U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-449 / S-059
Drug Name:	Taxotere® (docetaxel) Injection Concentrate
Indication(s):	Pediatric solid tumors.
Applicant:	Sanofi-aventis U.S. LLC
Date(s):	Submitted: November 13, 2009
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Review Priority:	Priority
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Somesh Chattopadhyay, Ph.D.
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Keywords: Exact test, intent-to-treat, pediatric exclusivity, power, randomization, sample size.

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

In response to a Pediatric Written Request (PWR), the applicant submitted results from three pediatric studies – a dose finding Phase I study of Taxotere monotherapy (ARD6005), a Phase 2 single-arm study to determine the response rate and safety of Taxotere monotherapy (ARD6006) and a randomized study to evaluate the addition of Taxotere to the combination of cisplatin and 5-fluorouracil (CF) in the induction treatment of nasopharyngeal carcinoma (NPC). The applicant sought only pediatric exclusivity based on this application and did not seek any pediatric indication. In the single-arm Phase 2 study, Taxotere monotherapy showed a poor response rate. In the randomized study the addition of Taxotere to CF did not show any statistically significant improvement in the primary efficacy endpoint complete response rate and the results for the secondary efficacy endpoints including overall survival were not submitted. The statistical results do not provide any support for efficacy of Taxotere therapy in pediatric patients. Based on the current application the Pediatric Review Committee determined that the applicant met the conditions in the PWR and pediatric exclusivity has been granted on March 17, 2010.

1.2. Brief Overview of Clinical Studies

This application is based on three pediatric studies – one Phase 1 study (ARD6005) and two Phase 2 studies (ARD6006 and EFC10339). Studies ARD6005 and ARD6006 were conducted by Children's Oncology Group (COG). The applicant conducted the study EFC10339.

Study 1 (ARD6005) was a dose finding Phase I study of Taxotere monotherapy in patients with relapsed/refractory solid tumors, including pharmacokinetics, with doses determined for all appropriate age groups. This dose finding and dose escalation study was conducted from 7 January 1993 to 17 September 1996 by a collaboration between Pediatric Branch of the National Cancer Institute and the Children's Oncology Group (COG). The objectives of this study were to determine the dose limiting toxicities (DLT), MTD, safety, and pharmacokinetics of escalating doses of Taxotere given as a 1-hour intravenous infusion.

Study 2 (ARD6006) was a Phase 2 single-arm study to determine the response rate and safety of Taxotere monotherapy in patients with relapsed/refractory Ewing sarcoma, rhabdosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, astrocytoma and other solid tumors. The study used a two-stage design within each of several disease categories. The primary efficacy endpoint was response rate. The secondary efficacy endpoint was overall survival.

Study 3 (EFC10339) was an international, open-label, randomized study in children and adolescents (age > 1 month and ≤ 21 years) with nasopharyngeal carcinoma (NPC). Patients

were randomized in a 2:1 ratio to Taxotere + cisplatin + 5-fluorouracil (TCF) or to Cisplatin + 5-fluorouracil (CF). Treatment consisted of an induction and consolidation period for both arms. Together, the treatment periods consisted of 18 weeks (9 weeks induction and 9 weeks consolidation). The primary endpoints was complete response (CR) rate at the completion of induction therapy (3 cycles) in all randomized patients. The secondary endpoints were overall response rate (ORR) at the completion of consolidation treatment and overall survival (OS).

1.3. Statistical Issues and Findings

Statistical Issues:

Study ARD6006

1. The study enrolled more disease categories than that are listed in the Pediatric Written Request.
2. Although for each disease category 10 patients were to be enrolled in the second stage if there was at least one response in the 10 patients in the first stage of that disease category, the study did not enroll all 10 second stage patients in rhabdomyosaroma and undifferentiated sarcoma (a response was observed in the 10^{th} enrolled patient in that disease category). On the other hand, the study enrolled total 21 patients in the Ewing sarcoma category although there was no response in the first 10 enrolled patients; a response was observed in the 16^{th} enrolled patient. Also in neuroblastoma, the enrollment did not stop after 10 patients; the 11^{th} enrolled patient showed a response in this category. Some of theses problems may have occurred due to reclassification of patients different disease categories after completion of the study.
3. The Study ARD6006 had already been completed before the Pediatric Written Request was issued.

Study EFC10339

1. The study was not properly powered to detect a meaningful difference. The interpretation of the above sample size calculation is that with 72 patients randomized in a 2:1 ratio, the TCF arm will show numerically better CR rate than that in the CF arm with 85% probability if the true underlying (unknown) CR rates for TCF and CF arms are 0.31 and 0.2, respectively. This sample size would have only about 25% power to detect a difference of 31% CR rate in the TCF arm vs. 20% CR rate in the CF arm with a 2 sided type I error rate of 0.05 and a 2:1 randomization ratio.

2. The submission did not provide any results or data for secondary efficacy endpoints. The applicant stated that the analyses of the secondary endpoints will be performed at completion of 3-year follow-up of the last patient. These results will be submitted in a revised clinical study report.

Findings:

The study ARD6006 enrolled 178 patients of which 174 were treated. There were 1 complete response and 4 partial responses. The Complete response was observed in a patient with undifferentiated sarcoma. One partial response was observed in each of the following disease categories: Ewing sarcoma, osteosarcoma, neuroblastoma and other (squamous cell carcinoma of the neck and mediastinum). The overall response rate all enrolled patients was 2.81% with an exact 95% confidence interval (0.92%, 6.43%).

The study EFC10339 randomized a total of 75 patients – 50 to the Taxotere-containing arm and 25 to the CF arm. There was only 1 complete response in TCF arm and no complete response in the CF arm. The partial response rates on 76% in the TCF arm and 80% in the CF arm are comparable. The 2-sided p-value for the comparison of CR rate using the Fisher's exact test is 1.00. The tumor response after induction therapy and the comparison of CR rate using Fisher's exact test are presented in Table 1.

Table 1: Overall Tumor Response after Induction Therapy in Study EFC10339

	Randomization Group					
	TCF (N=50)		**CF (N=25)**		**All (N=75)**	
Complete Response	1	(2%)	0	(0%)	1	(1.33%)
Partial Response	38	(76%)	20	(80%)	58	(77.33%)
Stable Disease	6	(12%)	2	(8%)	8	(10.67%)
Progressive Disease	2	(4%)	0	(0%)	2	(2.67%)
Unknown	1	(2%)	0	(0%)	1	(1.33%)
Missing	2	(4%)	3	(12%)	5	(6.67%)
P-value[1] for CR rate	1.00					

[1]: Using 2-sided Fisher's exact test.

2. INTRODUCTION

2.1. Overview

Nasopharyngeal carcinoma is a carcinoma of epidermoid origin that differs from other predominantly adult head and neck carcinomas by its very distinct histologic, epidemiologic, and biologic characteristics. Three histologic subtypes of NPC are recognized: Type I, or keratinizing squamous cell carcinoma, which is similar to carcinomas that arise from other head and neck sites; Type II, or non-keratinizing squamous cell carcinoma; and Type III, or undifferentiated carcinoma (also called "lymphoepithelioma"), which is the most common form of the disease. Nasopharyngeal carcinoma overall is very rare in children, and the National Institutes of Health recognizes it as a rare tumor in the US.

2.1.1. Background

Taxotere (docetaxel), 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.

Taxotere is approved in adult population for (1) monotherapy and as combination chemotherapy for metastatic or locally advanced breast cancer, (2) as combination chemotherapy for adjuvant treatment of operable node positive breast cancer, (3) as monotherapy and combination chemotherapy for locally advanced or metastatic non-small cell lung cancer, (4) in combination with prednisone for the hormone-refractory prostate cancer, (5) in combination with cisplatin and 5-fluorouracil for locally advanced or metastatic gastric cancer and (6) in combination with cisplatin and 5-fluorouracil for induction treatment of locally advanced squamous cell carcinoma of the head and neck.

On January 31, 2007 the applicant submitted a Proposed Pediatric Study Request (PPSR) to FDA. A formal Pediatric Written Request (PWR) was sent to the applicant on June 11, 2007. In the PWR three studies were requested and the written reports of those studies were to be submitted on or before February 12, 2010. The applicant submitted the NDA supplement containing the reports of the requested studies on November 13, 2009.

2.1.2. Specific Studies Reviewed

This application is based on three pediatric studies – one Phase 1 study (ARD6005) and two Phase 2 studies (ARD6006 and EFC10339).

Study 1 (ARD6005) titled "A Phase I study of Taxotere in pediatric patients with advanced neoplastic disease" was a dose finding Phase I study of Taxotere monotherapy in patients with relapsed/refractory solid tumors, including pharmacokinetics, with doses determined for all appropriate age groups. This dose finding and dose escalation study was conducted from 7

January 1993 to 17 September 1996 by a collaboration between Pediatric Branch of the National Cancer Institute and the Children's Oncology Group (COG). The objectives of this study were to determine the dose limiting toxicities (DLT), MTD, safety, and pharmacokinetics of escalating doses of Taxotere given as a 1-hour intravenous infusion. Refer to the clinical, clinical pharmacology and pharmacometrics reviews of this study for the details.

Study 2 (ARD6006) titled "A Phase 2 study of docetaxel (Taxotere®) in children with recurrent solid tumors" was a Phase 2 single-arm study conducted by COG to determine the response rate and safety of Taxotere monotherapy in patients with relapsed/refractory Ewing sarcoma, rhabdosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, astrocytoma and other solid tumors.

Study 3 (EFC10339) titled "International randomized study to evaluate the addition of docetaxel to the combination of cisplatin-5-fluorouracil (TCF) vs. cisplatin-5-fluorouracil (CF) in the induction treatment of nasopharyngeal carcinoma (NPC) in children and adolescents" was conducted by the applicant.

This review specifically focuses on studies ARD6006 and EFC10339. Study ARD6006 enrolled 178 patients of which 174 were treated. Study EFC10339 randomized a total of 75 patients – 50 to the Taxotere-containing arm and 25 to the CF arm.

2.2. Data Sources

Data used for this review are from the electronic submission dated November 13, 2009. The path is \\Cdsesub1\EVSPROD\NDA020449\0016\m5\datasets.

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

This application is based on three pediatric studies – one Phase 1 study (ARD6005) and 2 Phase 2 studies (ARD6006 and EFC10339). This review specifically focuses on studies ARD6006 and EFC10339. For the details of study ARD6005, refer to the clinical, clinical pharmacology and pharmacometrics reviews.

3.1.1. Study ARD6006 (Study 2)

3.1.1.1. Study Objectives

- To determine the response rate of Taxotere in various strata of recurrent solid tumors of childhood.
- To further assess the toxicity of Taxotere in a larger group of patients treated at the currently defined maximum tolerated dose (MTD).

3.1.1.2. Study Design

This was a single-arm Phase 2 study in pediatric patients with advanced neoplastic disease. Patients were to be premedicated with 2 doses of dexamethasone (each 3 mg/m2 oral or intravenous) 12 hours and 6 hours prior to the Taxotere administration, and with diphenhydramine (1 mg/kg) 30 minutes prior to the Taxotere administration. The dose of Taxotere was 125 mg/m^2 once every 21 days as a 1-hour intravenous infusion, for a maximum of 12 doses.

Taxotere was to be evaluated in the following target tumor categories:

- Sarcomas (rhabdomyosarcoma, Ewing's sarcoma, peripheral neuroectodermal tumor [PNET])
- Osteosarcoma
- Brain tumors (ependymoma, PNET, high grade astrocytoma, brain stem glioma)
- Neuroblastoma
- Other soft tissue sarcomas

Patients with other histologic diagnoses were also enrolled.

The study used a 2-stage design within each disease category. A maximum of 20 patients were to be enrolled to each target category. In the first stage, 10 patients were enrolled, treated, and evaluated. If no patient in a particular category demonstrated a complete response (CR) or partial response (PR) in the first stage, Taxotere was considered ineffective, and category accrual was terminated. If one or more patients in a particular category achieved a CR or PR in the first stage, Taxotere efficacy was considered indeterminate, and the study entered a second stage in which

10 patients were enrolled. If 2 or fewer patients out of 20 evaluable patients in a particular category demonstrated a CR or PR, Taxotere was determined ineffective. If 3 or more patients out of 20 evaluable patients in a category achieved CR or PR, Taxotere was determined effective in that category. If the true response rate of Taxotere was 30%, then Taxotere was to be identified as effective in a particular disease category with a probability of 95%.

Reviewer's Comment:

The study enrolled more disease categories than that are listed in the Pediatric Written Request. The Study ARD6006 had already been completed before the Pediatric Written Request was issued.

3.1.1.3. Efficacy Endpoints

The primary efficacy endpoint was response rate. Enrolled patients who received study drug for at least 14 days and did not receive other anticancer therapy were considered to be evaluable for response. Patients who died from complications related to Taxotere before Day 28 were considered to be nonresponders. Patients who died prior to Day 28 who were otherwise evaluable were considered to be nonresponders. Radodiologic assessments were done at baseline and following doses 2, 4, 6 , 8, 10 and 12 using the same method (CT or MRI) as used at the baseline. Two evaluations separated by 2 Taxotere doses were required to identify protocol defined complete and partial responses.

The secondary efficacy endpoint was overall survival, which was calculated as the time from enrollment to death or last contact.

Reviewer's Comment:

Time-to-event endpoints are not meaningful in a single-arm study. Therefore the analysis and results of overall survival from this study will not be discussed further in this review.

3.1.1.4. Sample Size Considerations

The study used a two stage design. According to the study design, at least 10 patients and a maximum of 20 patients were to be enrolled. The study actually enrolled 178 patients in total and 104 patients in the disease categories listed in the Pediatric Written Request. Table 2 provides the number of patients enrolled in each disease category. Table 3 provided the number of patients enrolled in each disease category listed in the Pediatric Written Request.

Table 2: Enrollment in Different Disease Categories in Study ARD6006

Disease Category	Number of Patients Enrolled
Astrocytoma	14
Brain stem tumors	12
Ependymoma	11
Ewing's tumor	21
Kidney tumors	9
Liver tumors	7
Medulloblastoma	20
Mixed gliomas	6
Neuroblastoma	13
Osteosarcoma	23
Rhabdomyosarcoma	9
Soft tissue sarcoma	14
Other	19
Total	178

Table 3: Enrollment in Different Disease Categories Listed in the Pediatric Written Request for Study 6006

Disease Category	Number of Patients Enrolled
Ewing sarcoma	21
Rhabdomyosarcoma and undifferentiated sarcoma	13
Osteosarcoma	23
Neuroblastoma	13
Medulloblastoma	20
Astrocytoma	14
Total	104

Reviewer's Comment:

Although for each disease category 10 patients were to be enrolled in the second stage if there was at least one response in the 10 patients in the first stage of that disease category, the study did not enroll all 10 second stage patients in rhabdomyosaroma and undifferentiated sarcoma (a response was observed in the 10^{th} enrolled patient in that disease category). On the other hand, the study enrolled total 21 patients in the Ewing sarcoma category although there was no response in the first 10 enrolled patients; a response was observed in the 16^{th} enrolled patient. Also in neuroblastoma, the enrollment did not stop after 10 patients; the 11^{th} enrolled patient showed a response in this category. Some of theses problems may have occurred due to reclassification of patients different disease categories after completion of the study.

3.1.1.5. Sponsor's Results and FDA Statistical Reviewer's Findings/Comments

The demographic characteristics of the patients are given in Table 4.

Table 4: Demographic Characteristics: Gender, Race and Age at Enrollment for Study ARD6006

		All Enrolled Patients (N=178)		In Disease Categories Listed in PWR (N=104)	
Gender	Female	68	(38.20%)	40	(38.46%)
	Male	110	(61.80%)	64	(61.54%)
Race	White	110	(61.80%)	63	(60.58%)
	Hispanic	32	(17.98%)	19	(18.27%)
	Black	24	(13.48%)	15	(14.42%)
	Oriental	5	(2.81%)	2	(1.92%)
	Native American	4	(2.25%)	2	(1.92%)
	Indian Subcontinent	1	(0.56%)	1	(0.96%)
	Other	2	(1.12%)	2	(1.92%)
Age in Years	Mean, SD	11.27, 5.74		12.31, 5.71	
	Min, Max	1, 26		1, 26	
	Q1, Median, Q3	6, 12, 16		7.5, 13, 17	

There were 1 complete response and 4 partial responses. The Complete response was observed in a patient with undifferentiated sarcoma. One partial response was observed in each of the following disease categories: Ewing sarcoma, osteosarcoma, neuroblastoma and other (squamous cell carcinoma of the neck and mediastinum). The overall response rate all enrolled patients was 2.81% with an exact 95% confidence interval (0.92%, 6.43%).

Reviewer's Comment:

Taxotere monotherapy in this study did not demonstrate efficacy as per protocol specification.

3.1.2. Study EFC10339

3.1.2.1. Study Objectives

The primary objective of this study was to compare the complete response rate after 9-week induction therapy in the patients with nasopharyngeal carcinoma (NPC) between the arm receiving Taxotere, cisplatin and 5-fluorouracil (TCF) and the arm receiving cisplatin and 5-fluorouracil (CF).

The secondary objectives of the study were:

- To determine the safety of TCF in comparison to CF after the induction treatment of NPC
- To determine the pharmacokinetics (PK) of Taxotere when added to CF
- To determine the overall response (OR) rate of TCF and CF on completion of consolidation (chemoradiotherapy) treatment of NPC
- To compare the overall survival between TCF and CF.

3.1.2.2. Study Design

This was an international, open-label, randomized study in children and adolescents (age > 1 month and ≤ 21 years) with nasopharyngeal carcinoma (NPC). Patients were randomized in a 2:1 ratio to the following two arms:

- TCF: Taxotere + cisplatin + 5-fluorouracil
- CF: Cisplatin + 5-fluorouracil.

Treatment consisted of an induction and consolidation period for both arms. Together, the treatment periods consisted of 18 weeks (9 weeks induction and 9 weeks consolidation). Once the consolidation treatment was completed, patients were to be followed for 3 years. Inclusion criteria included newly diagnosed Stage IIB-IV NPC with measurable disease.

Induction period consisted of three 21-day treatment cycles. The regimens for the induction period were as follows:
Experimental regimen (TCF):

- Taxotere 75 mg/m^2 intravenously (IV) over 1 hour on Day 1 every 3 weeks in combination with:
- Cisplatin 75 mg/m^2 IV Day 1 over 6 hours every 3 weeks and
- Fluorouracil 750 mg/m2/day IV continuous infusion (CI) Day 1–4 every 3 weeks.

Control regimen (CF):

- Cisplatin 80 mg/m^2 IV Day 1 over 6 hours every 3 weeks
- Fluorouracil 1000 mg/m^2/day IV continuous infusion Day 1-4 every 3 weeks

The consolidation period consisted of radiotherapy (RT) plus three 21 day cycles of cisplatin administered concurrently, which began on weeks 10, 13, and 16. All patients on both arms were to receive RT for 6 weeks and cisplatin 100 mg/m^2 every 21 days for 3 cycles.

3.1.2.3. Efficacy Endpoints

<u>Primary endpoint</u>:

- Complete response (CR) rate at the completion of induction therapy (3 cycles) in all randomized patients

Secondary endpoints:

- Overall Response Rate (ORR) at the completion of consolidation treatment
- Overall Survival (OS)

The Investigator and the IRC assessed all relevant data to determine individual patient disease progression and response according to a modified version of the Response Evaluation Criteria in Solid Tumors (RECIST). The modifications included a volumetric measurement of primary NPC and bi-dimensional assessment of associated adenopathy.

Complete response was defined as the complete disappearance of the target and non-target lesions after radiological evaluation and on completion of induction therapy (3 cycles).

3.1.2.4. Sample Size Considerations

Assuming a CR rate of 31% in the TCF arm and a CR rate of 20% in the CF arm after 3 cycles of induction chemotherapy, 72 patients would be needed to correctly select a treatment arm with the best CR rate with 85% probability. The study actually randomized 75 patients.

Reviewer's Comment:

The study was not properly powered to detect a meaningful difference. The interpretation of the above sample size calculation is that with 72 patients randomized in a 2:1 ratio, the TCF arm will show numerically better CR rate than that in the CF arm with 85% probability if the true underlying (unknown) CR rates for TCF and CF arms are 0.31 and 0.2, respectively. This sample size would have only about 25% power to detect a difference of 31% CR rate in the TCF arm vs. 20% CR rate in the CF arm with a 2 sided type I error rate of 0.05 and a 2:1 randomization ratio.

3.1.2.5. Efficacy Analysis Methods

Analyses of the primary and secondary endpoints were to be conducted in the intent-to-treat (ITT) population which is defined as all randomized patients.

The Fisher's exact test was used to compare proportions although the study was not designed to prove the difference is statistically significant. Kaplan-Meier method was to be used to analyze OS. A log-rank test was to be used to compare OS between two arms. The hazard ratio between two arms with 95% confidence interval was to be calculated using a Cox proportional hazards model.

Reviewer's Comment:

The submission did not provide any results or data for secondary efficacy endpoints. The applicant stated that the analyses of the secondary endpoints will be performed at completion of 3-year follow-up of the last patient. These results will be submitted in a revised clinical study report.

3.1.2.6. Sponsor's Results and FDA Statistical Reviewer's Findings/Comments

The baseline demographic characteristics (gender, race and age) are presented in Table 5. Two arms were balanced with respect to all demographic characteristics.

Table 5: Demographic Characteristics for Study EFC10339: Gender, Race and Age at Randomization in the ITT Population

		TCF (N=50)	CF (N=25)	All (N=75)
Gender	Female	15 (30%)	6 (24%)	21 (28%)
	Male	35 (70%)	19 (76%)	54 (72%)
Race	Asian/Oriental	13 (26%)	9 (36%)	22 (29.33%)
	Black	2 (4%)	0 (0%)	2 (2.67%)
	White	32 (64%)	16 (64%)	48 (64%)
	Other	3 (6%)	0 (0%)	3 (4%)
Age in Years at Randomization	Mean, SD	15.12, 2.52	15.68, 3.25	15.31, 2.78
	Min, Max	9, 21	9, 21	9, 21
	Q1, Median, Q3	14, 16, 17	13, 16, 19	13, 16, 17

The tumor response after induction therapy and the comparison of CR rate using Fisher's exact test are presented in Table 6. There was only 1 complete response in TCF arm and no complete response in the CF arm. The partial response rates on 76% in the TCF arm and 80% in the CF arm are comparable. The 2-sided p-value for the comparison of CR rate using the Fisher's exact test is 1.00.

Table 6: Overall Tumor Response after Induction Therapy in Study EFC10339

	Randomization Group				All (N=75)	
	TCF (N=50)		CF (N=25)			
Complete Response	1	(2%)	0	(0%)	1	(1.33%)
Partial Response	38	(76%)	20	(80%)	58	(77.33%)
Stable Disease	6	(12%)	2	(8%)	8	(10.67%)
Progressive Disease	2	(4%)	0	(0%)	2	(2.67%)
Unknown	1	(2%)	0	(0%)	1	(1.33%)
Missing	2	(4%)	3	(12%)	5	(6.67%)
P-value[1] for CR rate	1.00					

[1]: Using 2-sided Fisher's exact test.

Reviewer's comments:

1. CR rates were not statistically different between two arms. CR rate was very low in both arms and their numerical difference was also very small. Addition of Taxotere to cisplatin and 5-fluorouracil regimen in the induction therapy for nasopharyngeal carcinoma in pediatric patients was not beneficial.

2. As stated earlier, the data and results for the secondary endpoints were not submitted in the submission. Those results will be submitted in a revised report after completion of 3-year follow up of the last patient.

3.2. Evaluation of Safety

For safety evaluation, please refer to the clinical review of this application.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race and Age

All studies submitted in the application were small pediatric studies. The overall response rate in study ARD6006 was small (2.81%). Therefore gender, race specific subgroups do not show any differences. The response rate in different subgroups are shown in

Table 7: Subgroup Analysis of Response Rate by Gender and Race in ARD6006 Study

		All Enrolled Patients		
		N	**Number of Responses**	**Response Rate**
Gender	Female	68	2	(2.94%)
	Male	110	3	(2.72%)
Race	White	110	3	(2.72%)
	Hispanic	32	0	(0%)
	Black	24	2	(8.33%)
	Oriental	5	0	(0%)
	Native American	4	0	(0%)
	Indian Subcontinent	1	0	(0%)
	Other	2	0	(0%)

Also, in study EFC10339, the CR rate is very small in both arms (2% in TCF vs. 0% in CF). There is only one patient with complete response in the whole study; that patient was randomized to TCF arm. Therefore, gender, race and age specific subgroups do not show any differences also in this case.

4.2. Other Special/Subgroup Populations

No other special population has been identified.

5. SUMMARY AND CONCLUSIONS

The applicant submitted results from three pediatric studies in response to a Pediatric Written Request. The application sought only pediatric exclusivity but did not seen any pediatric indication for Taxotere.

Study 1 (ARD6005) was a dose finding Phase I study of Taxotere monotherapy in patients with relapsed/refractory solid tumors, including pharmacokinetics, with doses determined for all appropriate age groups. This dose finding and dose escalation study was conducted from 7 January 1993 to 17 September 1996 by a collaboration between Pediatric Branch of the National Cancer Institute and the Children's Oncology Group (COG). The objectives of this study were to determine the dose limiting toxicities (DLT), MTD, safety, and pharmacokinetics of escalating doses of Taxotere given as a 1-hour intravenous infusion.

Study 2 (ARD6006) was a Phase 2 single-arm study to determine the response rate and safety of Taxotere monotherapy in patients with relapsed/refractory Ewing sarcoma, rhabdosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, astrocytoma and other solid tumors. The study used a two-stage design within each of several disease categories. The primary efficacy endpoint was response rate. The secondary efficacy endpoint was overall survival. The study enrolled 178 patients of which 174 were treated. There were 1 complete response and 4 partial responses. The Complete response was observed in a patient with undifferentiated sarcoma. One partial response was observed in each of the following disease categories: Ewing sarcoma, osteosarcoma, neuroblastoma and other (squamous cell carcinoma of the neck and mediastinum). The overall response rate all enrolled patients was 2.81% with an exact 95% confidence interval (0.92%, 6.43%).

Study 3 (EFC10339) was an international, open-label, randomized study in children and adolescents (age > 1 month and ≤ 21 years) with nasopharyngeal carcinoma (NPC). Patients were randomized in a 2:1 ratio to Taxotere + cisplatin + 5-fluorouracil (TCF) or to Cisplatin + 5-fluorouracil (CF). Treatment consisted of an induction and consolidation period for both arms. Together, the treatment periods consisted of 18 weeks (9 weeks induction and 9 weeks consolidation). The primary endpoints was complete response (CR) rate at the completion of induction therapy (3 cycles) in all randomized patients. The secondary endpoints were overall response rate (ORR) at the completion of consolidation treatment and overall survival (OS). The study randomized a total of 75 patients – 50 to the Taxotere-containing arm and 25 to the CF arm. There was only 1 complete response in TCF arm and no complete response in the CF arm. The partial response rates on 76% in the TCF arm and 80% in the CF arm are comparable. The 2-sided p-value for the comparison of CR rate using the Fisher's exact test is 1.00.

5.1. Statistical Issues and Collective Evidence

Study ARD6006

1. The study enrolled more disease categories than that are listed in the Pediatric Written Request.
2. Although for each disease category 10 patients were to be enrolled in the second stage if there was at least one response in the 10 patients in the first stage of that disease category, the study did not enroll all 10 second stage patients in rhabdomyosaroma and undifferentiated sarcoma (a response was observed in the 10^{th} enrolled patient in that disease category). On the other hand, the study enrolled total 21 patients in the Ewing sarcoma category although there was no response in the first 10 enrolled patients; a response was observed in the 16^{th} enrolled patient. Also in neuroblastoma, the enrollment did not stop after 10 patients; the 11^{th} enrolled patient showed a response in this category. Some of theses problems may have occurred due to reclassification of patients different disease categories after completion of the study.
3. The Study ARD6006 had already been completed before the Pediatric Written Request was issued.

Study EFC10339

1. The study was not properly powered to detect a meaningful difference. The interpretation of the above sample size calculation is that with 72 patients randomized in a 2:1 ratio, the TCF arm will show numerically better CR rate than that in the CF arm with 85% probability if the true underlying (unknown) CR rates for TCF and CF arms are 0.31 and 0.2, respectively. This sample size would have only about 25% power to detect a difference of 31% CR rate in the TCF arm vs. 20% CR rate in the CF arm with a 2 sided type I error rate of 0.05 and a 2:1 randomization ratio.
2. The submission did not provide any results or data for secondary efficacy endpoints. The applicant stated that the analyses of the secondary endpoints will be performed at completion of 3-year follow-up of the last patient. These results will be submitted in a revised clinical study report.

5.2. Conclusions and Recommendations

In response to a Pediatric Written Request (PWR), the applicant submitted results from three pediatric studies – a dose finding Phase I study of Taxotere monotherapy (ARD6005), a Phase 2 single-arm study to determine the response rate and safety of Taxotere monotherapy (ARD6006) and a randomized study to evaluate the addition of Taxotere to the combination of cisplatin and 5-fluorouracil (CF) in the induction treatment of nasopharyngeal carcinoma (NPC). The applicant sought only pediatric exclusivity based on this application and did not seek any pediatric indication. In the single-arm Phase 2 study, Taxotere monotherapy showed a poor response rate. In the randomized study the addition of Taxotere to CF did not show any statistically significant improvement in the primary efficacy endpoint complete response rate and the results for the secondary efficacy endpoints including overall survival were not submitted.

The statistical results do not provide any support for efficacy of Taxotere therapy in pediatric patients. Based on the current application the Pediatric Review Committee determined that the applicant met the conditions in the PWR and pediatric exclusivity has been granted on March 17, 2010.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Somesh Chattopadhyay, Ph.D.
Date: May 5, 2010

Concurring Reviewer(s): Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Acting Director

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

cc:
HFD-150/Ms. Skarupa
HFD-150/Dr. Kristen Snyder
HFD-150/Dr. Ke Liu
HFD-711/Dr. Somesh Chattopadhyay
HFD-711/Dr. Shenghui Tang
HFD-711/Dr. Rajeshwari Sridhara
HFD-700/Ms. Lilian Patrician

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

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/s/

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05/05/2010

SHENGHUI TANG
05/05/2010

RAJESHWARI SRIDHARA
05/05/2010