2259	ND	ND	ND	ND

ND: not determined
NA: not applicable

Source: Study MIH0534 report

***In-vivo* induction**

No formal *in vivo* induction trials with strong CYP3A inducers have been conducted. Potent CYP3A inducers are expected to affect the PK of cabazitaxel *in vivo* as CYP3A contributes 80% to 90% to the cabazitaxel metabolic clearance.

Weak CYP3A inducers prednisone or its metabolite, prednisolone, did not decrease cabazitaxel exposure (AUC). The applicant evaluated the effect of concomitant use of prednisone and prednisolone on the pharmacokinetics of cabazitaxel in pivotal trial EFC6193. When given in combination with prednisone/prednisolone administered orally at 10-mg daily for three weeks (Cycle 2), the plasma CL of cabazitaxel was comparable to the one observed after the first administration of prednisone or prednisolone (Cycle 1) (28.9 versus 27.0 L/h/m²), where an induction effect of prednisone/prednisolone would not be present or be minimal.

In addition, the population PK analysis suggested that the clearance of cabazitaxel was not significantly different between PK with prednisone/prednisolone (N=50) and without prednisone/prednisolone (n=120), as shown in Figure 20.

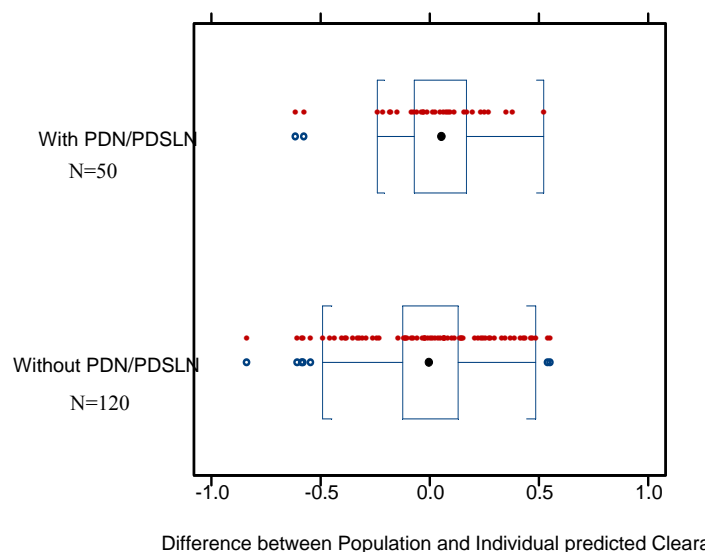


Figure 20: The effect of co-administration of prednisone/prednisolone on pharmacokinetics of cabazitaxel. Each red dot represents a patient.

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

Substrate

Cabazitaxel is a substrate for P-glycoprotein (P-gp).

In vitro experiments with Caco-2 cells demonstrated that cabazitaxel had a high intrinsic permeability (apparent permeability coefficient of 38×10^{-7} cm/s at pH = 6.5) and that it was a P-gp substrate (Study AIV0167) (Table 14).

Table 14. Bidirectional transport of cabazitaxel (XRP6258) using Caco-2 cells

XRP6258 (μ M)	Apical to basal		Basal to apical		P_{app} ratio $\frac{b \text{ to } a}{a \text{ to } b}$
	$P_{app} \times 10^{-7}$ cm.s ⁻¹ Mean \pm SD	Recovery (+/- cells) %	$P_{app} \times 10^{-7}$ cm.s ⁻¹ Mean \pm SD	Recovery (+/- cells) %	
1	10.2 \pm 1.1(*)	90 / 98	740 \pm 33	98 / 87	\approx 72.5
5	192 \pm 19	93 / 102	693 \pm 75	99 / 92	3.6
20	135 \pm 2.6	87 / 107	558 \pm 25	99 / 93	4.1
Digoxin (10 μ M)	1.6 \pm 0.12	97 / 97	149 \pm 5.9	100 / 97	93

(*): estimate: calculated with 2 kinetic points (due to BLQ values)

Source: Study AIV0167 report

Inhibitor

In vitro, cabazitaxel is a potent inhibitor of P-gp mediated transport.

Cabazitaxel inhibited P-gp dependent transport of 5 μM digoxin and 5 μM vinblastin with IC_{50} values of 10.5 and 16.9 μM , respectively. Under similar conditions, verapamil inhibits the P-gp dependent transport of digoxin and vinblastin with IC_{50} values of 10.8 and 26 μM , respectively. Based on the geometric means C_{max} observed in patients with hormone-refractory metastatic prostate cancer following a 1-hour infusion at 25 mg/m^2 (150 ng/mL [0.179 $\mu\text{mol}/\text{L}$]), the I/IC_{50} value was lower than 0.1, suggesting that inhibition potential of P-gp-mediated transport by cabazitaxel is low *in vivo* (Study AIV0167).

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

In vitro study suggested that the interaction potential of cabazitaxel on the transport of MRP1, MRP2, or BCRP is low in the clinical setting.

Using commercially available inside-out membrane vesicles containing hMRP1, hMRP2 and hBCRP and corresponding positive control substrates of [^3H]Leukotriene C4, [^3H]E17 β G, and methotrexate, *in vitro* study TRE0012 evaluated the potential of cabazitaxel as a substrate of the above drug transporters by comparing the uptake of cabazitaxel under ATP-stimulated membranes and by non-stimulated membranes. Results suggested cabazitaxel could not be identified as a substrate of MRP1, MRP2 or BCRP because the uptake of labeled cabazitaxel in stimulated and non-stimulated vesicles was indistinguishable.

Using commercially available inside-out membrane vesicles containing hMRP1, hMRP2 and hBCRP, the inhibitory potential of cabazitaxel was investigated by determine the IC_{50} value with radiolabeled probe substrates (MRP1: 0.05 μM [^3H]Leukotriene C4; MRP2: 50 μM [^3H]E17 β G; BCRP: 100 μM [^3H]Methotrexate) in the presence of corresponding control inhibitors of MK-571, MK-571, and Ko134. The K_{m} and V_{max} values were determined by plotting the net uptake (in $\text{pmol}/\text{min}/\text{mg}$) versus substrate concentration (in μM). Results were obtained using the Michaelis-Menten kinetics model ($\text{fit} = \text{V}_{\text{max}} / ([\text{S}] + \text{K}_{\text{m}})$). Results suggested that cabazitaxel was not an inhibitor of MRP1 and MRP2, but is a BCRP inhibitor with an IC_{50} value of 41.8 μM on the transport of methotrexate. Based on the geometric mean of C_{max} observed in patients with hormone-refractory metastatic prostate cancer following a 1-hour IV infusion at 25 mg/m^2 ($\text{I} = 0.179 \mu\text{M}$), the I/IC_{50} values was lower than 0.1, suggesting that drug interaction potential due to the inhibition of BCRP-mediated transport by cabazitaxel is low.

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?

The proposed dosing regimen of cabazitaxel requires the coadministration of prednisone and premedication with antihistamine (dexchlorpheniramine, or diphenhydramine), corticosteroid (dexamethasone or equivalent steroid), H2 antagonist (ranitidine or equivalent H2 antagonist), and antiemetic prophylaxis.

Weak CYP3A inducer prednisone or prednisolone did not show a decrease of cabazitaxel exposure (AUC). Dexamethasone inhibited the oxidative metabolism of cabazitaxel *in vitro* with an IC_{50} of 49.5 $\mu\text{mol}/\text{L}$, a concentration corresponding to 3.3 fold of the C_{max} reached for high doses *in vivo*. However, the effect of dexamethasone *in vivo* is difficult to predict, because its inhibition potency was likely to be countered by its known inductive effect on CYP isoenzymes.

In vitro, methylprednisolone, omeprazole, acetaminophen, and warfarin are weak inhibitors of cabazitaxel oxidation as these drugs produced 20% to 35% inhibition at concentrations 50-, 100-, 10-, and 8.6-fold of their C_{max} *in vivo*, respectively. Furthermore, morphine, dexchlorpheniramine, dextropropoxyphen, granisetron, ondansetron, or ranitidine were not CYP inhibitors. Since these drugs demonstrated weak or no inhibition of cabazitaxel oxidation *in vitro*, none are expected to alter the oxidative metabolism of cabazitaxel *in vivo*.

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

No formal drug-drug interaction studies have been conducted in humans to evaluate the effect of co-administration CYP3A4 inhibitors, inducers on the PK of cabazitaxel. PMRs will be required to conduct the drug-drug interaction studies for cabazitaxel with a strong CYP3A inhibitor (e.g. ketoconazole), a strong CYP3A inducer (e.g. rifampin).

Also see section 2.4.2.3.

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 to this intravenous administration formulation.

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

The drug product cabazitaxel is available as a non-aqueous concentrate for solution for infusion at 60 mg/1.5 mL. It is supplied with a solvent vial containing (b) (4) of a 13 % w/w aqueous solution of alcohol (USP), for preparation of an intermediate premix at 10 mg/mL, prior to dilution with 0.9 % sodium chloride solution or 5% dextrose solution an infusion bag. The concentration of cabazitaxel in the final infusion solution should be between 0.1 mg/mL and 0.26 mg/mL.

The same concentrate for solution for infusion formulation at 40 mg/mL of cabazitaxel was used throughout the development.

- The dosage strength of 80 mg/2 mL was used during the clinical studies,
- A new presentation at 60 mg/1.5 mL was developed in the late phase of development to better adjust to the clinical dose of 25 mg/m² and will be the commercial presentation.

The commercial formulation is thus identical to the formulation used in clinical studies. The only difference between the two presentations is the fill volume of the vials. The composition of the to-be-marketed cabazitaxel concentrate for solution for injection, 60 mg/1.5 mL is shown in Table 15.

Table 15. Composition of to-be-marketed cabazitaxel concentrate for solution for injection, 60 mg/1.5 mL

Components	Composition Per Unit	Function	Reference to standards ^(f)
Cabazitaxel acetone solvate ^(a)	60 mg	Active ingredient	In-house
Polysorbate 80 (b) (4)	1.56 g	(b) (4)	In-house
			(b) (4) based on Ph. Eur., USP-NF, JP
			USP-NF, Ph. Eur., JP
			USP-NF, Ph. Eur., JP
(a) : expressed as solvent-free and anhydrous drug substance			
			(b) (4)
			(b) (4)
			(b) (4)
(f) : when it is referred to a Pharmacopoeia, this means that the current edition of this Pharmacopoeia is applied.			

Source: NDA submission Section 3.2.P.1

2.5.3 What moieties should be assessed in bioequivalence studies?

Not applicable as cabazitaxel is administered intravenously.

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?

Cabazitaxel is administered intravenously. An evaluation of food effect is not needed.

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 as cabazitaxel is administered intravenously.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Cabazitaxel was the primary active moiety assessed in plasma of patients in the clinical studies. Plasma was chosen as the matrix for quantification of cabazitaxel concentrations since cabazitaxel was equally distributed between blood and plasma (Section 2.2.5.4). An LC/MS/MS method was developed to assay RPR123142, RPR112698, and docetaxel, in addition to cabazitaxel in the later clinical trials. Though RPR123142 was measured in the pivotal trial EFC6193, the low exposure of RPR123142, RPR112698, and docetaxel confirmed by the mass balance trial BEX6702 suggested that these active metabolites are not relevant.

During the drug development of cabazitaxel, five similar LC/MS/MS methods were validated for the assay of cabazitaxel or its active metabolites (RPR123142, RRR112698, and docetaxel) in the clinical efficacy/safety trials, in the excretion and metabolism trial, in the *in vitro* studies, as well as in the long-term stability studies in human matrices. These five methods are summarized in Table 16.

Table 16. Summary of bioanalytical studies associated with clinical pharmacology studies and efficacy/safety clinical studies

Methods Location	Analyte	Type of method	Matrix (anticoagulant)	Calibration Range (ng/mL)	LOQ (ng/mL)	Accuracy (%) ^a		Precision (%) ^a		Clinical studies
						Within run	Between run	Within run	Between run	
[DMPK/US-98-186] 5.3.1.4	Cabazitaxel	LC/MS/MS	Plasma (sodium heparinate)	5.00 – 500	5.00	-6.01% to 9.79%	-8.37% to 14.07%	1.46% to 14.32%	5.97% to 7.29%	TED6188
[DMPK/FR 2296] 5.3.1.4	Cabazitaxel	LC/MS/MS	Plasma (citrate and lithium heparinate)	1.00 – 500	1.00	-5.5% to 10%	-4.5% to 6.2%	2.6% to 8.4%	6.5% to 7.2%	TED6188 TED6189 TED6190 ARD6191
[DMPK/FR 2438] 5.3.1.4	Docetaxel	LC/MS/MS	Plasma (lithium heparinate)	1.00 – 500	1.00	-8.7% to 3.2%	-4.0% to 3.5%	3.3% to 8.6%	5.6% to 8.8%	TED6189 TED6190
	RPR112698					-22% to 0.25%	-7.1% to 1.5%	2.2% to 13%	4.7% to 13%	
	RPR123142					-14% to 0.75%	-3.8% to 3.2%	3.0 to 6.5%	6.6% to 10%	
[DOH0586] 5.3.1.4	Cabazitaxel	LC/MS/MS	Plasma (lithium heparinate)	1.00 - 500	1.00	-0.33 % to 4.37%		2.88% to 7.54%		BEX6702 TCD6945 EFC6193
	RPR123142			0.500 – 250	0.500	0.03% to 4.59%		4.18% to 10.5%		
[DMPK/FRA/2002-0237] 5.3.1.4	Cabazitaxel	LC/MS/MS	Urine	10.0 – 1000	10.0	-3.8% to 10%	5.0 to 16%	2.6% to 4.9%	6.5% to 9.7%	TED6190
	Docetaxel					-14 to -12%	-3.9% to 6.8%	5.1% to 17%	10% to 16%	
	RPR112698					-1.3% to 3.8%	3.6% to 14%	4.1% to 16%	6.8% to 15%	
	RPR123142					1.5 to 10%	3.0% to 14%	1.6% to 7.3%	7.7% to 15%	

^a total precision or total accuracy (combined within- and between- run data) for DOH0586

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were selected for routine analysis. Cabazitaxel was the primary compound assessed in plasma of patients in the clinical studies.

In plasma, cabazitaxel was the main circulating compound and accounted for 70%, on average, of total radioactivity. Seven minor metabolites (RPR123142, docetaxel, RPR111026, RPR111059, M09b, RPR130523, RPR112698) were quantified in human plasma and each represented <4% of the radioactivity AUC. Therefore, the pharmacologically active metabolites (docetaxel, RPR123142 and RPR112698) were not systematically monitored in clinical studies.

See section 2.2.5.5 and 2.2.5.6.

2.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total drug was measured for cabazitaxel with a range of 0 to 24,500 ng/mL. The total drug instead of free drug concentration measurement appears acceptable as cabazitaxel was highly bound to human plasma proteins *in vitro* (with a mean of 89.2% in study PKFAC 9902 and 91.9% in study LPR0995) in a concentration-independent manner up to 50, 000 ng/mL.

2.6.4 What bioanalytical methods are used to assess concentrations?

Plasma and urine samples were assayed for cabazitaxel primarily by two similar validated LC/MS/MS methods: DMPK/FR 2296 for studies TED 6188, TED 6189, TED 6190 and ARD6191; DOH0586 for studies BEX6702, TCD6945, and EFC6193.

DMPK/FR 2296: This LC/MS/MS method measures cabazitaxel concentrations in human plasma following an automated (b) (4) using RPR109881 as internal standard. Separation was obtained by reversed-phase HPLC using a BDS Hypersil C-18 column, and a mobile phase consisting of 0.1% formic acid in water and acetonitrile in the proportion 40/60 (v/v). Quantification was achieved with the API3000 instrument using MS/MS monitoring m/z of parent ions at 836.4 and 832.5 and their corresponding daughter ions at 555.3 and 491.2 for cabazitaxel and internal standard (RPR109881), respectively. Calibration curves, over the range of 1.00 to 500 ng/mL, were fitted to a linear model using a weighting of 1/x.

DOH0586: This LC/MS/MS method was validated for the simultaneous quantification of cabazitaxel and RPR123142 (10-O-demethyl-cabazitaxel) in heparinized human plasma,

following (b) (4) using D6-cabazitaxel (2H6-cabazitaxel) as internal standard. Chromatographic separation was achieved using a Hypersil BDS C18 column with a gradient mobile phase of 0.1% formic acid in acetonitrile and 0.1% aqueous formic acid at 0.250 mL/min. An API5000 triple quadrupole mass spectrometer was operated under the MRM mode. Parent ions at 836.5, 822.4, and 842.4 m/z, and their corresponding daughter ions at 555.1, 541.1, and 561.4 m/z were monitored for cabazitaxel, RPR123142, and D6-cabazitaxel, respectively. Calibration curves for cabazitaxel, over the range of 1.00 to 500 ng/mL, were fitted to a linear model using a weighting of $1/x^2$. Calibration curves for RPR123142, over the range of 0.500 to 250 ng/mL, were fitted to a linear model using a weighting of $1/x^2$.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The method demonstrates suitable accuracy, precision, and linearity (1.00 ng/mL to 500 ng/mL, up to 2000 ng/mL with 1/10 dilution) for the assessment of cabazitaxel from PK studies in human. This dynamic range of the standard curve adequately meet the needs for clinical studies.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

The lower limits of quantification (LLOQ) and the upper limits of quantification (ULOQ) for cabazitaxel were 1 ng/mL and 500 ng/mL, respectively.

2.6.4.3 What are the accuracy, precision and selectivity at these limits?

The specificity, recovery, linearity, quantification limit, precision, accuracy of the assay of cabazitaxel were established during the validation period in study DMPK/FR 2296 and DOH0586 using the quality control samples at 4 concentrations (1.00 [LOQ], 1.50, 40.0, and 400 ng/mL) over a 3-day period for cabazitaxel:

- Within- and between-run accuracy ranged from -3.3% to 10%
- Within- and between-run precision ranged from 2.6% to 8.4%
- Average recovery ranged from 91.0% (400 ng/mL) to 111% (1.50 ng/mL). The average recovery of internal standard (RPR109881) from plasma was 103%.
- Dilution studies (1/4, 1/10, and 1/100 dilutions) demonstrated that plasma concentrations of cabazitaxel up to 2000 ng/mL could be reliably analyzed within the calibration range.
- No effect of the type of anticoagulant (citrate or lithium heparin) was observed on accuracy and precision of the method.
- No interference from endogenous components was detected at the retention time of cabazitaxel or internal standard in extracts of individual human plasma samples.

2.6.4.4 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

Cabazitaxel was stable:

- in plasma at 37°C for at least 24 hours
- in whole blood at room temperature for at least 24 hours
- in plasma at -20°C for at least 12 months
- in plasma at 4°C for 12 hours

- in plasma after preparation and before extraction at room temperature for 24 hours
- in plasma after preparation and extraction at 15°C in the autosampler for 12 hours
- in plasma following 5 freeze-thaw cycles
- in acetonitrile stock solutions for at least 6 months at +4°C
- after extraction for at least 72 hours at $8 \pm 2^\circ\text{C}$

2.6.4.5 What is the QC sample plan?

Quality controls (QC) were prepared at 1.5 ng/mL, 40 ng/mL, 400 ng/mL for each run with duplicate samples. The analysis run was accepted when 75% of all standards and QC were within 20% of the nominal concentrations at the limit of quantitation and quality controls, and within 15% of the nominal concentration over the rest of standards, provided that at least 2/3 of the standards and 2/3 of the controls and at least one control at each concentration level was acceptable and that no analytically significant bias was observed. Dilution controls were assayed in duplicate and evaluated separately from the other controls. The dilution controls were accepted in duplicate if at least 1 of 2 of each dilution control was within 15% of the nominal value.

4 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRIC REVIEW

Application Number	201023
Submission Date	March 31, 2010
Compound (Dosing Regimen)	Cabazitaxel (25 mg/m ² IV infusion for 1-h every 3 weeks) in combination with oral prednisone 100 mg qd
Clinical Division	DDOP
Primary PM Reviewer	Nitin Mehrotra, Ph.D.
Secondary PM Reviewer PM Team Leader	Christine Garnett, Pharm.D.

Table of Contents

1	Summary of Findings	53
1.1	Key Review Questions.....	53
1.2	Recommendations.....	60
1.3	Label Statements.....	61
2	Pertinent Regulatory Background	62
3	Results of Sponsor's Analysis	63
3.1	Population PK Analysis	63
3.2	Exposure-Response Analysis.....	68
4	Reviewer's Analysis	71
4.1	Exposure-Response Analysis for Effectiveness.....	71
4.2	Exposure-Response Analysis for Safety	73

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The following key questions were addressed in this pharmacometric review.

1.1.1 Is there evidence of an exposure-response relationship for efficacy?

There was insufficient exposure data collected in the pivotal trial to support evidence of exposure-response for effectiveness endpoint of overall survival and time to tumor progression.

- Only 67 patients (18% of the total enrolled in the cabazitaxel arm) were included in the exposure-efficacy analysis.
- Data from only one dose level (25 mg/m²) was available so the range of exposures might not be wide enough to explore exposure-efficacy relationship.

Exploratory exposure-efficacy analysis was conducted using data from the pivotal trial (EFC6193) following 25 mg/m² dose of cabazitaxel. Primary efficacy endpoint (overall survival) and time to tumor progression were the response variables utilized in the analysis. Due to few patients with pharmacokinetic data from only one dose level (N=67), exposure data were divided by median into two groups: AUC <907 ng h/ml, N=35 and AUC>907, N=32). **Figure 1** (left panel) suggests that patients with higher exposures had lower overall survival. This relationship is, however, confounded by four neutropenia related deaths in the Cabazitaxel's arm (CBZ/PRED) within 30 days of dosing. When these four patients (three in higher and one in lower exposure groups) were removed from the dataset, the separation between the two survival curves disappeared (**Figure 1**, right panel).

The same analysis was conducted for time to tumor progression which showed numerically higher (not statistically significant) median time to progression time for the higher exposure group suggesting that progression of the disease is slower in patients with higher exposures (**Figure 2**). However, it is not clear why the separation between the two curves does not happen until 5 months.

Figure 1: Exposure-response relationship of cabazitaxel for overall survival (left panel) in comparison with the same relationship excluding four patients with neutropenia related deaths on CBZ/PRED arm from the dataset (Right panel). Small black, green and red vertical ticks on the plots are censored observations. MTX/PRED (Mitoxantrone/Prednisone) is the comparator arm.

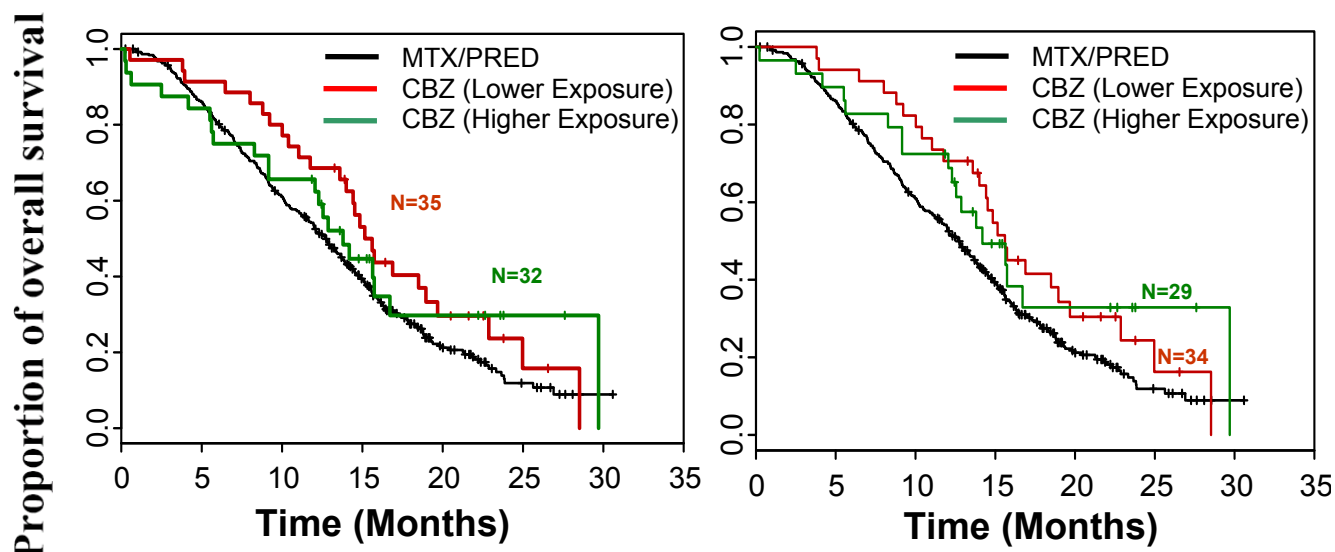
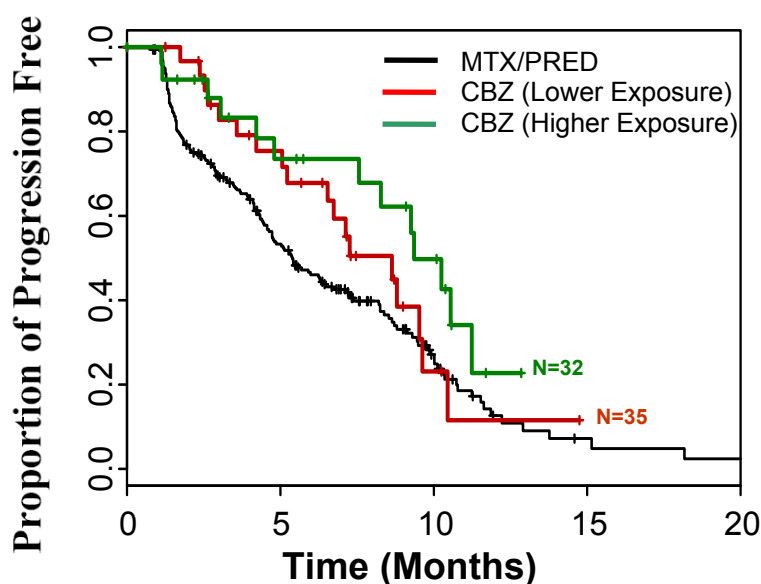


Figure 2: Exposure-response relationship of cabazitaxel for time to tumor progression. Small black, green and red vertical ticks on the plots are censored observation. MTX/PRED (Mitoxantrone/Prednisone) is the comparator arm.

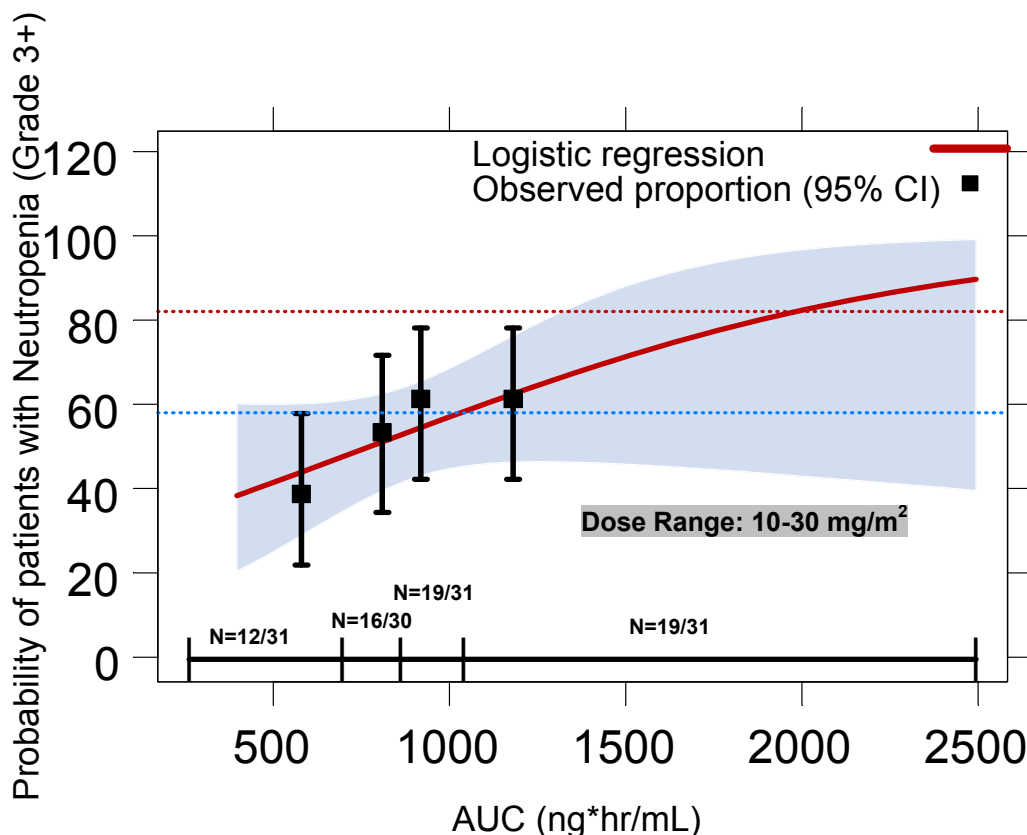


1.1.2 Is there an evidence of exposure-response for safety?

Yes, there is evidence of exposure-response relationship for \geq grade 3 neutropenia in patients with advanced solid tumors. Univariate logistic regression models were used to explore the relationship between exposure (AUC) and \geq grade 3 neutropenia at the end of first cycle. Safety data from only cycle 1 was taken to avoid the confounding effect of prophylactic G-CSF which was allowed later in the trial to treat \geq grade 3 neutropenia. Data from two phase 1 studies (TED6188 and TED6190) and the pivotal trial (EFC6193, N=67 with the PK data) were combined to explore the exposure-safety analysis. AUC was found to be a predictor of \geq grade 3 neutropenia with a p value <0.05 .

Because we had only a subset of patients (18%) with PK data from the pivotal trial and also there were few adverse reactions for \geq grade 3 diarrhea, febrile neutropenia and renal toxicity, these adverse reactions were not explored for the exposure-safety relationship.

Figure 3: The probability of patients with \geq grade 3 neutropenia-AUC relationship. Solid black symbols represent the observed proportion of patients experiencing \geq grade 3 neutropenia in each AUC quartile. The vertical black bars represent the 95% confidence interval. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval of the prediction. The exposure range in each AUC quartile is denoted by the horizontal black line along with the number of subjects with adverse reactions/total number of subjects in each quartile. The horizontal dotted red and blue line represents the % of \geq grade 3 neutropenic events observed in the CBZ/PRED and MTX/PRED arm of the pivotal trial (EFC 6193), respectively.

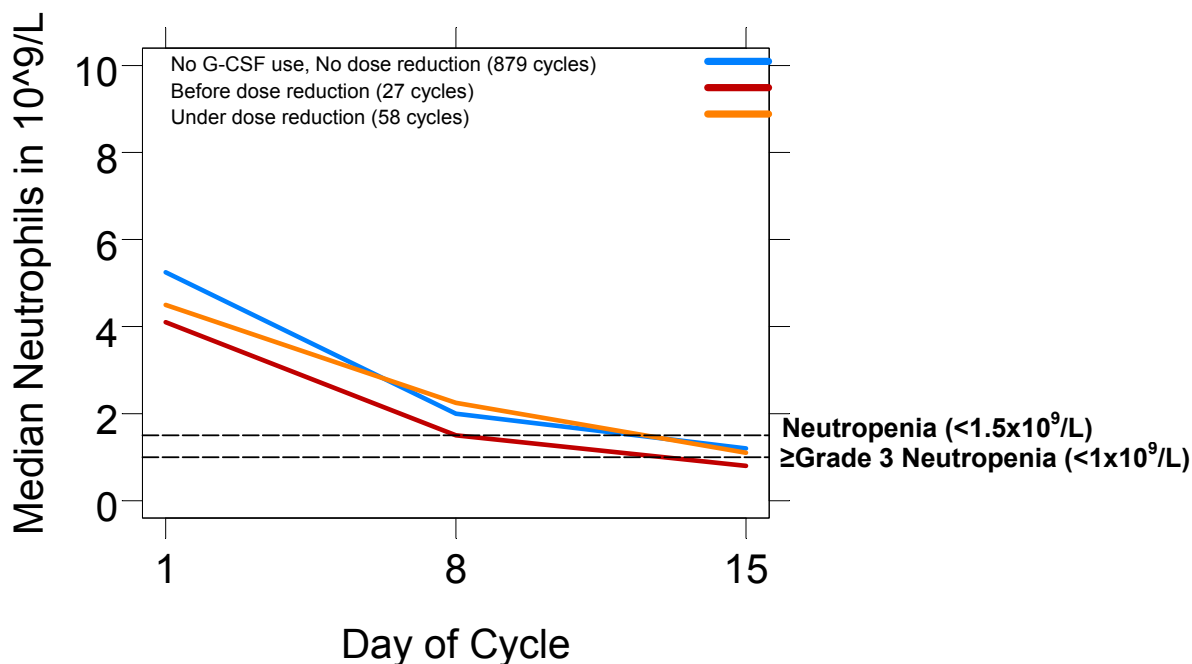


1.1.3 Is the proposed dose reduction from 25 to 20 mg/m² adequate to reduce the risk of neutropenia (Grade ≥ 3) based on exposure-safety relationship?

Dose reduction from 25 to 20 mg/m² will not cause significant reduction in ≥grade 3 neutropenic events because slope of the exposure-safety relationship in patients with advanced solid tumors was shallow (**Table 8**). The logistic regression model shows that decreasing the dose from 25 to 20 mg/m² would reduce the probability of patients experiencing neutropenia ≥grade 3 from 54% to 49%. It is important to note that the intersubject variability in clearance (39%) is larger than the proposed dose reduction from 25-20 mg/m² (20%). Moreover, since the dose reduction only causes decrease in risk of ≥grade 3 neutropenia by 5%, it is not justified from an exposure-safety relationship.

The sponsor provided data for the neutrophil count at different days within a cycle for patients in the cabazitaxel arm who never received G-CSF in the pivotal trial (EFC6193). Median neutrophil count in the patients who never received G-CSF decreased from Day 1 to Day 15 within the cycle (solid blue line in **Figure 4**). Solid red line and orange line represents the neutrophil counts in a subset of patients before and under dose reduction, respectively. The data suggest that dose reduction alone only provides modest benefit and neutrophil count still remain below the baseline and near neutropenic levels. This observation is in accordance with modest reduction in ≥grade 3 neutropenia with dose reduction from 25 to 20 mg/m².

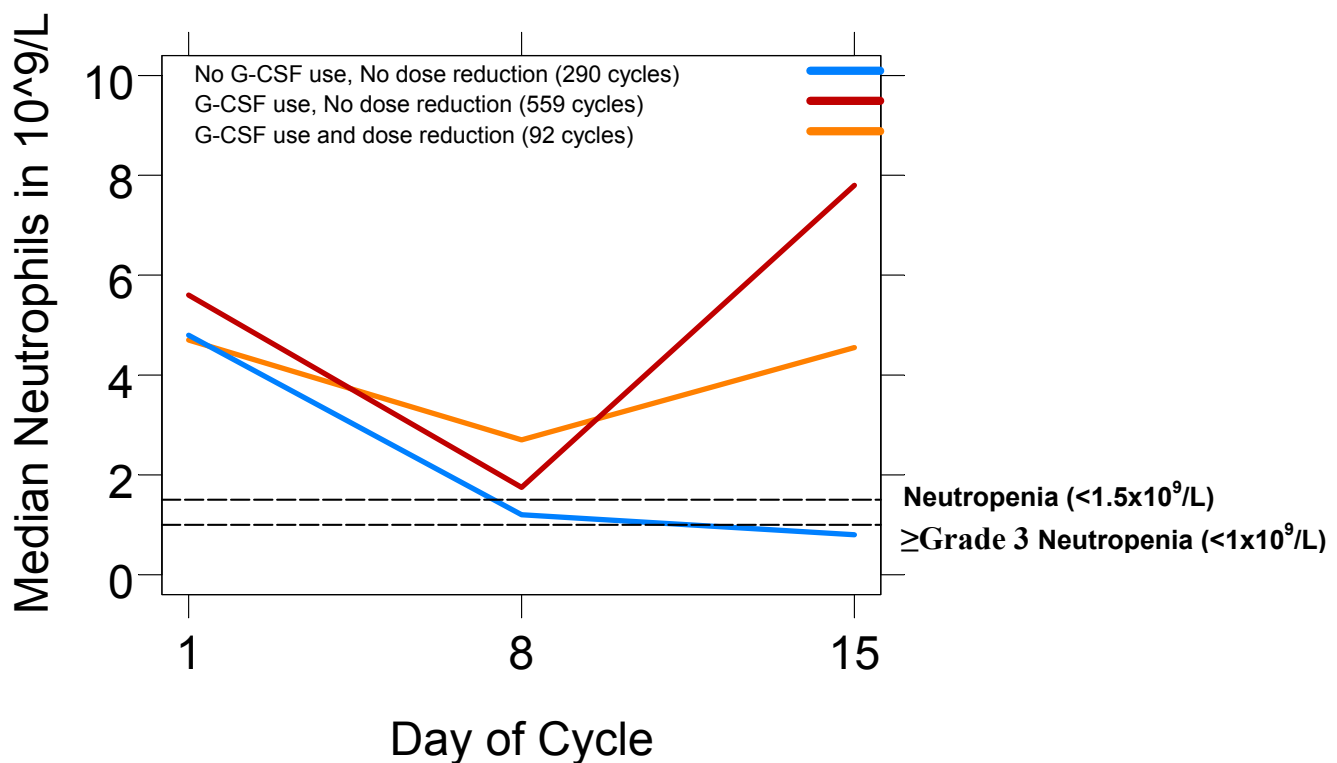
Figure 4: The median time course of neutrophils among patients in cabazitaxel arm who never received G-CSF during the pivotal trial (EFC6193). The two black dashed lines represents cutoff for neutropenia ($<1.5 \times 10^9/L$) and ≥grade 3 neutropenia ($<1.0 \times 10^9/L$).



Note: Reproduced from the figure submitted by the sponsor

The clinical management of neutropenia proposed by the sponsor involves the use of appropriate medications (including G-CSF) to treat neutropenia followed by dose-delay or reduction if the patient doesn't respond. The sponsor also provided data for the neutrophil count at different days within a cycle for the patients in the cabazitaxel arm who did receive G-CSF at some point in the pivotal trial. **Figure 5** shows that the use of G-CSF was able to bring the neutrophil counts back to baseline and the median neutrophil count at Day 8 was above $1.0 \times 10^9/\text{L}$. Use of combination of G-CSF and dose reduction does seem to keep the median neutrophil levels at Day 8 above when compared to patients with G-CSF alone. However, the median neutrophil count at Day 15 (orange line) was lower than neutrophil count for patients on G-CSF alone (red line). This analysis has some limitations as the patients in these two groups (red and orange line) may not be the same and only 92 cycles contribute to the data for the G-CSF use with dose reduction group (orange line).

Figure 5: The median time course of neutrophils among patients who received G-CSF at some point during the pivotal trial (EFC6193). The two black dashed lines represents cutoff for neutropenia ($<1.5 \times 10^9/\text{L}$) and \geq grade 3 neutropenia ($<1.0 \times 10^9/\text{L}$).



Note: Reproduced from the figure submitted by the sponsor

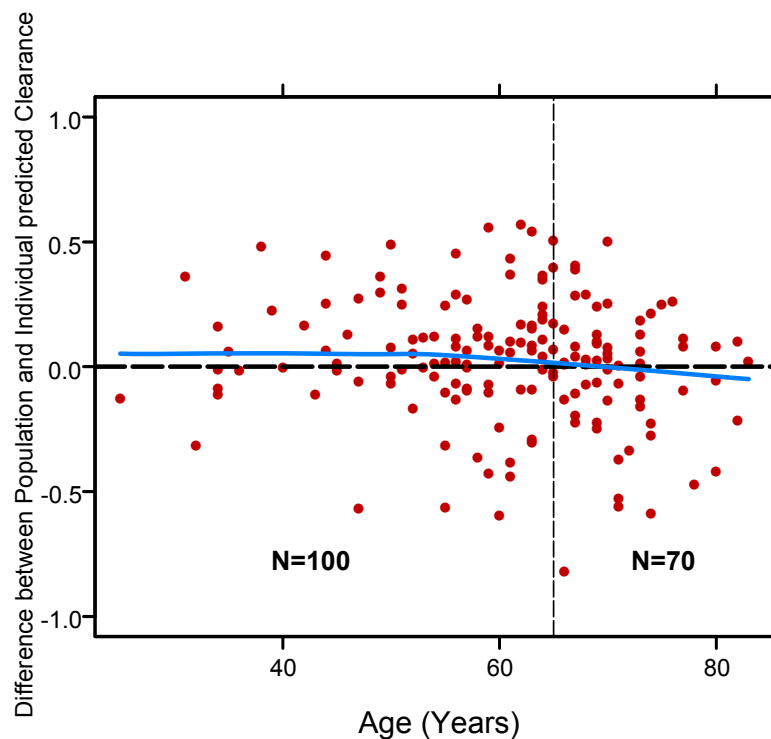
It is important to note that the sponsor did have experience with this dose reduction scheme in the trial with dose reduced in 9.7% of the cycles and in 14% (N=54) of patients in the CBZ/PRED arm, the trial showed an overall survival benefit and most important, this toxicity was manageable with G-CSF use. Considering these factors, the proposed dose modification scheme (use of G-CSF or dose reduction in combination with G-CSF) seems to be reasonable from a clinical management perspective. Patients who develop \geq grade 3 neutropenia despite appropriate medication including G-CSF, and have to be continued on CBZ/PRED therapy, dose reduction in combination with G-CSF use is a reasonable option.

1.1.4 Does age or renal function effect cabazitaxel pharmacokinetics?

No, age and renal function does not affect pharmacokinetics of cabazitaxel.

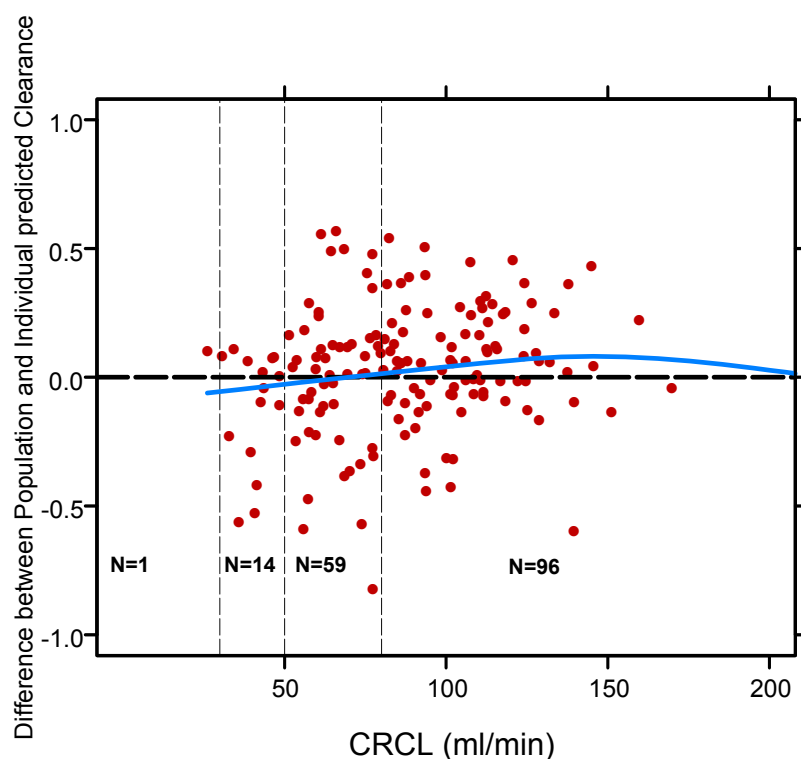
In general, the adverse reactions were higher in elderly patients (≥ 65 years, N=70) compared to patients less than 65 years of age (N=100). An attempt was made to see if this could be explained by higher exposures in elderly subjects. **Figure 6** shows that between subject variability in clearance cannot be explained by age. Non compartmental analysis of PK data also showed lack of age effect on cabazitaxel exposure (See Dr. Pengfei Song's Clinical Pharmacology Review for more details).

Figure 6: No effect of age on clearance of cabazitaxel as depicted by Age-Eta (CI) relationship. Each red dot represents a patient. The vertical line represents age=65 to better differentiate patients below and above 65 years. Solid blue line on the plot is the loess regression line.



The sponsor did not conduct a dedicated renal impairment study. Based on a population pharmacokinetic analysis, there is no effect of mild (50-80 ml/min, N=59) or moderate (30-50 ml/min, N=14) renal impairment on the clearance of cabazitaxel (**Figure 7**). It is expected as cabazitaxel is primarily eliminated via hepatic route with only 2.7% of the unchanged drug eliminated in urine.

Figure 7: No effect of renal function on clearance of cabazitaxel as depicted by CrCL-Eta (CI) relationship. Each red dot represents a patient. Three vertical lines represents cut off for mild, moderate and severe renal impairment. Solid blue line on the plot is the loess regression line.

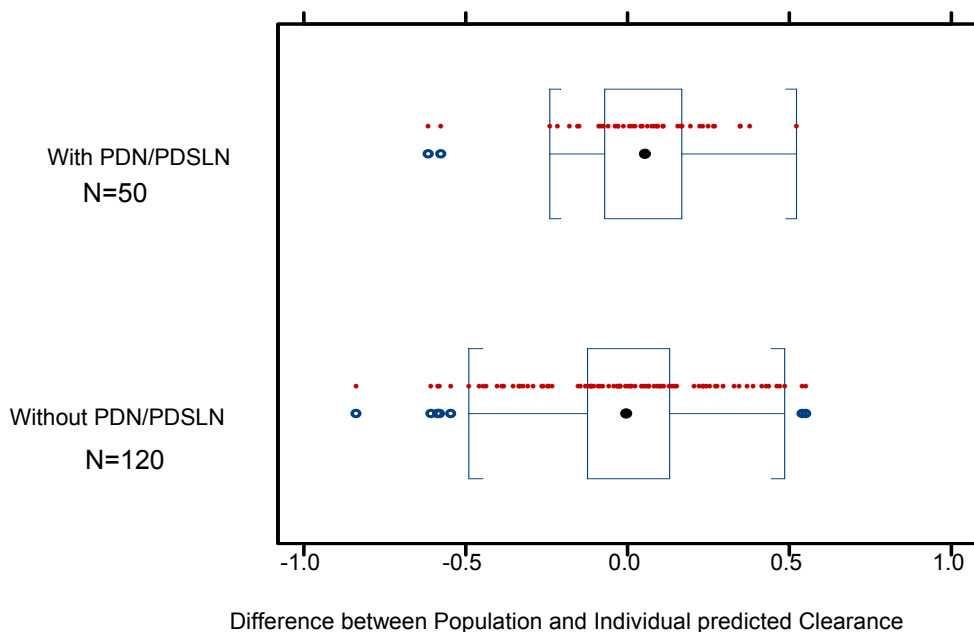


1.1.5 Is there an effect of co-administration of prednisone or prednisolone on pharmacokinetics of cabazitaxel?

No, co-administration of prednisone or prednisolone (weak CYP3A inducer) does not affect clearance of cabazitaxel (**Figure 8**). The sponsor did not conduct a dedicated drug-drug interaction study to determine the effect of prednisone/prednisolone on PK of cabazitaxel. Based on population PK analysis co-administration of prednisone or prednisolone did not influence clearance of cabazitaxel. The population PK dataset

contained patients from the pivotal trial who were on the background prednisone or prednisolone therapy (10 mg once daily) along with phase 1 patients who did not take prednisone/prednisolone.

Figure 8: No effect of co-administration of prednisone/prednisolone on pharmacokinetics of cabazitaxel. Each red dot represents a patient.



1.2 Recommendations

Division of Pharmacometrics finds the NDA acceptable from a clinical pharmacology perspective and has the following recommendations for the sponsor.

- The sponsor is encouraged to collect sparse pharmacokinetic data (at least for one cycle) from all subjects in their future trials. The purpose is to develop exposure response relationship for efficacy and safety endpoints to support proposed dosing recommendations.
- The sponsor should update their safety database with additional data from the ongoing and planned future trials to justify their dose reduction strategy (25-20 mg/m²) using exposure-safety analysis.

2 Pertinent Regulatory Background

Cabazitaxel is a new molecular entity and the proposed indication is the treatment of patients with hormone refractory prostate cancer (HRPC) previously treated with docetaxel based treatment. Prior to the approval of Taxotere[®] (Docetaxel) in 2004, cytotoxic chemotherapy was not routinely administered to patients with HRPC. Docetaxel in combination with prednisone was approved in 2004 for the treatment of androgen independent metastatic prostate cancer patients and demonstrated a 2.4 month survival benefit compared to mitoxantrone plus prednisone, prolonging survival from 16.5 to 18.9 months.

Sponsor in the current NDA submission conducted two phase 1 dose ranging studies to come up with 25 mg/m² once every three week dosing regimen of cabazitaxel for the pivotal trial. FDA reviewed the Phase 3 protocol and concurred on the special protocol assessment. Fast track designation was granted to this NDA in November 2009 for the proposed indication. Sponsor conducted a multicenter, open label phase 3 trial (EFC6193) of cabazitaxel at 25 mg/m² in combination of prednisone every three weeks compared to mitoxantrone (with prednisone) every three weeks for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel based dosing regimen. The proposed cabazitaxel dosing regimen in combination with 10 mg

oral prednisone daily for the duration of the treatment demonstrated that the primary endpoint of overall survival was statistically and clinically significantly longer compared to the active control regimen of mitoxantrone 12 mg/m² IV every 3 weeks in combination with 10 mg oral prednisone in the studied population. The median overall survival in the cabazitaxel arm was 15.1 months compared to 12.7 months in the mitoxantrone arm. This was also supported by statistically significant improvements observed for response rate for PSA and response rates by RECIST (Response Evaluation Criteria In Solid Tumors), as well as prolongation of time to tumor progression and time to PSA progression. The most frequent adverse reactions observed in the cabazitaxel group were neutropenia and its complications (febrile neutropenia and infections), asthenic conditions (asthenia and fatigue), and gastrointestinal toxicity (diarrhea, nausea, and vomiting).

3 Results of Sponsor's Analysis

3.1 Population PK Analysis

Sponsor performed population PK modeling utilizing data from five studies which evaluated cabazitaxel in advanced cancer. Primary objective of the population PK analysis was to investigate the influence of key demographic parameters (e.g. body surface area, age, etc.), renal function (measured by creatinine clearance) and hepatic function (measured by bilirubin, ALT, AST, and ALK), disease status (tumor type) and concomitant medication (CYP inducers, e.g. prednisone) on pharmacokinetics of cabazitaxel.

3.1.1 Methods

PK Data from a total of 170 patients (2322 observations) was available from three Phase 1, one phase 2 and one Phase 3 study. Description of the studies with other relevant information is provided in **Table 1**. Sponsor first utilized studies with rich PK sampling (TED 6188 and TED 6190) to develop the structural model. After structural model was identified all the studies were pooled for further analysis.

Table 1: Study characteristics.

Study No.	Sample size	Nominal doses studied (mg/m ²)	Indication	Sample collection
TED 6188	21	10, 15, 20, 25, 30 mg/m ² q 3wk	Advanced Solid Tumors	Rich
TED 6189	13	10 and 12 mg/m ² weekly	Advanced Solid Tumors	Rich
TED6190	35	10, 15, 20, 25, 30 mg/m ² q 3wk	Advanced Solid Tumors	Rich
ARD6191	34	10, 20, 25 mg/m ² as 1-h infusion q3w	Advanced Breast Cancer	Sparse
EFC6193	67	25 mg/m ² q 3wk	HRPC prostate cancer	Sparse

The population PK analysis was performed using a specialized PopPK software (NONMEM VI level 1.2) running on a Linux cluster. All runs were performed using first order conditional estimate (FOCE) method with the interaction option.

The relationship between the individual estimates and the covariates was then investigated. Demographic characteristics such as age, sex, race, weight, body surface area, liver function (bilirubin, ALT, AST, and ALK), renal function (creatinine clearance, CLCR), disease status (tumor type) and CYP inducers (i.e. prednisolone) were tested as potential model covariates. These covariates were added individually (forward selection) to the model and tested for statistical significance using a p-value of 0.05. Only covariates providing a significant change in the objective function (OFV) were included in the Full model and then tested in a backward deletion step using a p-value of 0.001. The population parameters were re-estimated considering the relationship with the covariates. Model verification was performed using goodness-of-fit plots and estimating several quality criteria such as bias, precision or Average Fold Error. The robustness of the final model and the accuracy of parameters estimates (computation of standard error of estimates) were assessed using a bootstrap method and visual predictive check.

3.1.2 Conclusions

- The PK of cabazitaxel was best described by a three compartment model.
- BSA and tumor type were identified as covariates on central clearance. For tumor type effect (i.e. CL 60% lower in breast cancer patients), it should be noted that gender effect could not be identified and that a majority (34 of 37) of breast cancer patients came from study ARD6191 while only about 50% of females (34 of 60) came from this same study. Given therefore that breast cancer type is highly

confounded with study, the clinical relevance of this finding is difficult to interpret from the data set available for this analysis and should be treated with caution.

- There was no effect of age, gender, renal function, concomitant administration of prednisone/prednisolone on pharmacokinetics of cabazitaxel.

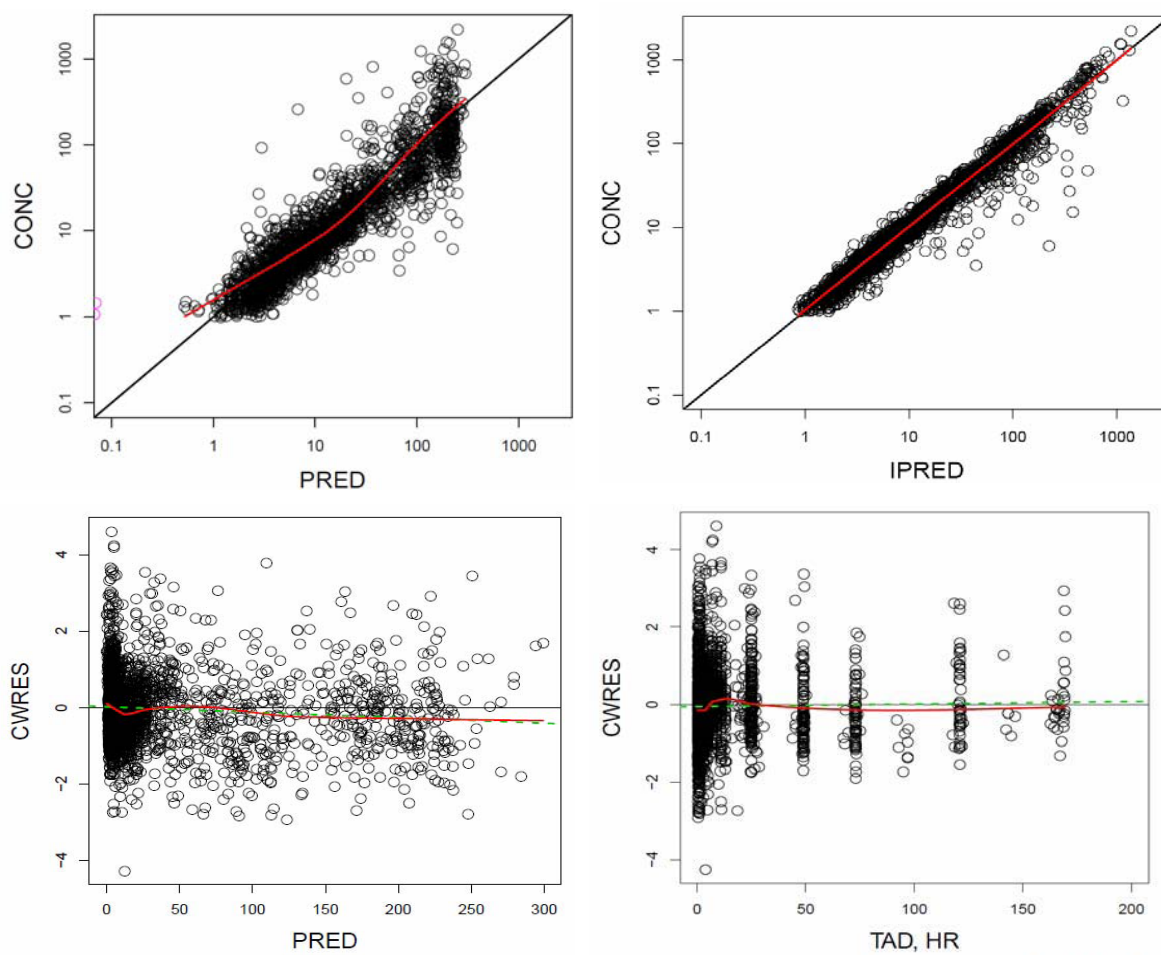
Parameter estimates for fixed effect and random effects with standard errors are presented in **Table 2**. Basic goodness of fit plots from the sponsor's final model and visual predictive check are presented in **Figure 9** and **Figure 10**.

Table 2: Summary of NONMEM/Population PK Parameters for cabazitaxel in the total dataset

Parameter	Estimate	RSE	95%CI Lower	95%CI Upper	Shrinkage (%)
θ_1 in $[CL = \theta_1 \cdot BSA/1.84 \cdot (1 - \theta_7 \cdot TT1)]$, L/h	48.5	5.48%	43.2	53.8	NA
θ_2 (V1, L)	26.0	12.5%	19.5	32.5	NA
θ_3 (K12, h ⁻¹)	2.48	9.60%	2.00	2.95	NA
θ_4 (K21, h ⁻¹)	0.604	6.67%	0.524	0.685	NA
θ_5 (K13, h ⁻¹)	4.84	10.4%	3.83	5.85	NA
θ_6 (K31, h ⁻¹)	0.0266	5.94%	0.0234	0.0297	NA
θ_7 in $[CL = \theta_1 \cdot BSA/1.84 \cdot (1 - \theta_7 \cdot TT1)]$	0.543	30.0%	0.217	0.869	NA
Interindividual variability (CV%)					
CL	38.8%	32.6%	22.8%	49.8%	30.4%
V1	93.4%	16.9%	76.0%	108.0%	14.0%
K12	84.0%	31.3%	51.4%	107.0%	14.1%
K13	64.2%	22.0%	48.0%	77.0%	12.8%
K31	28.2%	28.7%	18.4%	35.4%	35.4%
Interoccasion variability (CV%)					
CL	19.4%	41.0%	8.22%	26.2%	58.0%
V1	45.3%	33.2%	26.2%	58.4%	42.9%
Residual variability					
σ (proportional)	27.8%	6.71%	25.9%	29.6%	76.1%

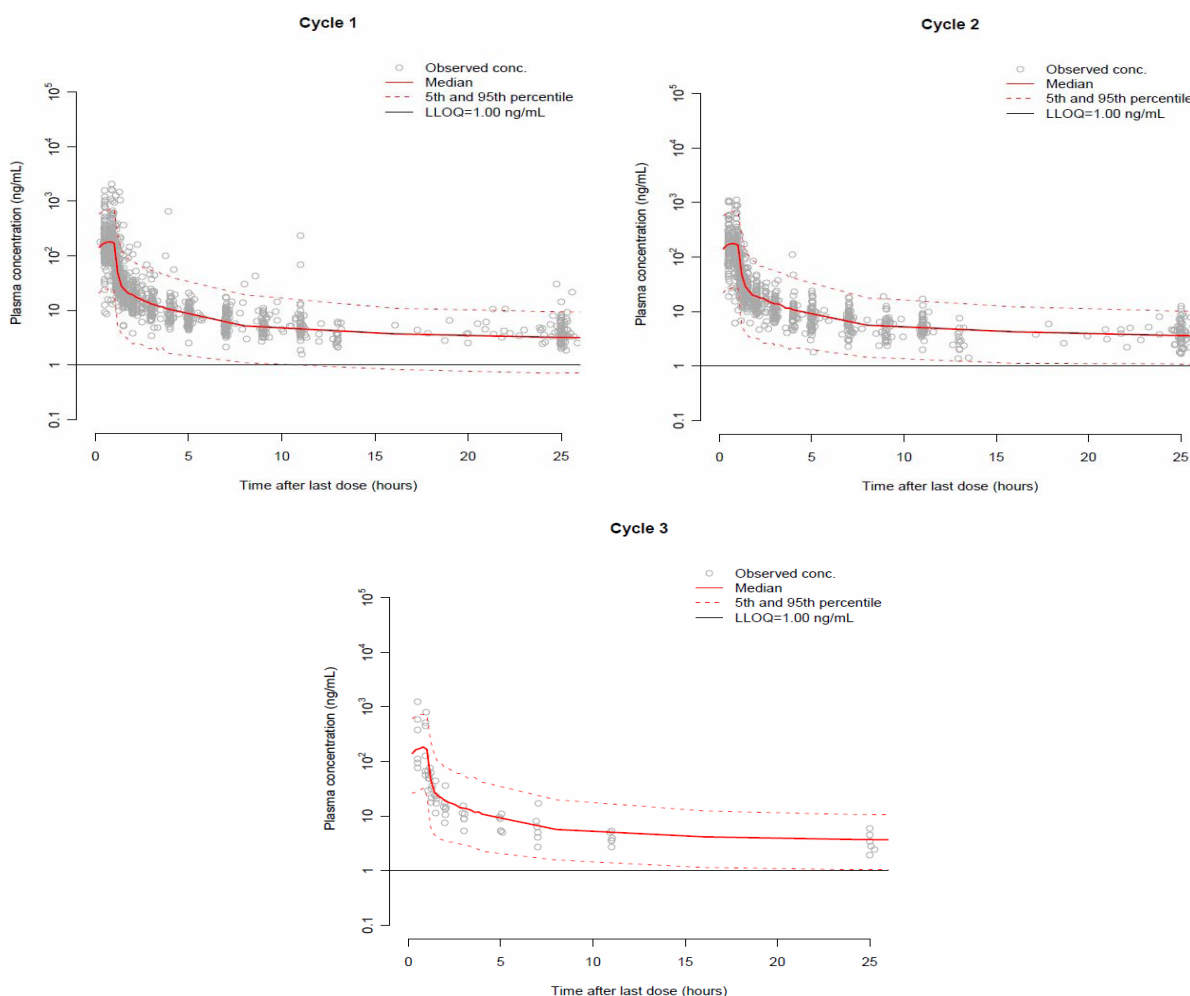
TT1=1 for breast cancer and 0 otherwise
Source: POH0124-pop-pk-report, Page 39

Figure 9: Basic goodness of fit plots for the Sponsor's final model



Source: POH0124-pop-pk-report, Page 43-46, Figure 13-18

Figure 10: Final model visual predictive check of plasma concentration vs. time by cycle (normalized to a therapeutic dose of 25 mg/m²) (0-25 h).



Source: POH0124-pop-pk-report, Page 49, Figure 20

Reviewer's comments:

- Sponsor's analysis followed a reasonable and thorough approach in describing the pharmacokinetics of cabazitaxel. Structural model was developed utilizing data from rich PK studies to establish that cabazitaxel was best described using a three compartment model. The reviewer agrees with the sponsor's conclusions regarding lack of effect of age, renal function and co-administration of prednisone on the pharmacokinetics of cabazitaxel.

3.2 Exposure-Response Analysis

The objective was to investigate PK estimates of cabazitaxel as prognostic factors for clinical outcome, including selected efficacy and safety end points.

3.2.1 Methods

Study designs

Data from two phase 1 studies (TED6188 and TED6190), one phase 2 study (ARD6191) and one phase 3 (EFC6193) study were combined for this PK/PD analysis referenced POH0258. Doses ranged from 10 to 30 mg/m² q3wk. A total of 145 patients with pharmacokinetic parameters from the first cycle were available for the analysis.

PK parameter estimates

Individual PK parameter estimates were computed for each patient from the population parameters obtained in the final population PK model (POH0124). The pharmacokinetic parameters were predicted C_{max} (maximum plasma concentration), area under the plasma concentration curve (AUC), and plasma clearance (CL). The derived parameter CLf (CLf=mean CL/individual CL estimate) was calculated to facilitate the interpretation of PK/PD models in term of CL changes. Cumulative AUC was also calculated until last cycle of treatment as follows: Σ (cycle 1 to n) Dose (mg) / cycle 1 clearance (L/h).

PK/PD analysis

The PK/PD analysis was conducted using as independent variables individual estimates of CLf, exposure parameters (C_{max} or AUC) at first cycle and several other covariates related to the patients, pathophysiologic status (demographics, disease spread, renal or hepatic function status) and extent of prior treatment.

In the PK/safety analysis, the following end points (dependant variable) were first selected among all tumor type (N=145) based on PK data availability:

- Febrile neutropenia,
- Nausea/vomiting,
- Mucositis/stomatitis,
- Peripheral neurotoxicity,
- Renal toxicity \geq grade 3 (National Cancer Institute (NCI) grade) at the first cycle and
- All other severe toxicities leading to a dose reduction at subsequent cycle.

The relationship between safety parameters at cycle 1 (binary variable, any event occurring or not at Cycle 1) and the prognostic PK parameters AUC, C_{max} or CLf were analyzed using a logistic regression model. Due to the low frequency of febrile neutropenia, nausea/vomiting, mucositis/stomatitis, peripheral neurotoxicity, renal toxicity with \geq grade 3, only neutropenia \geq grade 3 was finally considered.

In the PK/efficacy analysis, only overall survival data in patients with prostate cancer was considered (N=67 from study EFC6193). The relationship between overall survival and

the prognostic PK parameters including cumulative AUC until last cycle of treatment was evaluated using a proportional hazards model.

3.2.2 Conclusions

Safety

Seventy four out of 145 patients (51%) experienced at least grade 3 neutropenia at cycle 1. No significant relationship was found between any PK parameter of cabazitaxel (C_{max} , AUC, CLf) and neutropenia grade ≥ 3 (**Table 3**). Age was the only significant prognostic variable for neutropenia grade ≥ 3 ($P < 0.05$). According to the models, an each one year increment in age at baseline resulted in about 5% increase in odds ratio of experiencing grade ≥ 3 neutropenia and a 14 years increase in age would cause a 2 fold increase in odds ratio. Of note ECOG performance as a prognostic factor for neutropenia reached a marginal significance ($P=0.09$).

Table 3: Summary of impact of AUC at cycle 1 on the incidence of neutropenia with grade ≥ 3 .

Parameters	p-value	Estimated odds ratio ^a	95% CI
AUC (per 100 ng.h/ml)	0.2757	1.050	(0.962,1.145)
Age	0.0101	1.046	(1.011,1.082)
ECOG performance	0.0867	0.610	(0.346,1.074)

^a The odds ratio is the ratio in the odds of having the specified event for any increase of one unit of the prognostic factor.

PGM=PRODOPS/XRP6258/OVERALL/SCS_SCE_09/REPORT/PGM/pk_auc_neut.sas OUT=REPORT/OUTPUT/pk_auc_neut_i.rtf (29JAN2010 - 15:40)

Source: POH0258, Page 18, Table 9

Reviewer's Comments :

- There were two main differences in the reviewer's exposure-safety analysis compared with sponsor which might have resulted in AUC as a prognostic predictor of neutropenia.
 - Based on the population PK analysis done by the sponsor, breast cancer patients had 60% lower clearance than rest of the population. Since majority of the breast cancer patients came from the study ARD6191 study, it is not clear if lower clearance relates to tumor type or a study effect. Thus reviewer removed the patients on study ARD6191 (N=22) from the exposure-safety dataset and repeated the analysis with 123 patients from studies TED6188, TED6190 and EFC6193.
 - The reviewer explored both univariate and multivariate regression analysis. The AUC was a predictor of neutropenic events in univariate

analysis but when multivariate analysis was done adjusting for age, AUC was no longer a significant predictor for grade ≥ 3 neutropenia.

- Since G-CSF was allowed prophylactically later in the trial, reviewer agrees with the sponsor approach to perform the exposure safety analysis using \geq grade 3 neutropenic events at cycle 1. Sponsor looked diarrhea and renal toxicity also only at first cycle. For the pivotal trial, these events could be explored irrespective of when they happened during the treatment period as exposures are expected to be similar at different cycles and use of G-CSF is not a confounding factor for these adverse reactions.
- Odds ratio of 0.6 (p value=0.08) suggests that people with higher ECOG score have less chance to experience these neutropenic events. This finding is difficult to interpret as higher ECOG score means more disease severity and thus the patients with higher ECOG score are expected to experience more adverse reactions.

Efficacy

Cumulative AUC was the most significant prognostic factor ($P=0.0003$) of the overall survival. However, the effect could be confounded with the duration of treatment exposure (**Table 4**). There is a concomitant increase of the cumulative AUC with the duration of treatment exposure associated with a longer overall survival.

Hepatic function appeared to be a significant prognostic factor for overall survival with a 3.7-to 3.9-fold increase in risk of death in patients with abnormal liver function (ALAT or ASAT ratios > 1.5 ULN or Bilirubin ratio > 1 ULN). However, these results are inconclusive and should be interpreted with caution because of the small number of patients with abnormal liver function at baseline (8 patients in efficacy analysis) and only 3 out of these 8 patients experienced adverse events associated with death.

Table 4: Summary of impact of AUC at cycle 1 on overall survival.

Parameters	p-value	Estimated hazard ratio ^a	95% CI
AUC (per 100 ng.h/ml)	0.0611	1.088	(0.996,1.187)
ECOG performance	0.0513	1.636	(0.997,2.684)
Liver function status: abnormal normal	0.0028	3.784	(1.580,9.062)
Cumulative AUC (per 100 ng.h/ml)	0.0003	0.981	(0.972,0.991)

^a The HR is the change in the hazard rate of having the specified event for any increase of one unit of the prognostic factor. PGM=PRODOPS/XRP6258/OVERALL/SCS_SCE_09/REPORT/PGM/pk_auc_os.sas OUT=REPORT/OUTPUT/pk_auc_os_i.rtf (29JAN2010 - 15:41)

Source: POH0258, Page 20, Table 12

Reviewer's comments:

- *The use of both AUC (per 100 ng h/ml) and cumulative AUC in the model is not appropriate as they provide similar information and will exhibit co-linearity. Moreover, as stated by the sponsor, the effect of cumulative AUC on survival cannot be interpreted as it is confounded by the treatment duration.*

4 Reviewer's Analysis

4.1 Exposure-Response Analysis for Effectiveness

4.1.1 Objectives

To explore the exposure-efficacy relationship using the primary end point (overall survival) and secondary end points (time to tumor progression and responder analysis) in the pivotal trial. The aim of the present analysis in combination with exposure-safety analysis is to explore if the use of lower dose (20 mg/m²) could be as beneficial as 25 mg/m².

4.1.2 Methods

The primary efficacy assessment was overall survival (OS) defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, the survival time was censored at the last date patient was known to be alive or at the cut-off date, whichever had come first. Time to tumor progression was defined as the number of months from the date of randomization to evidence of progression based upon tumor measurements (RECIST). Patients without PD (Progressive Disease) were censored at their last tumor assessment. Responder analysis (Percent of patients with objective response) was to be conducted only for patients with measurable disease at baseline. 204/377 patients in the MTX/PRED and 201/378 patients in the CBZ/PRED arm had measurable disease at baseline.

Data from only Phase 3 trial (EFC6193) was used for this analysis to focus only on efficacy in patients (HRPC patients) for which the indication is proposed. Pharmacokinetic data was available for 67/378 (18%) of the subjects. Therefore the exposure-response dataset only consisted of these 67 patients which is a major limitation of the analysis. Since only 67 patients were available, the data was divided into two groups by median AUC (907 ng h/ml): Lower exposure group (AUC < 907 ng h/ml) and higher exposure group (AUC > 907 ng h/ml).

Kaplan Meier analysis was performed for both overall survival and time to tumor progression. Only 49% patients (N=33) in the exposure-response dataset had measurable disease and were eligible for responder analysis. This reduced the dataset to 33 patients with 5 patients exhibiting objective response. Thus exposure-response analysis for objective response was not conducted.

4.1.3 Datasets

The datasets utilized for the analysis are summarized below.

Study Number	Name	Link to EDR
ISS	adpkpd.xpt	\\cdsesub1\evsprod\NDA201023\0002\m5\datasets\iss\analysis
EFC6193	adds.xpt	\\cdsesub1\evsprod\NDA201023\0002\m5\datasets\efc6193\analysis
	addp.xpt	
	adex.xpt	

4.1.4 Software

SAS 9.2 and S-PLUS 7.0 were used for analyses.

4.1.5 Model

Kaplan Meier analyses were conducted to explore the exposure-overall survival and exposure-time to tumor progression relationship.

4.1.6 Results

The **Table 5** below shows the median and 90% CI of exposures in the lower and higher exposure groups suggesting the range of exposures may not be large enough to demonstrate exposure-efficacy relationship.

Table 5: AUC in the lower and higher exposure groups.

Group	N*	Median AUC (5 th , 95 th percentile)
Lower exposure (AUC < 907 ng h/ml)	35	826.5 (648, 906)
Higher exposure (AUC > 907 ng h/ml)	32	1067.1 (924, 2027)

*Median was 906.6 but for simplicity 907 ng h/ml was chosen for dividing the groups which resulted in 35 and 32 subjects in lower and higher exposure groups, respectively.

Exposure-efficacy analysis for overall survival analysis revealed that higher exposure group had numerically lower median survival (**Figure 1**). This analysis was however confounded by four neutropenia related deaths that happened in the CBZ/PRED arm within 30 days of dosing. One patient was part of the lower exposure group while three belonged to the higher exposure group. When these subjects were removed from the

dataset there was no significant separation was observed in between the survival curves (**Figure 1**, right panel).

Exposure-efficacy analysis for time to tumor progression analysis also did not show any significant difference between the two exposure groups even though the lower and higher exposures curves seem to separate after approximately five months (**Figure 2**).

There were 54 of 378 subjects in the treatment arm who had dose reduction. An attempt was made to see the impact of dose reduction in these patients on efficacy, but since the dose reduction happened at various cycles (Cycle 2-9), time is a confounding factor (**Table 6**).

Table 6: Table showing the time (cycle) of dose reduction for patients in the CBZ/PRED arm.

Cycle Number	Number of patients with Dose Reduction (%)
1	5 (9)
2	14 (26)
3	10 (19)
4	9 (17)
5	4 (7)
6	6 (11)
7	3 (6)
8	1 (2)
9	2 (4)

In summary, lack of exposure response relationship for efficacy could be due low number of subjects who had PK data in the phase 3 trial and data from only one dose level (25 mg/m²). Thus, nothing conclusive could be said about efficacy at lower dose of 20 mg/m².

4.2 Exposure-Response Analysis for Safety

4.2.1 Objectives

The objective of this analysis was to explore if the proposed dose reductions from 25 to 20 mg/m² are adequate to reduce toxicities. Toxicities here are referred to as febrile neutropenia, \geq grade 3 neutropenia, or \geq grade 3 diarrhea. Sponsor recommends reducing the dose from 25 to 20 mg/m² in case these toxicities persist despite intervening with appropriate medications. This 20% dose reduction is rather empirical, based on the clinical practice.

6/371 patients in the CBZ/PRED arm had acute renal failure. Exposures in these patients if available could be explored to see if these patients have unexpectedly high exposures of cabazitaxel.

4.2.2 Methods

Data from two phase 1 studies (TED6188 and TED6190) and the pivotal study (EFC6193) were combined to generate the exposure-safety dataset. Total of 123 patients were included in the exposure-safety dataset. The data comprised of doses ranging from 10-30 mg/m² q 3wk.

4.2.3 Datasets

The datasets utilized for the analysis are summarized below.

Study Number	Name	Link to EDR
ISS	adpkpd.xpt	\\cdsesub1\evsprod\NDA201023\0002\m5\datasets\iss\analysis
EFC6193	adae.xpt	\\cdsesub1\evsprod\NDA201023\0002\m5\datasets\efc6193\analysis

4.2.4 Software

SAS 9.2 and S-PLUS 7.0 were used for analysis.

4.2.5 Model

Logistic regression models were used to explore the relationship between exposure and the above mentioned adverse reactions (Section 4.2.1) as the sponsor has recommended dose adjustments for these in the label.

4.2.6 Results

Grade \geq 3 neutropenia was the most common adverse event observed in the CBZ/PRED arm in the pivotal trial (

Table 7).

Table 7: Adverse reaction in CBZ/PRED compared to MTX/PRED arm.

Adverse Reaction	CBZ/PRED (N=371)		MTX/PRED (N=371)	
	All Grades N (%)	Grade 3+ N (%)	All Grades N (%)	Grade 3+ N (%)
Neutropenia	347 (93.5)	303 (81.7)	325 (87.6)	215 (58)
Febrile neutropenia	-	28 (7.5)	-	5 (1.3)
Renal failure Acute	8 (2.2)	6 (1.6)	0	0
Diarrhea	173 (46.6)	23 (6.2)	39 (10.5)	1 (0.3)

Table 8 below shows univariate logistic regression analysis for various prognostic factors. Age and AUC were significant covariates in predicting probability of \geq grade 3 neutropenia. AUC was not a significant predictor if adjusted for age and ECOG status in multivariate analysis. The logistic regression analysis of AUC- \geq grade 3 neutropenia with mean prediction overlaid with observed data is shown in **Figure 3**.

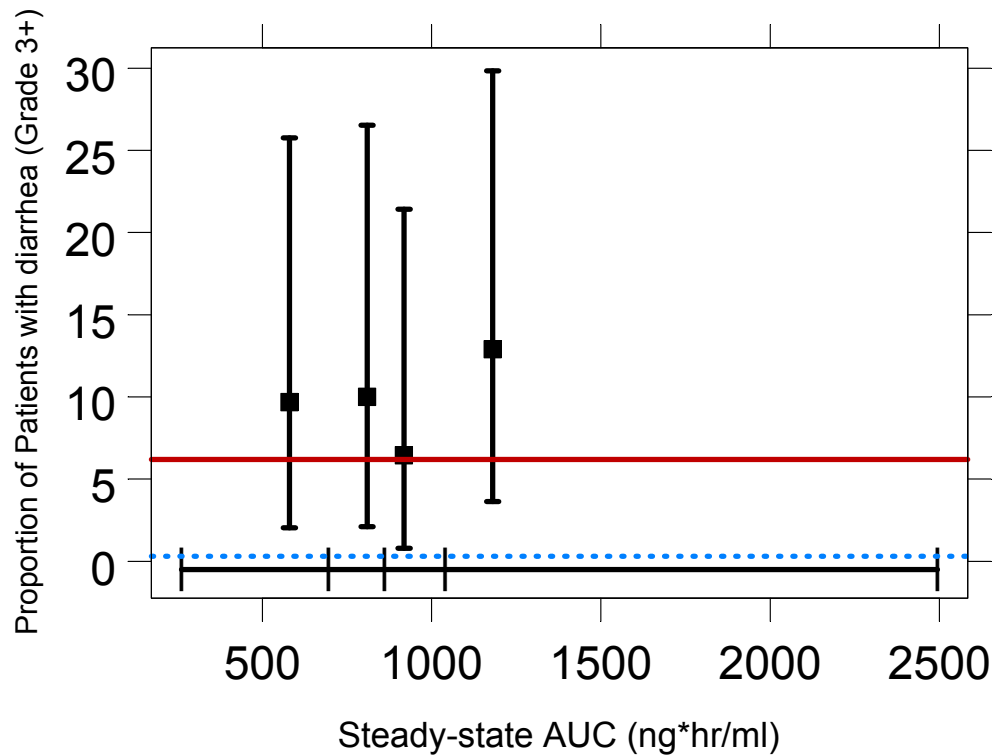
Table 8: Reviewer's Logistic Regression Analysis Parameter Estimates.					
Parameter	Intercept Estimate	Slope Estimate	P-value	Odds Ratio (95% CI)	N
AUC	-0.97	0.0013	0.048	1.001 (1-1.003)	123
ECOG	0.47	-0.46	0.13	0.63 (0.35-1.15)	123
Age	-3.5	0.06	0.003	1.06 (1.02-1.1)	123
AUC*	-3.7	0.00094	0.15	1.001 (1-1.002)	123

* Multivariate adjusted for age and ECOG status

Due to shallow slope in the logistic regression analysis, the same percent decrease in dose is not expected to cause similar percent decrease in \geq grade 3 neutropenia. Based on the predicted median AUC (904 ng h/ml) following 25 mg/m² based on the population PK analysis, the reduction in dose from 25 to 20 mg/m² is expected to reduce the probability of having \geq grade 3 neutropenia from 54 to 49%.

For pivotal trial, acute renal failure and diarrhea (Grade ≥ 3) were explored irrespective of when they occurred. Six patients in the CBZ/PRED arm had acute renal failure (Grade ≥ 3) but pharmacokinetic data was available for 2/6 patients and therefore exposure-safety analysis was not performed for acute renal failure. Similarly, 23 patients CBZ/PRED arm had \geq grade 3 diarrhea with pharmacokinetic data available only for 8/23 patients, and thus exposure-safety analysis was not conducted. Exploratory analysis shows that incidence of \geq grade 3 diarrhea does not increase with AUC (**Figure 11**).

Figure 11: Observed proportion of patients experiencing \geq grade 3 diarrhea in each AUC quartile. The vertical black bars represent the 95% confidence interval. The exposure range in each AUC quartile is denoted by the horizontal black line. The horizontal solid red and dotted blue line represents the % of \geq grade 3 diarrhea events observed in the CBZ/PRED and MTX/PRED arm of the pivotal trial (EFC 6193), respectively.



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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