Clinical Pharmacology NDA Review	
NDA/Supplement No.	NDA 201023/Supplement 20
Type/Category	Efficacy supplement; Standard
Brand Name	JEVTANA
Generic Name	Cabazitaxel
Receipt Date	November 21, 2016
PDUFA Date	May 21, 2017
Approved Indication	In combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen
Dosage Form	60 mg/1.5 mL single dose vial, supplied with diluent (5.7 mL)
Route of Administration	Intravenous infusion over one hour
Approved Dosing Regimen and Strength	25 mg/m^2 every three weeks in combination with prednisone 10 mg administered orally daily
Applicant	Sanofi
OND Division	Division of Oncology Products 2 (DOP2)
OCP Divisions	Division of Clinical Pharmacology V (DCPV) Division of Pharmacometrics (DPM)
OCP Reviewers	Ruby Leong, Pharm.D. (DCPV), Jiang Liu, Ph.D. (DPM)
OCP Team Leaders	Hong Zhao, Ph.D. (DCPV), Jiang Liu, Ph.D. (DPM)

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1 EXECUTIVE SUMMARY

JEVTANA (cabazitaxel) is a microtubule inhibitor indicated in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen. The recommended dosing regimen in adults is cabazitaxel 25 mg/m^2 intravenously every three weeks (Q3W) in combination with prednisone 10 mg orally daily (QD).

The original pediatric Written Request (WR) was issued on March 20, 2012 for the development of cabazitaxel in pediatric patients with recurrent or refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG) for whom no further effective therapy is available. The WR specified submission of pharmacokinetic (PK) information from a dose escalation and expansion trial (Study TED12689) in pediatric patients with refractory solid tumors including tumors of the central nervous system (CNS) such as HGG and DIPG. This pediatrics supplement contains the final study report for Study TED12689, as well as population PK and exposure-response (E-R) analyses.

The maximum tolerated dose (MTD) in pediatric patients was determined to be cabazitaxel 30 mg/m^2 Q3W by an 1-hour intravenous (IV) infusion. Thirty-nine pediatric patients ranging from 3 to 18 years of age were enrolled (23 patients with advanced solid tumors and 16 patients with recurrent/refractory HGG or DIPG). There were no objective responses observed in 11 evaluable patients with HGG or DIPG. Given that responses were not observed in patients treated with cabazitaxel in Study TED12689, the planned E-R analysis for activity/efficacy was not conducted. An E-R analysis for safety using logistic regression suggested a trend for Grade 4 neutropenia at cycle 1 with increased cabazitaxel AUC and C_{max}. Based on the population pharmacokinetics (popPK) analysis conducted in 31 pediatric patients (9 in 2-6 years old, 10 in 7-11 years old, and 12 in 12-18 years old), the estimates of geometric mean clearance by body surface area (BSA) were comparable to those in adults. There is a trend that individual volume of distribution and clearance increase with BSA.

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1.2 RECOMMENDATIONS

This efficacy supplement fulfills the clinical pharmacology components of the WR as summarized in the table below. For labeling recommendations regarding use of cabazitaxel in pediatric patients, please refer to **Section 3**.

Pediatric Written Request (WR) Component	Sufficiently Supported?	Relevant Language in WR
Number of Patients for Pharmacokinetics	☒ Yes ☐ No Refer to **Section 2.2.4**	At least 7 patients within each of the following specified age groups (2-6, 7-11 and 12-18 years old) must be evaluated. The number of patients may include patients from Part 1 and Part 2 of the study.
Pharmacokinetic Endpoints	☒ Yes ☐ No Refer to **Sections 2.2.1, 2.2.3**	Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or non-compartmental analysis. If appropriate, develop pharmacokinetic and pharmacodynamics (PK-PD) models to explore exposure-response relationships as measures of safety and activity.

1.3 PHASE 4 REQUIREMENTS AND COMMITMENTS

There are no clinical pharmacology requested postmarketing requirements (PMRs) or postmarketing commitments (PMCs).

Signatures:

Reviewer: Ruby Leong, Pharm.D. Division of Clinical Pharmacology V	Team Leaders: Hong Zhao, Ph.D. Division of Clinical Pharmacology V
	Team Leader: Jiang Liu, Ph.D. Division of Pharmacometrics

Cc: DOP2:   RPM - A Patel; MTL - S Demko; MO - A Barone
       DCPV: DDD - B Booth; DD - NA Rahman

2   QUESTION-BASED REVIEW

For brevity, only QBR questions related to the current submission are addressed below. For additional details, please refer to the original NDA 201023 submission (SDN 5, receipt date of 03/31/2010) and the corresponding clinical pharmacology review in DAARTS (DARRTS date 06/02/2010).

PERTINENT REGULATORY HISTORY AND BACKGROUND INFORMATION

Pediatric study requirements under the Pediatric Research Equity Act (PREA) was waived for the use of cabazitaxel in the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen. The original pediatric WR was issued on March 20, 2012, WR Amendment #1 on May 8, 2013, and WR Amendment #2 on March 3, 2015 for the development of cabazitaxel in pediatric patients with recurrent or refractory HGG or diffuse intrinsic pontine glioma DIPG for whom no further effective therapy is available.

The absorption, distribution, metabolism, and excretion (ADME) properties of cabazitaxel in adults is summarized below.

Absorption
- Following an IV dose of cabazitaxel 25 mg/m^2 Q3W in patients with metastatic prostate cancer, the mean C_{max} (CV%) was 226 ng/mL (107%) and AUC (CV%) was 991 ng·h/mL (34%).
- Based on a popPK analysis with data from 170 patients with solid tumors treated with cabazitaxel 10 to 30 mg/m^2 weekly or Q3W, dose proportionality was observed from 10 to 30 mg/m².

Distribution
- The steady-state volume of distribution ($V_{d,ss}$) was 4864 L.
- In vitro, 89 to 92% binding to human serum proteins (mainly albumin) that was not saturable up to 50,000 ng/mL, which covers the maximum concentration observed in clinical trials.
- The in vitro blood-to-plasma concentration ratio in human blood ranged from 0.90 to 0.99, indicating that cabazitaxel was equally distributed between blood and plasma.

Metabolism
- Extensively metabolized in the liver (>95%), mainly by CYP3A4/5 (80% to 90%) and to a lesser extent by CYP2C8.
- Cabazitaxel is the main circulating moiety in human plasma. Seven metabolites were detected in plasma (including the 3 active metabolites resulting from O-demethylation), with the main one accounting for 5% of cabazitaxel exposure.

Elimination
- After a one-hour IV infusion [^{14}C]-cabazitaxel 25 mg/m^2, cabazitaxel was mainly excreted in the feces as numerous metabolites (76% of the dose); while renal excretion of cabazitaxel and metabolites accounted for 3.7% of the dose (2.3% as unchanged drug).
- Based on the popPK analysis, cabazitaxel has a mean (%CV) plasma clearance (CL) of 48.5 L/h (39%) and α-, β-, and γ- half-lives of 4 minutes, 2 hours, and 95 hours, respectively.

Specific Populations
- Renal Impairment: A popPK analysis of 14 patients with moderate renal impairment (CLcr 30 to <50 mL/min) and 59 patients with mild renal impairment (CLcr 50 mL/min <80 mL/min) showed that mild to moderate renal impairment did not have clinically meaningful

effects on the PK of cabazitaxel. This was confirmed by a dedicated comparative PK study in patients with solid tumors with normal renal function (n=8, CLcr >80 mL/min/1.73m^2), and moderate (n=8, CLcr 30 to <50 mL/min/1.73m^2) and severe (n=9, CLcr <30 mL/min/1.73m^2) renal impairment. Limited PK data were available in patients with end-stage renal disease (n=2, CLcr <15 mL/min/1.73m^2).

- Hepatic Impairment: A dedicated study in 43 cancer patients with hepatic impairment showed no influence of mild (total bilirubin >1 to ≤1.5 × ULN or AST >1.5 × ULN) or moderate (total bilirubin >1.5 to ≤3.0 × ULN) hepatic impairment on cabazitaxel PK; however, based on safety and tolerability data, the MTD of cabazitaxel was 20 and 15 mg/m^2 in patients with mild and moderate hepatic impairment, respectively. In 3 patients with severe hepatic impairment (total bilirubin > 3 x ULN), a 39% decrease in clearance was observed when compared to patients with mild hepatic impairment. The MTD of cabazitaxel in patients with severe hepatic impairment was not established.

Drug Interactions
- Ketoconazole, a strong CYP3A inhibitor, 400 mg QD increased cabazitaxel exposure by 25% in 23 patients with advanced cancers.
- Aprepitant, a moderate CYP3A inhibitor, 125 or 80 mg QD did not affect cabazitaxel exposure in 13 patients with advanced cancers.
- Rifampin, a strong CYP3A inducer, 600 mg QD decreased cabazitaxel exposure by 17% in 21 patients with advanced cancers.
- Cabazitaxel 25 mg/m^2 did not affect the exposure of midazolam, a sensitive CYP3A substrate, in 11 patients with advanced cancers.
- Prednisone or prednisolone 10 mg QD did not affect the PK of cabazitaxel.
- Substrate of P-gp, but not a substrate of MRP1, MRP2, BCRP, OCT1, OATP1B1 or OATP1B3.
- Did not inhibit CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2D6, 2E1, CYP3A4/5) or transporters (MRP1, MRP2, OCT1) in vitro.
- Inhibited P-gp, BCRP, OATP1B1, OATP1B3; however, the in vivo risk of cabazitaxel inhibiting these transporters is low at the dose of 25 mg/m^2.
- Cabazitaxel did not induce CYP1A2, 2C9, or 3A4/5 in vitro.

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?

Study TED12689 was a two-part trial consisting of a dose escalation phase in 23 patients with advanced solid tumors (4 to 18 years of age) treated at doses of 20 mg/m^2 (n=6), 25 mg/m^2 (n=3), 30 mg/m^2 (n=7), and 35 mg/m^2 (n=7) Q3W to determine the MTD and an expansion phase in 16 patients with recurrent/refractory HGG or DIPG (3 to 16 years of age) treated at the MTD of 30 mg/m^2 to determine antitumor activity and safety of cabazitaxel. In addition, cabazitaxel plasma concentration data from Study TED12689 were used for the popPK and E-R analyses to fulfill the clinical pharmacology components as stated in the WR:

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Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or non-compartmental analysis. If appropriate, develop pharmacokinetic and pharmacodynamics (PK-PD) models to explore exposure-response relationships as measures of safety and activity.

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 outcome measure of the expansion phase in Study TED12689 was Investigator-assessed objective response rate (ORR) using the modified Response Assessment in Neuro-Oncology (RANO) criteria. There were no objective responses observed in 11 evaluable patients with HGG or DIPG. One patient with ependymoma in the dose escalation phase had a partial response.

2.2.3 Exposure-response

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

Given that responses were not observed in patients treated with cabazitaxel in Study TED12689, the planned E-R analysis for activity/efficacy was not conducted.

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

An E-R analysis for safety was conducted for Grade 4 neutropenia using logistic regression. Consistent with the relationship observed in adults, there was a trend that Grade 4 neutropenia at cycle 1 increased with cabazitaxel AUC and C_{max} (Figure 1) (although the E-R relationship was not significant (Table 1)). In adults, there was a significant relationship between exposure (AUC) and $\geq$ Grade 3 neutropenia at the end of first cycle; data from cycle 1 was utilized to avoid the confounding effect of prophylactic granulocyte-colony stimulating factor (G-CSF).

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Figure 1. Relationship Between AUC (Left) and C_{max} (Right) and Grade 4 Neutropenia in Pediatric Patients
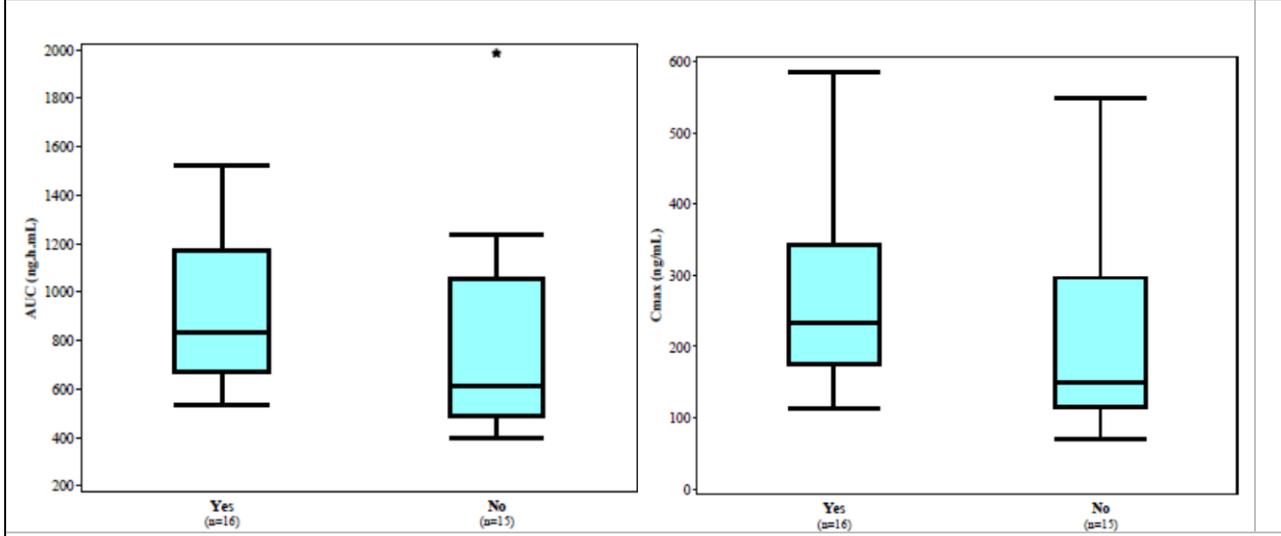
Source: Study TED12689 Report, Figures 8 and 9, Page 112.

Table 1. Odds Ratios for Grade 4 Neutropenia

Parameters	p-value	Estimated odds ratio[a]	95% CI
Cmax (per 50 ng/ml)	0.1986	1.197	(0.910,1.573)
AUC (per 100 ng.h/ml)	0.3536	1.103	(0.896,1.359)
CL adjusted for BSA	0.1188	0.949	(0.890,1.013)

Source: Study TED12689 Report, Table 63, Page 113.

2.2.3.4 *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?*

The MTD in pediatric patients was determined to be cabazitaxel 30 mg/m^2 Q3W by IV administration over one hour. DLTs of febrile neutropenia occurred in one patient treated at 20 mg/m^2 and two patients at 35 mg/m^2.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 *What are the single dose and multiple dose PK parameters?*

PK data were available from 31 patients, 9 patients in the 2-6 years old age group, 10 patients in the 7-11 years old age group, and 12 patients in the 12-18 years old age group. This fulfills the clinical pharmacology component stated in the WR:

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Pharmacokinetics: At least 7 patients within each of the following specified age groups (2-6, 7-11 and 12-18 years old) must be evaluated. The number of patients may include patients from Part 1 and Part 2 of the study.

PK samples were collected at 5 minutes before end of infusion (EOI), 10 min post-EOI, and 1.5, 4, 8, and 72 hours after the start of infusion. Cabazitaxel exposure appeared to be dose proportional in the range of 20 to 35 mg/m^2 in pediatric patients, similar to dose proportionality observed in adults in the range of 10 to 30 mg/m^2. The PK of cabazitaxel was well described by a three-compartment model with a first order elimination from the central compartment and inter-compartmental rate constant parameterization. The pediatric popPK model estimated the following PK parameters: CL of 35.6 L/h/m^2, $V_{d,ss}$ of 1889 L, and α-, β-, and γ- half-lives of 3.5 minutes, 1 hour, and 59 hours, respectively. BSA (range: 0.66 to 2.38 m^2) had a significant effect on central volume (V1) (with an explanation of 35% of the variability in V1). The inter-patient variability in cabazitaxel CL was 43%. There is a trend that the individual clearances are increasing with body surface area and age (Figure 2). Cabazitaxel mean CL by body surface area was 35% higher in pediatric patients than in adults (CL of 26.4 L/h/m^2), which is not clinically important given the inter-patient variability in CL of 43%. Furthermore, individual clearances in pediatric patients were generally in the range of those in adults (Figure 3).

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

PopPK analysis was conducted using data from 31 pediatric patients of 3 to 18 years of age enrolled in Study TED12689. There is a trend that the individual clearances are increasing with body surface area and age (Figure 2). Cabazitaxel CL values by body surface area in pediatric patients were generally in the range of those in adults (Figure 3). The popPK analysis showed that gender, height, performance status, race, tumor type, CLcr, total protein, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were not clinically important covariates on cabazitaxel PK in pediatrics.

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Figure 2. Cabazitaxel Clearance Versus Age and Body Surface Area
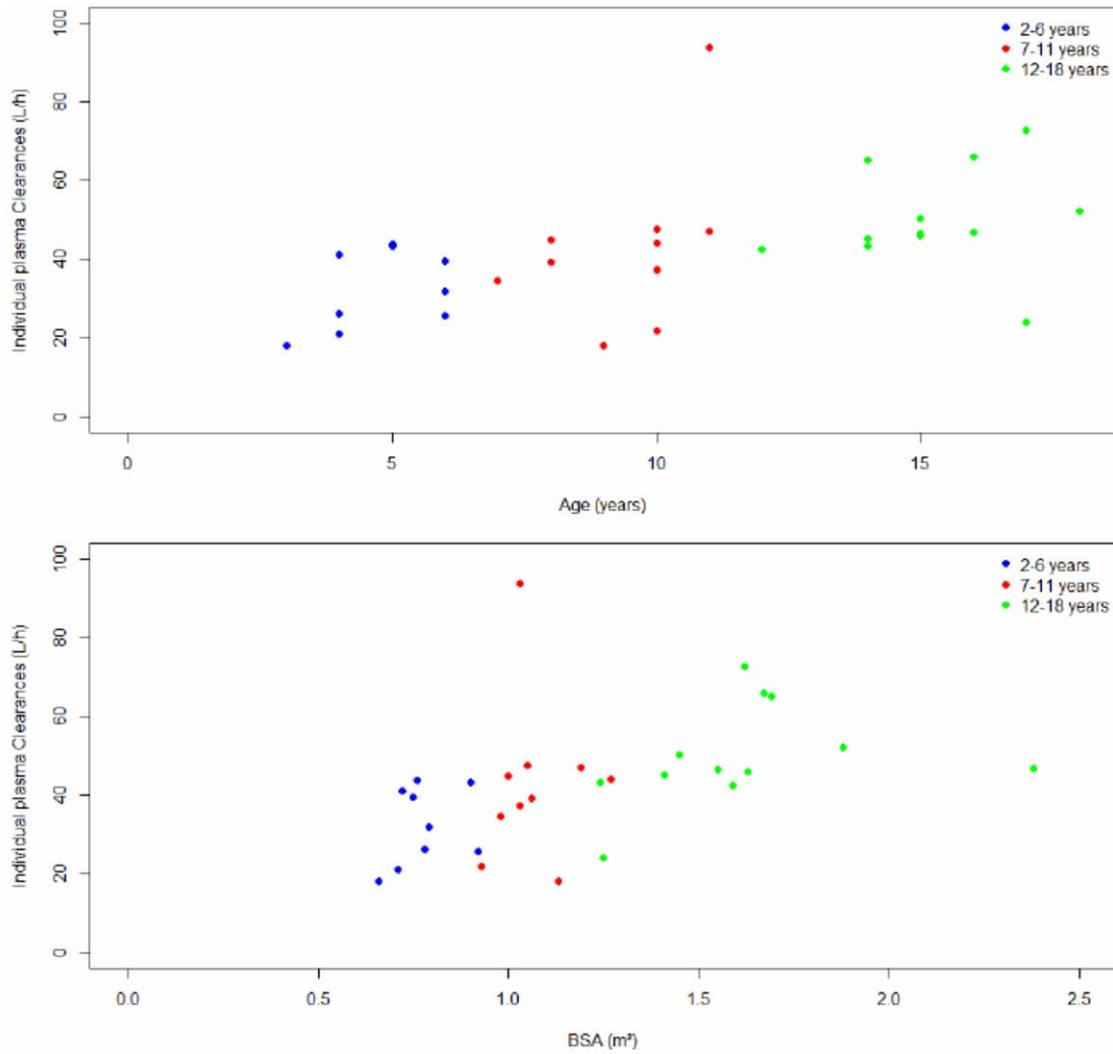
Source: Population Pharmacokinetic Study Report, Figure 5, Page 29.

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Figure 3. Cabazitaxel Individual Clearance by Body Surface Area in Pediatrics Compared to Those Observed in Adults
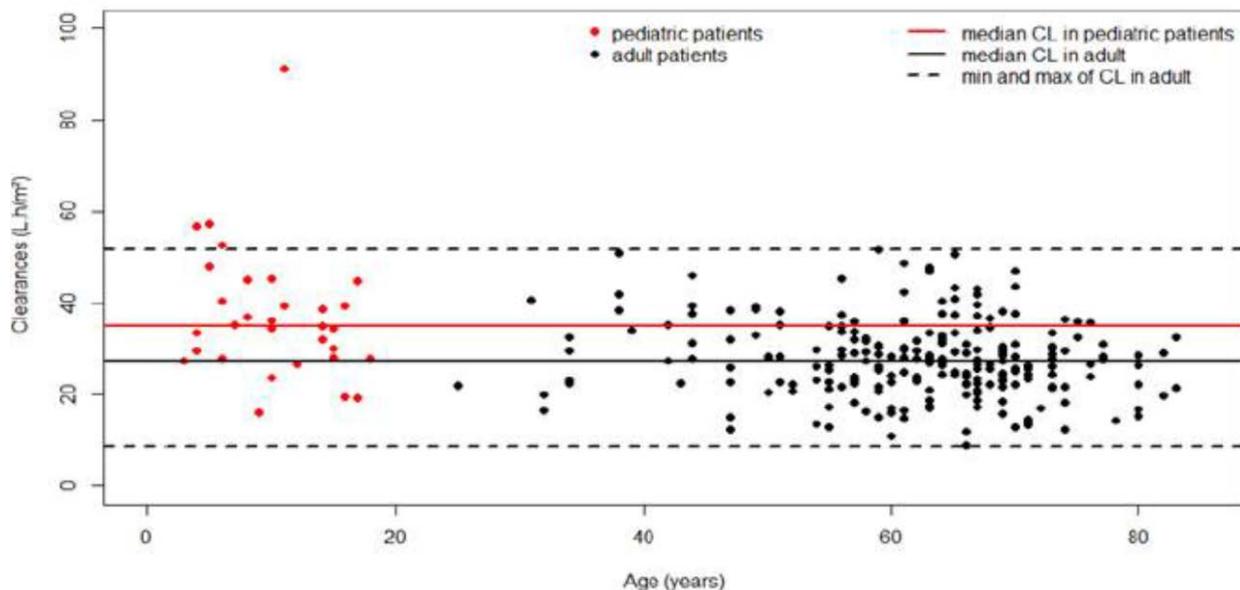
Source: Summary of Clinical Pharmacology Studies, Figure 6, Page 25.

2.4 EXTRINSIC FACTORS

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

The popPK analysis showed that concomitant use of a moderate CYP3A inducer (dexamethasone in 5 patients) was not a clinically important covariate on cabazitaxel PK in pediatrics. Pediatric patients requiring treatment with enzyme inducing anti-epileptic drugs (EIAEDs) and strong inhibitors or inducers of CYP3A4 were excluded from Study TED12689. Non-EIAEDs were permitted.

2.5 ANALYTICAL SECTION

2.5.4 What bioanalytical methods are used to assess concentrations?

Cabazitaxel plasma concentrations from pediatric patients in Study TED12689 were measured using a validated LC/MS/MS method over the concentration range of 1 to 500 ng/mL (Report DOH0598). This method was cross validated with that used for measuring cabazitaxel concentrations in adults (Report DOH0586). Accuracy (%bias) and precision (%CV) of the quality controls (QCs) for the runs used in measuring cabazitaxel concentrations in Study TED12689 were acceptable (≤15% for %bias or %CV) based on the 2013 FDA Guidance for Industry Bioanalytical Method Validation.

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3   DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Applicant's proposed labeling changes are in BLUE and modifications made by the Agency are in RED.

8   USE IN SPECIFIC POPULATIONS

8.4   Pediatric Use

(b) (4)

The safety and effectiveness of JEVTANA in pediatric patients have not been established.

JEVTANA was evaluated in 39 pediatric patients receiving prophylactic G-CSF. The maximum tolerated dose (MTD) was 30 mg/m2 intravenously over 1 hour on Day 1 of a 21 day cycle (doses studied ranged from 20 mg/m2 and 35 mg/m2) in pediatric patients (ages 4 to 18 years) with solid tumors based on the dose-limiting toxicity (DLT) of febrile neutropenia. No objective responses were observed in 11 patients with refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG). One (1) patient had a partial response (PR) among the 9 patients with ependymoma.

Infusion related/hypersensitivity reactions were seen in 10 patients (26%). Three patients experienced serious adverse events of anaphylactic reaction. The incidence of infusion related/hypersensitivity reactions decreased with steroid pre-medication. The most frequent treatment-emergent adverse events were similar to those reported in adults.

Based on the population pharmacokinetics analysis conducted in 31 pediatric patients with cancer (3 to 18 years of age), the geometric mean clearance by body surface area were comparable to those in adults.

4 APPENDICES

4.1 POPULATION PK REVIEW

Monolix was used by the sponsor for the population PK modeling. According to the sponsor, the PK of cabazitaxel was well described by a three-compartment model with a first order elimination from the central compartment and inter-compartmental rate constant parameterization. BSA (range: 0.66 to 2.38 m^2) had a significant effect on central volume (V1) (with an explanation of 35% of the variability in V1). The inter-patient variability in cabazitaxel CL was 43%. There is a trend that the individual clearances are increasing with body surface area and age, however both covariates were not tested significant by the sponsor during model selection (based on OF decreasing of 3.84 for 1 degree of freedom, χ^2, 1ddl; p-value of 0.05) (see the following table).

Summary Table 1: Cabazitaxel Parameters following Final POP PK model

Fixed effects			Interindividual variability	Shrinkage	Residual variability
Parameter	Estimate (RSE%)	p-value	ω (%) (RSE%)	η$_{sh}$%	σ (%) (RSE%)
V (L)	9.35 (15)		73.6 (15)	2	20.3 (9)
β for BSA	1.8 (21)	1.2 10^{-6}	-	-	
CL (L/h)	37.7 (8)		42.6 (15)	15	
k12 (h^{-1})	5.61 (11)		53.9 (14)	0	
k13 (h^{-1})	2.20 (12)		43.1 (24)	1	
k21 (h^{-1})	0.0283 (7)		-	-	
k31 (h^{-1})	0.795 (8)		-	-	
Corr (V,CL)	0.398 (48)				
Corr (V,k13)	0.974 (21)				
Corr (CL,k13)	0.595 (36)				

RSE: Relative standard error; V: Central volume of distribution; CL: clearance of elimination; k12: rate constant from central volume of distribution to the first peripheral volume of distribution; k21: rate constant from the first peripheral volume of distribution to the central volume of distribution; k13: rate constant from central volume of distribution to the second peripheral volume of distribution; k21: rate constant from the second peripheral volume of distribution to the central volume of distribution; Corr: correlation between two parameters; β: covariate effect; ω: Inter-individual variability; η$_{sh}$: Shrinkage; σ: Residual variability for the proportional part; -: Not applicable

The relationship between the central volume of distribution and the BSA can be summarized as follow:

$$V_i = 9.35 * \left(\frac{BSA_i}{1.06} \right)^{1.8}$$

Because the sponsor's analysis was primary based on PK micro parameters (elimination rate constant K), the assessment of covariate effect on CL might not be sensitive. The reviewer therefore conducted independent sensitivity analysis using pkmodel (V,Cl, k12, k21, k13, k31) and a slightly different covariance model. The selected final model is comparable or slightly better compared to the sponsor's final model (based on inter-patient variability on parameters, OFV, information criteria, and goodness-of-fit plots). With the reviewer's model, BSA had a significant effect on both CL and central volume (V1) (see Table and Figures below).

Table 2. Estimation of the Population PK Parameters (the reviewer's model)

		parameter	s.e. (lin)	r.s.e.(%)	p-value
V_pop	:	7.47	1.1	14	
beta_V_t_BSA	:	2.55	0.41	16	8e-010
Cl_pop	:	38.3	2.7	7	
beta_Cl_t_BSA	:	1.03	0.22	22	4.1e-006
k12_pop	:	6.71	0.49	7	
k21_pop	:	0.0353	0.003	9	
k13_pop	:	2.06	0.21	10	
k31_pop	:	0.969	0.096	10	
omega_V	:	0.66	0.11	17	
omega_Cl	:	0.361	0.051	14	
omega_k12	:	0.283	0.061	22	
omega_k21	:	0.341	0.075	22	
omega_k13	:	0.187	0.2	110	
omega_k31	:	0	-	-	
corr_V_Cl	:	0.56	0.15	27	
b	:	0.217	0.023	11	

Figure 4. Comparison of the Goodness-of-fits Plots (Top: from the Sponsor's Final Model and Bottom: from the Reviewer's Model)
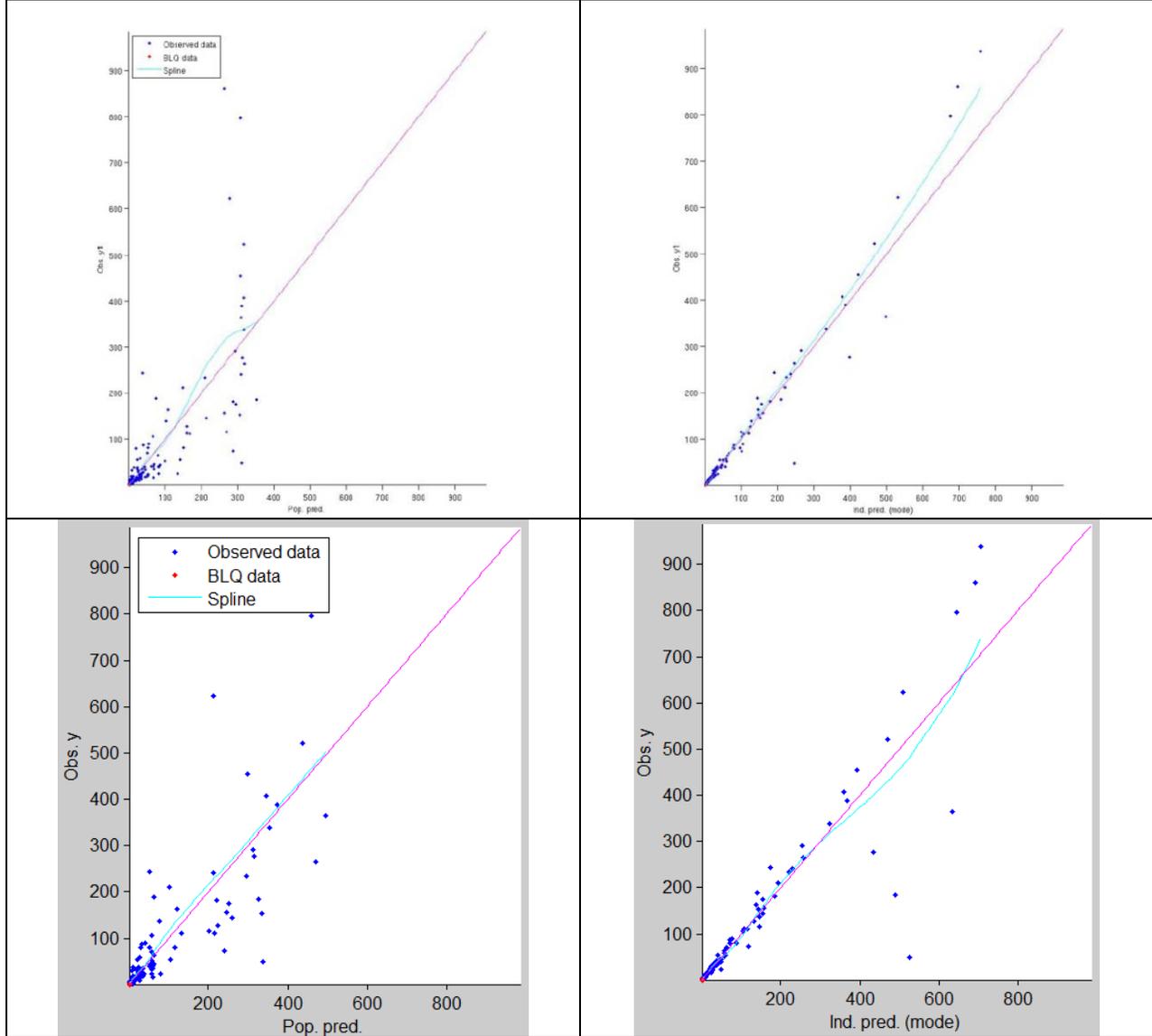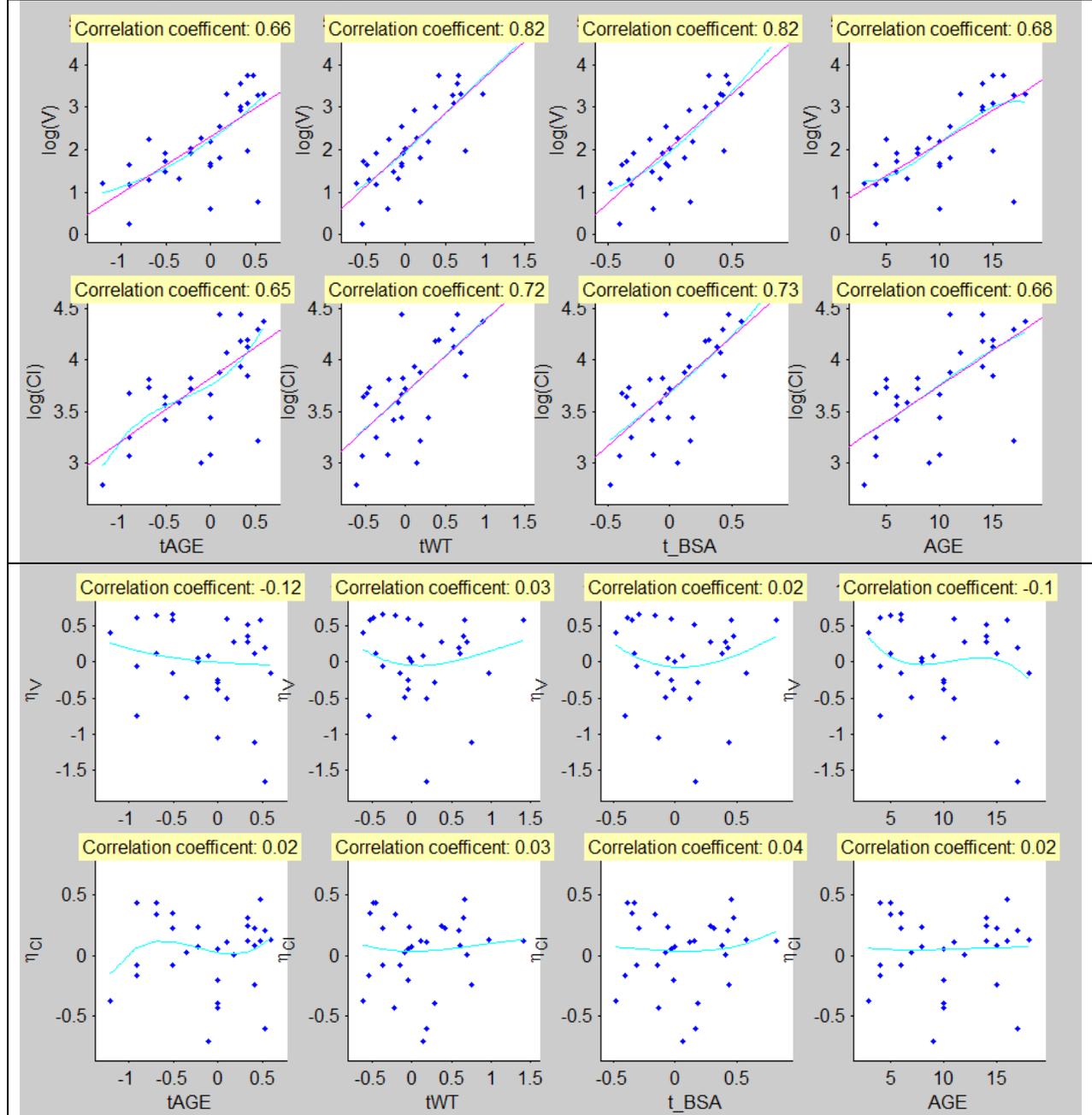
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Figure 5. The Correlation between CL or Volume of Distribution (V) and Body Size or Age (top) Can Be Well Explained by Adding BSA as a Covariate on CL or V (Based on the Reviewer's Model)

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/s/

RUBY LEONG
04/26/2017

JIANG LIU
04/26/2017

HONG ZHAO
04/27/2017
I concur.