OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**20-449**
	Submission Date: 11/12/09
Brand Name	**Taxotere®**
Generic Name	**Docetaxel sodium**
Clin Pharm Reviewer	**Joseph A. Grillo, Pharm.D.**
Clin Pharm Team Leader	**Qi Liu, Ph.D.**
OCPB Division	**5**
PM Reviewer	**Justin C. Earp, Ph.D.**
PM Team Leader	**Christine Garnett, Pharm.D.**
ORM division	**OND/DDOP**
Sponsor	**Sanofi-Aventis**
Submission Type; Code	**Labeling Supplement, S059**
Formulation; Strength(s)	**Solution for IV Infusion; 75 mg/m^2**
Indication	**For use in adults with solid tumors: breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck cancer.**

1   Executive Summary

Sanofi-aventis received a Pediatric Written Request (PWR) for docetaxel (Taxotere®) from the Food and Drug Administration (FDA) in June 2007. Sanofi-aventis has submitted reports for 3 studies to fulfill this PWR. Sanofi-aventis will not seek an indication for docetaxel therapy in pediatric patients.

In the phase 3 study, taxotere was studied in combination with cisplatin and 5-fluorouracil (TCF) versus cisplatin and 5-fluorouracil (CF) for the induction treatment of nasopharyngeal carcinoma in pediatric patients prior to chemoradiation consolidation. Seventy-five patients (median age 16 years, range 9 to 21 years) were randomized (2:1) to Taxotere (75 mg/m²) in combination with cisplatin (75 mg/m²) and 5-fluorouracil (750 mg/m²) (TCF) or to cisplatin (80 mg/m²) and 5-fluorouracil (1000 mg/m²/day) (CF). The primary endpoint was the CR rate following induction treatment of NPC. One patient out of 50 in the TCF group (2%) had a complete response while none of the 25 patients in the CF group had a complete response

The pharmacokinetics of docetaxel in pediatrics was characterized from data collected in the phase 1 (rich PK samples) and randomized (sparse PK samples) trials using PK modelling approach. The exposures and clearance values in pediatrics (AUC = 4.3 ug•hr/mL, CL=17 L/hr/m^2) appeared to be comparable to that in adults (AUC = 3.6 ug•hr/mL) at the recommended dose level for adults (75 mg/m^2, CL=20 L/hr/m^2). Thus the lack of efficacy is not likely due to differences in exposure between adults and pediatrics.

1.1   Recommendation

The application is acceptable from a Clinical Pharmacology perspective, provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the PI.

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in <u>underline blue font</u>.

(b) (4)

1.2   Post Marketing Requirements

None

1.3   Comments to the Applicant

1. The value of pediatric clearance in the section 12.3 of the package insert was changed from ▓▓▓▓▓ **(b) (4)** to 17.3 L/hr/m^2 to reflect the geometric mean, since clearance values generally follow a log-normal distribution.

2. In the second paragraph of pediatric PK under section 12.3, the values were changed to the geometric means of the results. These were determined using priors from the standard-two-stage analysis of the pediatric phase I data. This is a less biased test of whether pediatric PK determined from the sparsely sampled data is similar to adults.

1.4   Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The pharmacokinetics of docetaxel in pediatrics was characterized from data collected in the phase 1 (docetaxel monotherapy) and phase 3 (TCF combination) studies using PK modelling approach. The

pharmacokinetic parameters in pediatrics (AUC = 4.3 ug•hr/mL, CL=17 L/hr/m^2) were comparable to those in adults. (AUC = 3.6 ug•hr/mL, CL=20 L/hr/m^2)

The question of whether or not lack of effectiveness was due to different exposures in pediatric patients compared to adults was examined using AUC and CL values. In most cases the AUC of the pediatric patient (geometric mean AUC = 4.3 ug•hr/mL) was generally greater than for the adult patients (AUC = 3.6 ug•hr/mL). Thus the lack of efficacy is not likely due to differences in exposure between adults and pediatrics as with higher exposure a greater response is anticipated.

No exposure-response relationships for complete or partial responders were observed. There was neither sufficient PK sampling or effectiveness observed in patients to establish exposure-response for either complete or partial responders to Taxotere. PK concentrations were sparsely sampled and only one of the 50 patients exhibited complete response (the primary endpoint).

Signatures

_____
Justin Earp, Ph.D.
Pharmacometrics Reviewer
Division of Pharmacometrics

_____
Christine Garnett, Pharm.D.
Team Leader Pharmacometrics
Division of Pharmacometrics

_____
Joseph A. Grillo, Pharm.D
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5

_____
Qi Liu, Ph.D.
Team Leader
Division of Clinical Pharmacology 5

_____
Nam Atiqur Rahman, Ph.D.
Division Director
Division of Clinical Pharmacology 5

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?

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:
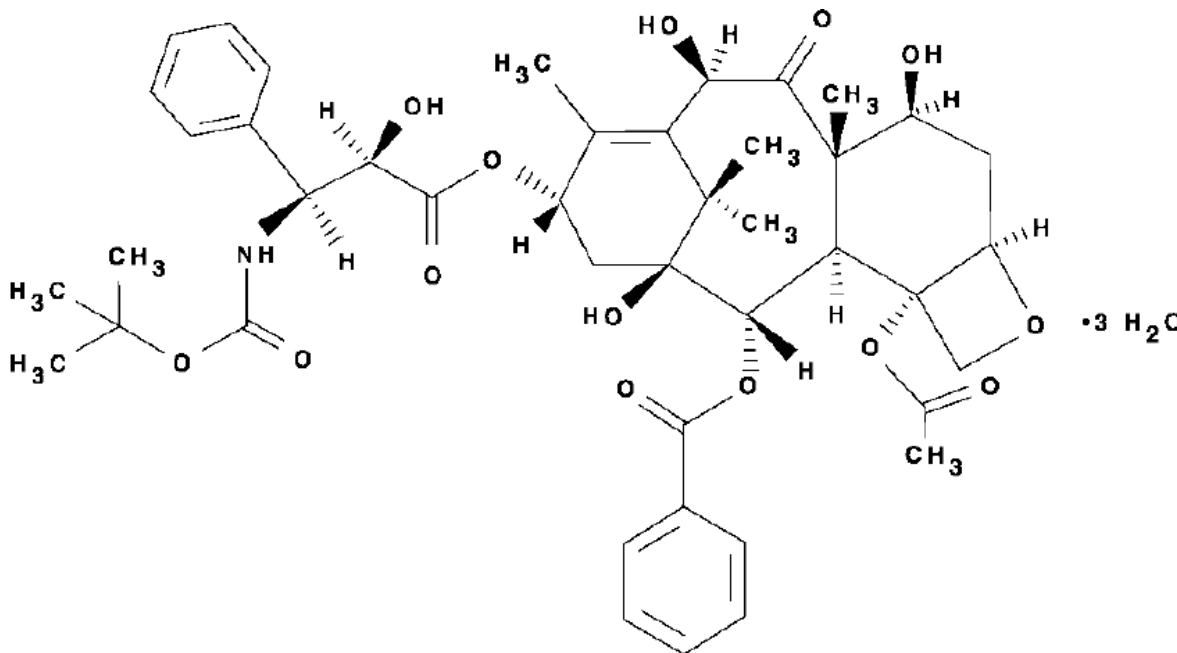
Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14} \cdot 3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. TAXOTERE (docetaxel) Injection Concentrate is a clear yellow to brownish-yellow viscous solution. TAXOTERE is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80. TAXOTERE Injection Concentrate requires dilution prior to use. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13% ethanol in water for injection, and is supplied in vials.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Docetaxel (also known as XRP6976 or Taxotere), a member of the taxoid family of compounds, inhibits cancer cell proliferation by inhibiting microtubule depolymerization and thereby blocking cells in the M Phase of the cell cycle. The clinical development of docetaxel has focused on adult solid tumors: breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck cancer. Sanofi-Aventis is not seeking an indication in pediatric patients due to lack of efficacy.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Pediatrics

Not applicable. Sanofi-Aventis is not seeking for use of Taxotere in pediatric patients.

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?

There are two supportive studies:
- ARD6005 (Study 1): A dose-finding and dose escalation study of docetaxel monotherapy and pharmacokinetics (PK). This study enrolled 61 patients with PK data on a subset of 29 patients.

- ARD6006 (Study 2): An efficacy and safety study of docetaxel monotherapy in pediatric patients. This study enrolled 178 patients.

There is one pivotal study:
EFC10339 (Study 3): A randomized, international, multicenter study in pediatric patients comparing docetaxel + cisplatin + 5-fluorouracil (5-FU) (TCF) to cisplatin + 5-FU (CF) in the induction treatment of nasopharyngeal carcinoma (NPC). This pivotal study enrolled 75 patients in a 2:1 randomization. Pharmacokinetics data are available for 28 patients.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint was the percentage of patients with complete response. In pediatric patients and adult patients with nasopharyngeal carcinoma. The response has been historically measured with the overall response rate or only complete response. To show improvement in pediatrics over other combination therapies without taxotere, the sponsor chose to use primarily complete 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?

Development of an exposure-response relationship for effectiveness was hindered by two factors. 1) The sampling of PK in study 3 (the main pediatric efficacy study) was incomplete (28 of 50 docetaxel treated patients had evaluable PK data) and no covariates were identified to predict exposures in the other patients who received docetaxel. 2) There was a general lack of efficacy (complete responders) across the population. One of the 50 patients exhibited complete response (the primary endpoint) and 38 patients exhibited partial response. The rate of partial response was no different than the placebo group. Of the 21 patients with AUC values in study 3, 17 showed a partial response to the docetaxel-cisplatin-5flurouracil treatment. Figure 1 shows the percentage of patients partially responding against docetaxel concentrations.

Figure 1. No exposure-response relationship was evident from limited efficacy data. The mean % of patients partially responding is shown by symbols ± the 95% confidence interval for the binomial distribution. The control group (cisplatin and 5-fluorouracil) is shown in red, while the treatment group (docetaxel, cisplatin, and 5-fluorouracil) data are shown in black. The black bar at the bottom of the plot represent the quartiles of docetaxel AUC in the population with PK sampling. The numbers in the graph correspond to the number of partial responders/sample size for the respective groups (control, Q1, Q2, Q3, Q4)
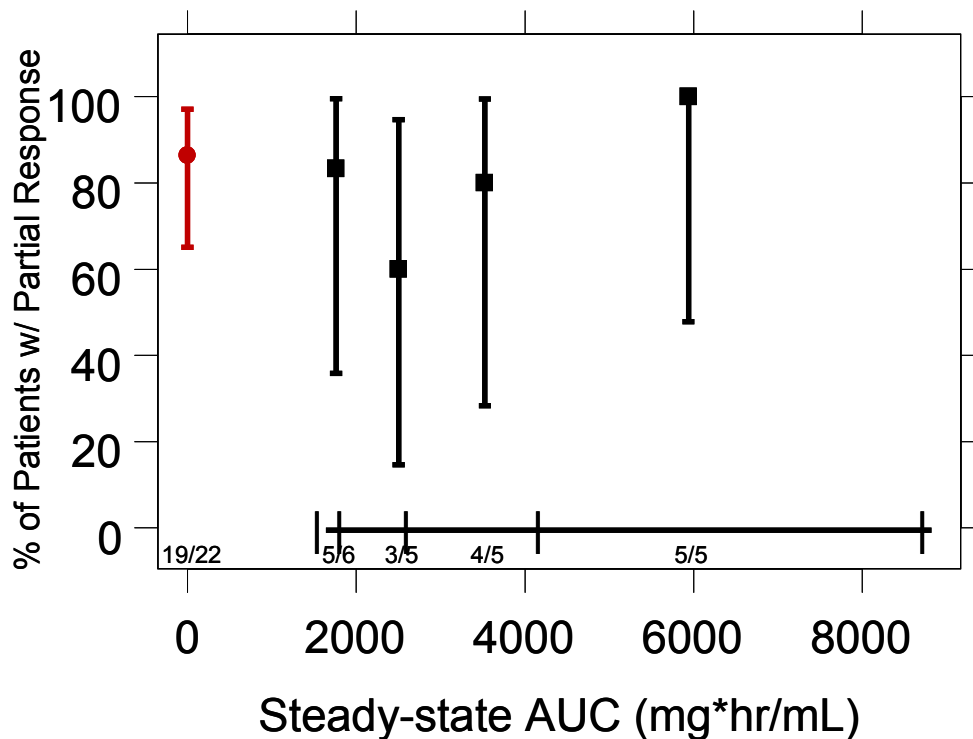
There is no evident exposure-response relationship for effectiveness from Figure 1. Note the small number of patients in each AUC quartile and large degree of variation in the secondary endpoint (partial overall response). There were 22 patients in the CF group and 21 patients in the TCF group with available PK data. For a logistic regression with binary data, these numbers are too small given the variation in the response to detect a signal in effectiveness. Further, a few exposures in the pediatric population surpassed that in the adult population. This combined with the similarity in PK between pediatrics and adults suggests that the range of exposures was sufficient to determine that lack of efficacy is not due to under-dosing in the pediatric population. It should finally be noted that the partial response was a secondary endpoint and does not reflect that rate of the primary endpoint (complete response).

2.2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Of the 29 patients included in the PK analysis, 4 (840016, 840042, 840046, 840048) experienced at least one grade 4 neutropenia. Patients 840016 and 840042 received G-CSF. Pharmacokinetic parameters of these patients are documented in Table 4. No particular trend was observed between AUC and experience of grade 4 neutropenia.

Table 1. Individual Pharmacokinetic Parameters (Bayesian Estimation) in Patients who Experienced at Least One Grade 4 Neutropenia.

Patient number	Cycle	Dose mg/m²	Dosetot mg	Infdur h	BSA m²	Age yr	Gender	AUC ng.h/mL	CL L/h	CL L/h/m²	Vss L
840046	1	125	155	1	1.24	11	1	4473	34.7	27.9	145
840048	1	150	150	1	0.831	9	0	7158	21.0	25.2	207
840016	1	185	130	1	0.676	4	0	79143	1.64	2.43	41.5
840042	1	235	370	1	1.74	17	0	10110	36.6	21.0	127
n			29		29	29		29	29	29	29
mean			178		1.20	11.3		13815	25.2	20.9	133
SD			115		0.513	6.39		20396	15.2	10.1	76.1
median			140		1.24	12		7710	25.5	22.0	135
min			30		0.450	1		1694	1.13	1.69	3.44
max			400		1.9	20		86918	50.8	37.9	328

Patients that received GCSF are in grey

2.2.3.3 Does this drug prolong the QT or QTc interval?

Not applicable to this submission. Thorough QT prolongation studies have not been performed for Taxotere.

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

The dose is consistent with producing exposures in pediatrics similar to the therapeutic exposures in Adults. No concentration-response or dose-response relationships were evidenced for effectiveness of Taxotere.

2.2.4 PK characteristics of the drug and its major metabolite

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

See the approved label for values in adults. Values from pediatric patients for single dose are shown Table 2 under Study 1. Values from pediatric patients receiving multiple dose Taxotere are shown in Table 2 under Study 3. Adult values in Table 2 are the results of the population PK analysis with both single and multiple dose PK data.

Table 2. Docetaxel Pharmacokinetic Parameters in Pediatric and Adult Patients

PK Parameter	Descriptor	WinNonlin (2,3CM) Study 1	NONMEM Study 3 Values	Adult PopPK Values
CL (L/hr/m²)	Geometric Mean	17.3	17.9	20.2
	Arithmetic Mean	20.3	19.9	21.3
	Standard Dev	10.9	8.75	6.76
	CV%	53.6	44.0	31.7
	Relative Std. Error %	10.7	8.32	1.29
AUC_{75mg} (μg•hr/mL)	Geometric Mean	4.33	4.20*	3.62
	Arithmetic Mean	5.23	4.75*	3.82
	Standard Dev	3.61	2.57*	1.38
	CV%	69.0	54.1*	36.2
	Relative Std. Error	13.8	9.29*	5.07

*Predicted based on individual clearance values

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

Not applicable to this submission. See the original NDA review by Dr. Grillo dated August 11, 2008 and available in DARRTS.

2.2.4.3 What are the characteristics of drug absorption?

Not applicable to this submission. Please refer to the approved PI for further information in adults.

2.2.4.4 What are the characteristics of drug distribution?

Not applicable to this submission. Please refer to the approved PI for further information in adults.

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

Not applicable to this submission. Please refer to the original NDA 20-449 (Submission Date: 27-July-1994).

2.2.4.6 What are the characteristics of drug metabolism?

Not applicable to this submission. Please refer to the approved PI for further information in adults.

2.2.4.7 What are the characteristics of drug excretion?

Not applicable to this submission. Please refer to the approved PI for further information in adults.

2.2.4.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The PK in adults appears to be linear for doses between 50 and 200 mg/m^2.

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

The available PK data in pediatrics is too sparse (3 samples per subject in 26 subjects) to address this question.

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

Pediatrics:

Inter and Intra-subject variation could not be isolated from each other in the analyses conducted by the sponsor and the FDA. The data did not permit a comprehensive population PK assessment of the data. The CV% for clearance after a standard-two-stage analysis was 53.6% for study 1 (rich data) and 47.3% for study 3 (sparse data, using results from study 1 as prior estimates). No covariates were identified to explain sources of variation in the data. Dosing was done by body surface area to reduce variation in exposure based on body size.

Adults:

Taxotere PK in adults was assessed by a population PK analysis. Intersubject variation as CV% of eta on clearance is 47.5% while the CV% for residual error is 20.5%. Dosing was done by body surface area to reduce variation in exposure based on body size.

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?

Since it was not feasible to conduct a population PK analysis no intrinsic factors were identified that influence exposure beyond body surface area. Dosing by body surface area reduces inter subject variation in exposures. For intrinsic factors that influence the PK in adults please refer to the original NDA 20-449 (Submission Date: 27-July-1994)

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 (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

2.3.2.1 **Pediatric patients**

Not applicable to this submission. No doses are recommended in pediatrics based on lack of efficacy.

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?**

Not applicable. No dose- or exposure-response for effectiveness was identified in pediatric patients.

2.5 General Biopharmaceutics

Not applicable to this submission. See the sNDA review by Dr. Sophia Abraham available in DARRTS.

2.6 Analytical Section

Not applicable to this submission. See the sNDA review by Dr. Sophia Abraham available in DARRTS.

3 DETAILED LABELING RECOMMENDATIONS

3.1 Product Label

3 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

3.2   Patient Product Labeling

There were no Clinical Pharmacology Reviews to the Patient Product Labeling

4 APPENDICES

4.1 Proposed Labeling

3 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

4.2 Consult Review (including Pharmacometric Review)

4.2.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions
The purpose of this review is to address the following key questions.

1.1.1 Do the pharmacokinetic data and population PK analysis support the labeling conclusions?

The labeling claims with regards to the PK of docetaxel in pediatric patients are not entirely consistent with the PK data and population PK analysis. The PK parameter estimates based on the rich phase I PK data are consistent with the FDA's analysis. However, the values reported for the data from the randomized study in pediatric patients are consistent with the adult data when prior adult information is used. When prior pediatric information is used then the values for the PK parameters in the label need to be adjusted. Since the quality of the data (3 samples per patient) in the randomized pediatric study is so sparse it is not possible to precisely distinguish difference from adult and pediatric PK using this data alone. Therefore it is better to use the rich phase I pediatric data as prior information for the analysis and report these values.

1.1.2 Are there any significant covariates that can be identified by a Pop-PK analysis that would affect the label statements proposed?

No, covariates were identified that affected the clearance of volume of distribution of docetaxel in pediatric patients. Given the review timeline and the limited nature of the pediatric data 26 subjects with rich data and only 28 subjects with evaluable sparse data, it was not possible to develop a robust pediatric population PK model. Further exploration of pop PK covariates were limited because of this.

1.1.3 Is the lack of efficacy observed in the pediatric trial due to differences in exposure between pediatrics and adults?

No, the exposures in pediatrics (AUC = 4.28 ug•hr/mL) appeared to be similar or greater than that in adults (AUC = 3.62 ug•hr/mL) at the recommended dose level for adults (75 mg/m^2). Since it is expected that greater exposures will have greater efficacy, this cannot explain the lack of efficacy observed in the randomized pediatric trial.

1.1.4 Is there evidence for exposure-response for effectiveness in pediatrics?

No, there is neither sufficient PK sampling or effectiveness observed in patients to establish this relationship. PK concentrations were sparsely sampled from only 28 of the 50 docetaxel-treated subjects in study 3. Further only 1 of the 50 patients exhibited complete response (the primary endpoint) and 38 patients exhibited partial response. The rate of partial response was no different than the placebo group. Study 3 was the pivotal efficacy trial conducted in pediatric patients with nasopharyngeal carcinoma. Study 1 and 2 did not contain efficacy data from these patients.

1.2   Recommendations

The Division of Pharmacometrics in the Office of Clinical Pharmacology has reviewed this application and found the labeling language to be acceptable.

1.3   Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in <u>underline blue font</u>.

(b) (4)

2 PERTINENT REGULATORY BACKGROUND

Sanofi-aventis received a Pediatric Written Request (PWR) for docetaxel (Taxotere®) from the Food and Drug Administration (FDA) in June 2007. Sanofi-aventis is submitting the reports of 3 studies to fulfill this PWR. Sanofi-aventis will not seek an indication for docetaxel therapy in pediatric patients.

The submission package consists of 3 studies:

Two supportive studies:

- ARD6005 (Study 1): A dose-finding and dose escalation study of docetaxel monotherapy and pharmacokinetics (PK). This study enrolled 61 patients with PK data on a subset of 29 patients.

- ARD6006 (Study 2): An efficacy and safety study of docetaxel monotherapy in pediatric patients. This study enrolled 178 patients.

One pivotal study:

EFC10339 (Study 3): A randomized, international, multicenter study in pediatric patients comparing docetaxel + cisplatin + 5-fluorouracil (5-FU) (TCF) to cisplatin + 5-FU (CF) in the induction treatment of nasopharyngeal carcinoma (NPC). This pivotal study enrolled 75 patients in a 2:1 randomization. Pharmacokinetics data are available for 28 patients.

3 RESULTS OF SPONSOR'S ANALYSIS

The sponsor provided population PK results for ARD6005 (Study 1) and EFC10339 (Study 3) in separate reports for two independent population PK analyses. No PK results for ARD6006 (Study 2) or PK analyses using combined data from Study 1 and Study 3 were performed.

3.1 Study 1 – Population PK & PK/PD Analyses:

3.1.1 Population PK Analysis

The objectives of this PK study were to assess the pharmacokinetic profile of docetaxel in pediatric patients with refractory solid tumors and to validate the 3-optimal sampling time strategy that could be used in further clinical studies. Twenty nine pediatric patients received docetaxel as a 1-hour infusion every 3 weeks at doses ranging from 55 to 235 mg/m². Blood samples for PK analysis were collected at cycle 1 or 2 before infusion, immediately prior to the end of infusion, and 5, 15, 30, 60 min and 2, 4, 6, 10, 24 and 48 hours post infusion. The plasma study samples were analyzed using a high performance liquid chromatography method with a limit of quantification of 0.025 μM corresponding to 20.2 ng/mL. In a first step, compartmental pharmacokinetic analysis was performed using WinNonlin software, version 3.3. A two or three compartment model was used. Then, the evaluation of the 3-optimal sampling time strategy (End of infusion, End of infusion + 45 minutes and 6 hours) was performed. Pharmacokinetic parameters of each subject were estimated by Bayesian estimation, using concentration-time data and the adult population pharmacokinetic model as prior information. Finally, the predictive performance was evaluated by comparing docetaxel clearance assessed by Bayesian estimation in NONMEM and by compartmental analysis with WinNonlin.

Of the 29 patients, 26 were evaluable for WinNonlin compartmental pharmacokinetic analysis, 10 were male and 18 were female, and the median body surface area was 1.24 m². The median age was 11 (range: 1-20) years. According to the ICH E11 age classification of pediatric patients, 1 was infant (28 days to 23 months), 13 were children (2 to 11 years), 4 were adolescent (12 to 15 years) and 11 were 16 years old and older. The median docetaxel clearance was 19.1 (range: 3.98-65.8) L/h corresponding to 18.1 (range: 4.76-47.0) L/h/m², which is slightly lower than the median value of 20.9 (range: 5.78-48.0) L/h/m² observed in 600 adult patients, treated at 75 or 100 mg/m² and without concomitant elevations of transaminases (SGOT or SGPT $\geq$ 1.5×ULN) and alkaline phosphatase ($\geq$ 2.5×ULN). Using the 3-optimal sampling time strategy, Bayesian analysis in 29 patients showed that the median clearance was 25.8 (range: 1.64-50.8) L/h corresponding to 22.4 (range: 2.43-37.9) L/h/m² which is similar to that observed in adult patients. Age was observed to have no effect on pharmacokinetics across the pediatric age groups. The optimal sampling strategy can be applied to estimate docetaxel clearance in further pediatric pharmacokinetic studies. Bayesian estimation with three measured concentrations performs well with respect to both bias (me% = +11.4%) and precision (rmse% = 21.7%) for estimating docetaxel clearance.

3.1.2 Pharmacokinetic-Pharmacodynamic Relationship

Of the 29 patients included in the PK analysis, 4 (840016, 840042, 840046, 840048) experienced at least one grade 4 neutropenia. Patients 840016 and 840042 received G-CSF. Pharmacokinetic parameters of these patients are documented in Table 4. No particular trend was observed between AUC and experience of grade 4 neutropenia.

Table 1. Individual Pharmacokinetic Parameters (Bayesian Estimation) in Patients who Experienced at Least One Grade 4 Neutropenia.

Patient number	Cycle	Dose mg/m²	Dosetot mg	Infdur h	BSA m²	Age yr	Gender	AUC ng.h/mL	CL L/h	CL L/h/m²	Vss L
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840016	1	185	130	1	0.676	4	0	79143	1.64	2.43	41.5
840042	1	235	370	1	1.74	17	0	10110	36.6	21.0	127
n			29		29	29		29	29	29	29
mean			178		1.20	11.3		13815	25.2	20.9	133
SD			115		0.513	6.39		20396	15.2	10.1	76.1
median			140		1.24	12		7710	25.5	22.0	135
min			30		0.450	1		1694	1.13	1.69	3.44
max			400		1.9	20		86918	50.8	37.9	328

Patients that received GCSF are in grey

3.2 Study 2

No PK data was collected for study 2. No exposure response for safety or effectiveness was performed with data from study 2

3.3 Study 3 - Population PK Analysis:

3.3.1 Pharmacokinetic Parameters

Individual pharmacokinetic parameters were estimated by Bayesian estimation using concentration–time data for each patient and the previously defined adult population model as prior information. A three-compartment structural model with first-order elimination was used. Briefly, estimates of adult population pharmacokinetics were clearance of 36.8 L/h, a volume of distribution of central compartment of 7.83 L, a steady state volume of distribution of 122 L and a terminal half-life of 10.0 hours. Of note, the combined administration of docetaxel, cisplatin, and fluorouracil in adult patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

The Bayesian analysis was performed using the NONMEM program (version VI) implemented on a Linux cluster. The analysis was focused on docetaxel plasma clearance and area under the curve parameters. CL (L/h/m²) was provided after BSA normalization and area under the curve was calculated as: AUC = dose/clearance.

3.3.2 Population Pharmacokinetic Analyses

Pharmacokinetic evaluation was performed in 28 patients. Of the patients evaluable for PK analysis, 18 were male and 8 were female, 19 were Caucasian/white, 1 Black, and 3 Asian/Oriental. The median age was 16 (range: 10 to 21) years. According to the ICH age classification of pediatric patients (2 were children (2 to 11 years), 9 were adolescent (12

to 15 years), and 17 were 16 years old and older. The median BSA was 1.49 (range: 0.81 to 1.89) m².

Mean AUC was similar compared to that observed in adult patients (n=52) with several tumor types, treated with docetaxel monotherapy at a dose of 75 mg/m² with a mean value of 3.51 ± 1.76 (range: 1.74 to 12.7) μg.h/mL (mean adult clearance 42.4 ± 13.3 L/h, 24.3 ± 7.09 L/h/m²).

3.3.3   Pharmacokinetic Conclusions

Pharmacokinetic analysis was performed in 28 evaluable PK patients at Cycle 1. Of the patients evaluable for PK analysis, the median age was 16 (range: 10 to 21) years. According to the ICH age classification of pediatric patients, 2 were children (2 to 12 years) 9 were adolescents (12 to 16 years), and 17 were older than 16 years old. Mean AUC in pediatric patients treated at 75 mg/m² was similar to that observed in adult patients with several tumor types who were treated with docetaxel monotherapy (n=52), with mean values of 3.43 and 3.51 μg.h/mL, respectively.

Figure 1: Docetaxel Concentration Time Profile of Pooled Data After Administration of 75 mg/m^2 with the Prediction for a Pediatric Patient with a Median BSA of 1.49 m^2
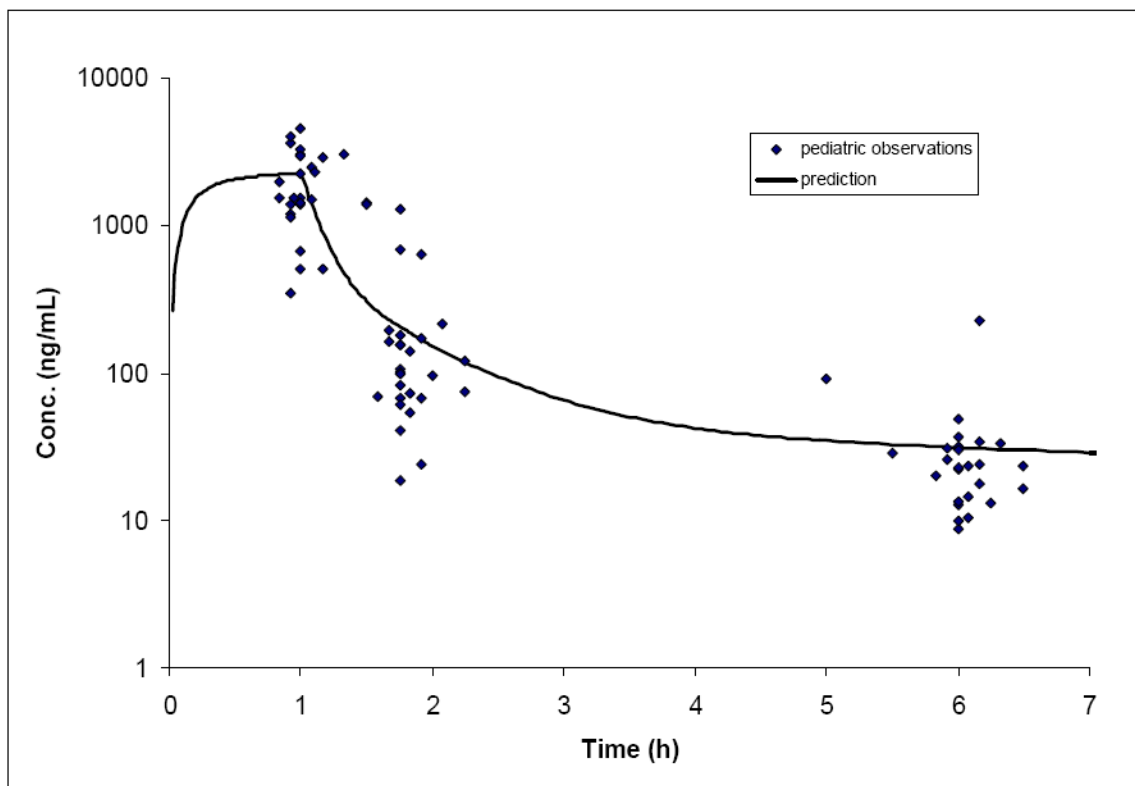
3.4   Reviewer's Comments on Sponsor's Analysis

The sponsor chose a method that was suboptimal, but acceptable for the available PK data from study 1. The best method would have been a full population PK model using all the pediatric PK data to compare the kinetics with the adult PK. Several aspects of the

sponsor's methods cause concern for the rigor of the PK analysis results and reliability of comparing the PK in pediatric patients with the adult data:

The sponsor used the adult PK model as a reference to compare the PK data with the adult data. The major flaw with this approach is the quality of the pediatric data that were used. Rather than using all the pediatric PK data, the sponsor selected 3 optimally sampled points from study 1 to test the adult PK model with. This gives much more flexibility with which the adult model can fit the pediatric data. If the adult model fit all the pediatric PK data well, than this would have been a more convincing argument for using the model to test the hypothesis that pediatric and adult PK are similar. However, it did not fit the data well as for the pediatric standard-2-stage analysis in WinNonlin some individuals were classified as having a 2-compartment model and others were assigned a 3-compartment model. The adult model was only a 3-compartment model. A better unbiased test to compare pediatric and adult PK is to compare the results of an independent PK analysis from all the data in studies 1 and 3 (combined analysis if possible) with the results of the adult analysis.

It does appear the sponsor removed the other data to justify using this approach for study 3 (using the adult PK model) which contained only sparse sampling. By showing the parameter estimates from this population PK approach for study 1 are similar to the standard-2-stage results in WinNonlin, the sponsor may be attempting to validate this method for analyzing the sparse PK data from study 3 (this was not explicitly stated in their report). However, this is based on the assumption that PK in pediatrics is similar to that in adults and does not test that assumption.

The sponsor analyzed the data from studies 1 and 3 separately. The best approach to test if pediatric PK is different than adult PK would have been to develop a population PK model based on study 1 and study 3 and compare the results to the adult pop PK results. The independent analysis for study 1 is okay, since the data is rich and provides precise estimates of clearance, volume of distribution, C_{max}, and AUC. However, analyzing the data from study 3 alone is questionable. Bias is introduced by using the adult PK model on sparse data and it is not possible to define the PK parameters from three sampled points from this study alone in pediatrics. Further, even though docetaxel was administered under different dosing scenarios between studies it is unlikely that the coadministration with cisplatin or 5 fluorouracil caused changes in docetaxel PK.

Finally, the sponsor did not conduct a population analysis. The sponsor also did not report whether they tried to estimate population parameters. This could have been a more robust option for assessing the pharmacokinetics of docetaxel in pediatric patients.

Note on why this is not a population PK analysis: The sponsor's evaluation utilizes the maxeval=0 option in NONMEM for study 1 and study 3. This essentially means that the sponsor fixed the population parameter estimates to the adult estimates and let each individuals eta values for the PK parameters be estimated based on the supplied estimates of between subject variability for the adult data. Only eta values were estimated after the first iteration of the NONMEM run. This is NOT a population analysis of the data. Rather this approach is similar to the standard two-stage analysis used in WinNonlin for study 1, with individual PK estimates confined to the distributions of the adult PK parameters.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The sponsor is seeking patent exclusivity after completing 3 studies for a Pediatric Written Request. The sponsor is not seeking an indication for docetaxel in pediatric patients because no effectiveness was observed in the primary efficacy trial. They are, however, proposing to modify the label to include PK information for pediatric patients.

4.2 Objectives

The objectives of the Pharmacometric review are:

1) To confirm the sponsor's labeling statments that describe the PK in pediatric patients

2) To determine if there are any additional covariates that may help describe the PK of docetaxel in individual pediatric patients

3) To determine if the dose administered in the randomized trial produced exposures in pediatrics similar to those in adults

4) To determine if there is exposure-response for effectiveness in pediatric patients with nasopharyngeal carcinoma

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 2.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
bay0008	adpc.xpt	\\Cdsesub1\evsprod\NDA020449\0016\m5\datasets\bay0008\analysis
bay0008	bay0008.xpt	\\Cdsesub1\evsprod\NDA020449\0018\m5\datasets\bay0008\analysis
ARD6005, EFC10339	txph1ph2.xpt	\\Cdsesub1\evsprod\NDA020449\0018\m5\datasets\ibp-biodyn-1835\analysis
All Adult Pop PK Data	bm5476e	\\Cdsesub1\evsprod\NDA020449\0018\m5\datasets\ibp-biodyn-1835\analysis

4.3.2 Software

NONMEM VI (Icon, Ellicott City, MD) and WinNonlin version 5.2 (Pharsight, Mountain View, CA) were used to review the sponsor's pharmacokinetic and pharmacodynamic analysis. S-PLUS 7.0 (Insightful Corp., inspehouseww was used to generate all plots and manage datasets.

4.3.3 Models

There were two major issues of the sponsor's analysis that led the FDA Pharmacometrics reviewer to reanalyze all the pediatric PK data using the sponsor's model. 1) The sponsor did not use all possible data from studies 1 and 3 for their population PK analysis in

NONMEM. Docetaxel concentrations were not sampled in study 2. 2) The sponsor's model was not a population fitting of the available data.

In light of these two issues the reviewer attempted to fit the adult population PK model to the combined data for both studies 1 and 3 simultaneously. The concentration data from study 1 was richly sampled and fittings in WinNonlin confirmed that the 3 compartment, linear pharmacokinetic model predict the data best. Despite the rich data in 26 patients from study 1, the 3-compartment model parameters were not resolved with the data from study 1 alone, study 3 alone, study 1 and study 3 combined, or even from all the adult and pediatric data combined.

Over 60 NONMEM codes were run using the 3-compartment model structure with either study 1 data alone, study 1 and study 3 data combined, or all of the pediatric and adult data combined. Different initial estimates, parameter boundaries, and inclusion of different inter-subject variation parameters were tested. One error primarily prevented a final stable PK model. In most cases several of the parameters were estimated at their boundary. However, another issue evolved in that depending on the initial estimates the model would converge to different local minima meaning that the parameters at their boundary changed with different initial estimates. Boundaries were selected for each parameter based on both prior distribution of the standard-2-stage analysis and also with 10-100 fold increase or decrease from the initial parameter value.

The rich PK data from the 26 patients in study 1 was insufficient to produce a stable population PK model, when used alone or in combination with the other data. The stability of the model was confounded by the large number of model parameters (6 PK and 6 between-subject variability parameters) compared to the limited number of subjects.

No covariate relationships were explored without a stable population PK base model to work with and larger patient population. This step was not as critical as the sponsor made no claims about covariates in the pediatric population and demographics such as race and weight were not available for some of the subjects in the earlier studies.

4.4   Results

Review of the Sponsor's Label Statements

The labeling statements made by the sponsor are summarized by the following points:

- Pediatric PK from study 1 is similar to the Adult PK and pediatric PK parameter values are provided.

- Pediatric PK from study 3 is similar to the Adult PK and pediatric PK parameter values are reported.

Further, The sponsor's PK analysis for studies 1 and 3 showed that clearance values when adjusted for body surface area (relevant to dosing by body surface area) and AUC values for the same dose level were similar to that in adults (Figure 2).

Figure 2. Estimated Clearance divided by body surface area (top panel) and AUC (bottom panel) Values versus Age show Pharmacokinetics of Pediatrics are Similar

to that in Adults. Red circles represent pediatric values from studies 1 and 3. Black circles are values from the adult population PK analysis.
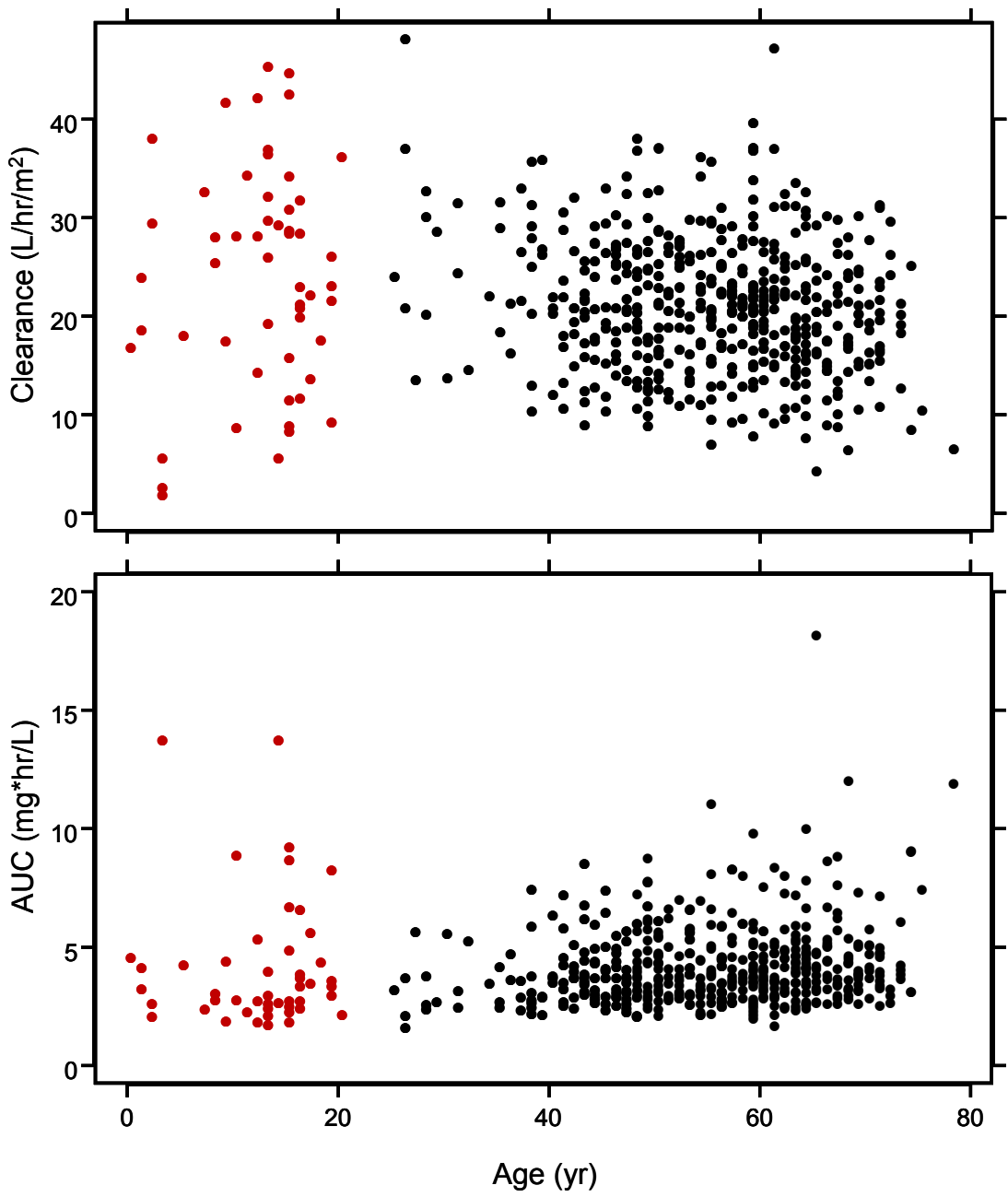
The FDA reviewer's analysis is consistent with sponsor's first conclusion, however the PK parameter values for second point will be adjusted based on the FDA's analysis.

A combination of two and three-compartment pharmacokinetic models fit the individual data from study 1 in WinNonlin well, but the 3-compartment model could not be run as a population analysis. Therefore, the pediatric versus adult PK comparison was considered for each study independently by standard-2-stage analysis. This comparison was also made by running the NONMEM code with the final estimates from WinNonlin fixed ("maxeval" option fixed to zero) only estimating between subject variation.

Standard-two-stage (STS) analysis for Study 1 using 2- and 3-compartment linear PK models indicated that the docetaxel PK clearance values for study 1 (mean 20.3, CV%=53.6) were similar to that from the population PK analysis in adults (mean 21.3, CV%=31.7). Not all the data fit a standard linear 3-compartment model, but since the aim was to identify clearance, AUC, and Vss, any number of compartments could be used as long as it was a linear, mamillary PK model. Therefore, a 2-CM model was fit to data from 4 individuals whose PK profiles contained less than three exponential phases.

The assumption that PK was similar between pediatrics and adults was tested for study 3 by an independent analysis from the adult data using NONMEM VI. Incorporating the WinNonlin pediatric PK values into the NONMEM 3-compartment PK model and running this (estimating only between subject variation) yielded different PK between the pediatric and adult patients (Table 3).

Table 3. Docetaxel Pharmacokinetic Parameters in Pediatric and Adult Patients

PK Parameter	Descriptor	WinNonlin (2,3CM) Study 1	NONMEM Study 3 Values	Adult PopPK Values
CL ($L/hr/m^2$)	Geometric Mean	17.3	17.9	20.2
	Arithmetic Mean	20.3	19.9	21.3
	Standard Dev	10.9	8.75	6.76
	CV%	53.6	44.0	31.7
	Relative Std. Error %	10.7	8.32	1.29
AUC_{75mg} ($\mu g \cdot hr/mL$)	Geometric Mean	4.33	4.20*	3.62
	Arithmetic Mean	5.23	4.75*	3.82
	Standard Dev	3.61	2.57*	1.38
	CV%	69.0	54.1*	36.2
	Relative Std. Error	13.8	9.29*	5.07

*Predicted based on individual clearance values

The WinNonlin standard-2-stage analysis for study 1 can be used to independently verify that the PK of pediatrics is similar to that in adults because the data was rich. However, the data for study 3 was too sparse (3 samples per subject) to perform a standard-two-stage analysis and too few to perform a population analysis. Further since its model was conditioned on the adult population PK analysis this can introduce bias into the comparison between adult and pediatric data. The sampling scheme was too sparse to independently compare pediatric PK results from study 3 with the results from the adult data. It is therefore recommended that the labeling language for pediatric PK regarding study 3 be adjusted to reflect values determined from NONMEM using pediatric PK parameters from study 1 as priors for the NONMEM analysis.

Exposure-Response for Effectiveness of Docetaxel

Determining whether the PK is different between pediatric and adult populations is important to more than labeling. This also provides an answer to the question: Is the lack of efficacy observed in the pediatric trial due to differences in exposure between pediatrics and adults? At the 75 mg/m^2 dose, there is not expected to be a difference in exposure (Figure 2, bottom panel). This is primarily because patients are dosed by their

body surface area. While other doses were studied in adults, 75 mg/m^2 is the dose level recommended in the label for use. For evaluating whether differences in exposure were the underlying cause of lack of efficacy, development of an exposure-response relationship for efficacy was essential.

Development of an exposure-response relationship for effectiveness was hindered by two factors. 1) The sampling of PK in study 3 (the main pediatric efficacy study) was incomplete (28 of 50 docetaxel treated patients had evaluable PK data) and no covariates were identified to predict exposures in the other patients who received docetaxel. 2) There was a general lack of efficacy (complete responders) across the population. 1 of the 50 patients exhibited complete response (the primary endpoint) and 38 patients exhibited partial response. The rate of partial response was no different than the placebo group. Study 3 was the pivotal efficacy trial conducted in pediatric patients with nasopharyngeal carcinoma. Study 1 and 2 did not contain efficacy data from these patients.

Of the 21 patients with AUC values in study 3, 17 showed a partial response to the docetaxel-cisplatin-5flurouracil treatment. Figure 3 shows the percentage of patients partially responding against docetaxel concentrations.

Figure 3. No exposure-response relationship was evident from limited efficacy data. The mean % of patients partially responding is shown by symbols ± the 95% confidence interval for the binomial distribution. The control group (cisplatin and 5-fluorouracil) is shown in red, while the treatment group (docetaxel, cisplatin, and 5-fluorouracil) data are shown in black. The black bar at the bottom of the plot represent the quartiles of docetaxel AUC in the population with PK sampling. The numbers in the graph correspond to the number of partial responders/sample size for the respective groups (control, Q1, Q2, Q3, Q4)
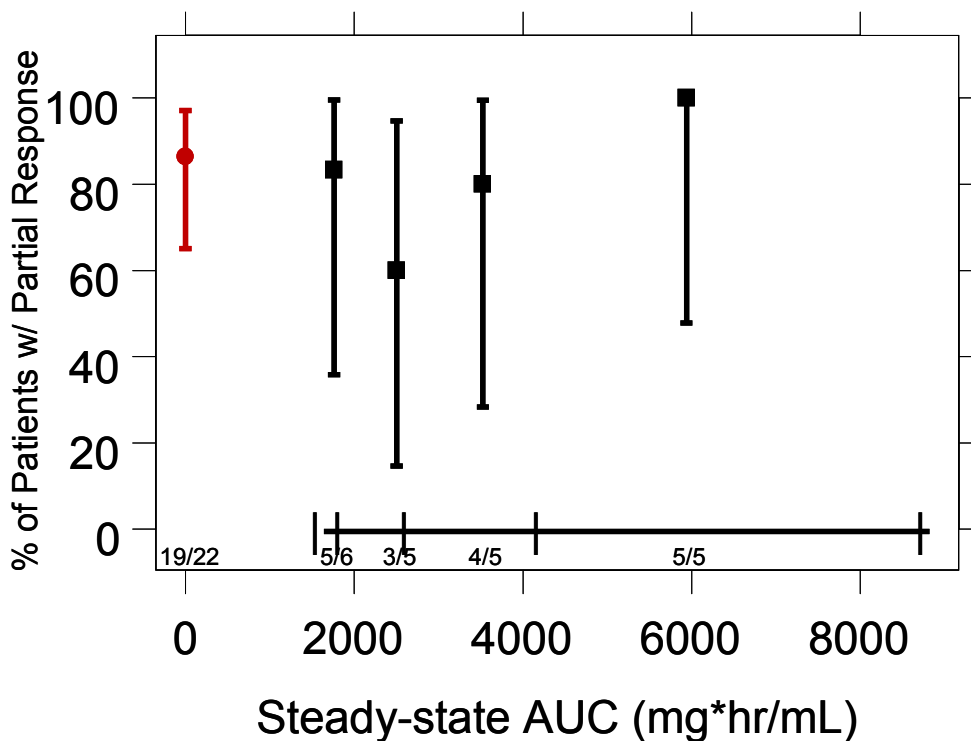
There is no evident exposure-response relationship for effectiveness from Figure 3. Note the small number of patients in each AUC quartile and large degree of variation in the secondary endpoint (partial overall response). There were 22 patients in the CF group and 21 patients in the TCF group with available PK data. For a logistic regression with binary data, these numbers are too small given the variation in the response to detect a signal in effectiveness. Further, a few exposures in the pediatric population surpassed that in the adult population. This combined with the similarity in PK between pediatrics and adults suggests that the range of exposures was sufficient to determine that lack of efficacy is not due to under-dosing in the pediatric population. It should finally be noted that the partial response was a secondary endpoint and does not reflect that rate of the primary endpoint (complete response).

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\ Docetaxol_NDA022049_S0059\
PedVsAdultCLPlot.ssc	Analysis Code for Figure 2 Top Panel	\PPK Analyses
PedVsAdultAUCobsPlot.ssc	Analysis Code for Figure 2 Bottom Panel	\PPK Analyses
TaxoterePPKValues.ssc	Analysis Code for Table 3: Pediatric	\PPK Analyses
TaxotereER.ssc	Analysis Code for Figure 3	\ER Analyses
modelfit_dir##/NM_run1/	Directory of All NONMEM Runs	\PPK Analyses\Codes & Output\Docetaxel Cluster NONMEM Runs
patab7	Directory of Final NONMEM Runs: Pediatric	\PPK Analyses\Final Model\modelfit_dirFinal\NM_run 1\
PKCheckFinal.ssc	Code to check PK Results	\PPK Analyses
TaxoterePopPK1.ssc	Plot to Compare Nonmem and Standard-2-stage approaches	\PPK Analyses
TaxoterePopPK2.ssc	Plot to Compare Nonmem and Standard-2-stage approaches	\PPK Analyses
PK Analysis Set.ssc	Code to Construct PK Datasets	\PPK Analyses
Taxotere3CM_WNLNEW.xls	Winnonlin Output for 3cm model with 1.y^ weighting	\PPK Analyses

4.3 Cover sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-449 S-059 (Pediatric)	**Brand Name**	Taxotere®
OCPB Division (I, II, III)	5	**Generic Name**	Docetaxel
Medical Division	OND/OODP/DDOP	**Drug Class**	Microtubule inhibitor
OCP Reviewer **PM Reviewer** **OCPB Team Leader** **PM Team Leader**	Joseph Grillo, Pharm.D. Justin Earp, Ph.D. Qi Liu, Ph.D. Christoffer Tornoe, Ph.D.	**Indication(s)**	• **Locally advanced or metastatic BC** • **Locally advanced or metastatic NSCLC** • **With prednisone for HRPC** • **With cisplatin and fluorouracil for untreated, advanced GC** • **With cisplatin and fluorouracil for induction treatment of locally advanced SCCHN**
		Dosage Form	**Injection Concentrate**
		Dosing Regimen	• **Adult: 60-100 mg/m2 depending on indication.** • ▓▓▓▓▓▓ **(b) (4)**
Date of Submission	11/13/2009	**Route**	1 hr Intravenous Infusion
Estimated Due Date of OCPB Review	3/12/2010	**Sponsor**	Sanofi-Aventis
PDUFA Due Date	5/13/2010	**Priority**	Priority Review
Division Due Date	4/13/2010		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			**Validation report for P2 submitted but report for P1 dose ranging study not submitted**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**	**3**		**The noncompartmental analysis dataset was not submitted for ARD6005. A request has been made to provide the full dataset.**
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**X**	**1**		**Only partial dataset was submitted in electronic format. A request has been made for the full PK dataset**
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Studies unrelated to indication				
Total Number of Studies		**4**		

<p align="center">**Filability and QBR comments**</p>

	"X" if yes	Comments
Application filable ?	**X**	
Comments sent to firm ?	**X**	• **Please submit docetaxel assay validation report for ARD6005** • **Please provide full dataset for noncompartmental analysis in ARD6005** • **Please provide full dataset for POP-PK analysis**
QBR questions (key issues to be considered)		1) **Do the NC and Pop-PK results support the dosing regimens proposed** 2) **Are there any significant covariates identified in the Pop-PK analysis that would affect the dosing regimens proposed** 3) **Are there any safety signals that are related to exposure, intrinsic factors, or extrinsic factors and can they be minimized with individualized dosing**

Other comments or information not included above	
Primary reviewer Signature and Date	**/s/ Joseph Grillo & Justin Earp 12/11/09**
Secondary reviewer Signature and Date	**/s/ Qi Liu & Christoffer Tornoe 12/11/09**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-20449	SUPPL-59	SANOFI AVENTIS US LLC	TAXOTERE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUSTIN C EARP
05/05/2010

JOSEPH A GRILLO
05/05/2010

QI LIU
05/05/2010

CHRISTINE E GARNETT
05/05/2010

NAM ATIQUR RAHMAN
05/11/2010