CLINICAL REVIEW

Application Type	Commercial
Application Number(s)	NDA 20-449 S-059
Priority or Standard	Priority
Submit Date(s)	November 13, 2009
Received Date(s)	November 13, 2009
PDUFA Goal Date	May 13, 2010
Division / Office	DDOP/OODP
Reviewer Name(s)	Kristen M. Snyder, MD
Clinical Team Leader	Ke Liu, MD, PhD
Review Completion Date	May 3, 2010
Established Name	Docetaxel
(Proposed) Trade Name	TAXOTERE®
Therapeutic Class	Inhibitor of microtubule depolymerization
Applicant	sanofi-aventis
Formulation(s)	Intravenous injection
Dosing Regimen	Not applicable
Indication(s)	none
Intended Population(s)	none

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that the Pediatric Exclusivity be granted for TAXOTERE and the pediatric information be included in the TAXOTERE labeling.

My recommendation is based on the review finding that the Applicant *fairly*, although not completely, responded to the Pediatric Written Request.

- A randomized trial (EFC10339) conducted according to the PWR demonstrated the lack of efficacy of adding TAXOTERE to the induction regimen with cisplatin and 5-FU in the treatment of pediatric patients with nasopharyngeal carcinoma. This information contained in the revised TAXOTERE labeling will be beneficial to physicians and should be made available to the healthcare community.

- Although four deficiencies were identified in which the Applicant did not completely meet the requirements set forth in the PWR, these deficiencies as listed below would not change the overall conclusion that TAXOTERE did not have overall benefits in the treatment of pediatric population including a variety of different solid tumors.
    - Lack of data regarding race of the patients enrolled on Study 1 (ARD6005)
    - Failure to enroll an adequate number of patients within neuroblastoma category and undifferentiated sarcoma and rhabdomyosarcoma category in Study 2 (ARD6006) as stated in the PWR.
    - Failure in collecting time to toxicity resolution data for Study 2 (ARD6006)
    - Failure of submission to include all Study 3 (EFC10339) data

1.2 Risk Benefit Assessment

Risk profile of TAXOTERE in pediatric population appears to be similar to that of adult population. However, this submission provided no evidence of efficacy for TAXOTERE in the pediatric population. Therefore, the risks associated with TAXOTERE use in the pediatric population are without benefit and such a use is not recommended.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Docetaxel

Proprietary Name: TAXOTERE®

Applicant: sanofi-aventis U.S. LLC
55 Corporate Drive
Bridgewater, NJ 08807

Pharmacological Class: microtubule depolymerizing agent

Proposed Indication: There is no proposed pediatric indication.

Proposed Dosage and Administration: There is no proposed dose or route of administration in pediatric patients.

2.2 Tables of Currently Available Treatments for Proposed Indications

There is no proposed indication in pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

TAXOTERE is available in 20 mg (0.5 mL) or 80 mg (2 mL) of docetaxel (anhydrous) forumation.

2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Docetaxel is approved for the following indications in adults: breast cancer, locally advanced or metastatic non-small cell lung cancer after platinum therapy failure, metastatic gastric cancer, hormone-refractory prostate cancer, and squamous cell carcinoma of the head and neck. However, there is no approved indication for the pediatric population.

Table 1 includes a brief regulatory history regarding the proposed pediatric development plan, Proposed Pediatric Study Request (PPSR), and issued Pediatric Written Request (PWR) for use of TAXOTERE in children with cancer.

Table 1: Pediatric Regulatory History

August 18, 2004	Meeting with legacy company Aventis and FDA to discuss Pediatric Written Request plan with regard to the use of TAXOTERE in pediatric patients with Ewing's Sarcoma, osteosarcoma, and chondrosarcoma. FDA stated the following: --No published study establishes kinetics of TAXOTERE alone in the pediatric population --Other solid tumor types should be included in a pediatric oncology clinical development plan
October 2006	TAXOTERE approved for use in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN) based progression-free survival.
December 11, 2006	Type C Meeting with sanofi-aventis to discuss revised PPSR --FDA advised that that new information regarding TAXOTERE would be required to support a Pediatric Written Request (PWR). Specifically, the two completed trials (two Phase 1 and one Phase 2) of TAXOTERE monotherapy in children would not alone support a PWR. -- FDA suggested that the sponsor pursue TAXOTERE in a combination setting including a randomized study that isolates the contribution of TAXOTERE. The sponsor proposes to conduct a randomized trial in pediatric patients with NPC comparing induction regimens of TAXOTERE + cisplatin + 5-FU (TCF) vs cisplatin + 5-FU (CF) with a primary endpoint of complete response (CR). --FDA advised the sponsor to submit a plan including background on current treatment for NPC and its

	epidemiology in the US and sparse PK sampling proposal for TAXOTERE --FDA asked that the PPSR include a plan to obtain PK data from all appropriate pediatric age groups representative for the population being studied --FDA stated that appropriate pediatric studies may be conducted outside of the US and Europe and should be well-designed and well-conducted.
February 2, 2007	PPSR received by the FDA
May 2007	FDA stated the PPSR dated January 31, 2007 was, in general, acceptable but asked sanofi-aventis to increase the sample size of the randomized study in children with Nasopharyngeal Carcinoma from 51 to 72 to increase the probability to 85% from the proposed 80%.
June 11, 2007	Formal Written Request issued to investigate the use of TAXOTERE in the treatment of children with cancer. --Deadline for submitting final study reports: February 12, 2010 --TAXOTERE patent 4814470 expiration date: May 14, 2010.
November 12, 2009	Submission of Supplemental New Drug Application to NDA 020449 to provide pediatric study reports for pediatric exclusivity determination. Proposed labeling changes to sections 8.4 Pediatric Use and 12.3 Human Pharmacokinetics.

Since the initial issuance of the PWR, the Applicant has not requested any amendments to the PWR and the FDA has not issues any revisions to the PWR.

2.6 Pediatric nasopharyngeal carcinoma (NPC) and its treatment

This submission contains a randomized international study to evaluate the addition of TAXOTERE to the combination of cisplatin and 5-fluorouracil (TCF) compared to cisplatin and 5-fluorouracil (CF) in the induction treatment of nasopharyngeal carcinoma (NPC) in children and adolescents.

Pediatric nasopharyngeal carcinoma (NPC) is extremely rare in pediatric patients. Approximately 3% of all NPCs occur in patients younger than 19 years of age. Although accounting for less than 1% of all pediatric cancers, it represents 20-50% of all nasopharyngeal malignancies in children.

NPC is categorized into two types: sporadic and endemic. Sporadic NPC is more common in the Western world, is more often WHO type I (keratinizing squamous cell carcinoma) and is thought to be associated to exposures such as

alcohol and tobacco. Endemic NPC is found most commonly in China, Southeast Asia, the Mediterranean basin and Alaskan Eskimos where the annual incidence can be as high as 80/100,000. In contrast, there is approximately 1 case per 100,000 in the US. The endemic form is typically WHO type II or III. Endemic NPC is associated with virological (Epstein-Barr virus), environmental and genetic risk factors. Nearly all cases in children are histologic type III and present at advanced stages of the disease (stage III or IV) [1].

When this randomized trial was designed, the standard of care for children and adolescents with NPC included induction therapy consisting of cisplatin and 5-fluorouracil every 21 days for four cycles followed by a total dose of radiation therapy of approximately 60 to 70 Gy. Historical five-year survival rates ranged from 45 to 52% in patients who received similar induction regimens of cisplatin with or without doxorubicin. The St. Jude NPC-1 protocol of methotrexate, cisplatin, 5-fluorouracil, and leucovorin administered every 21 days for four cycles achieved a complete response in 21 of 21 patients with long term survival seen in 20 of 21 patients.[2] Based on preliminary results of the St. Jude NPC-1 study, a Pediatric Oncology Group study treated patients with induction therapy of methotrexate, cisplatin, 5-fluorouracil, and leucovorin every 21 days for four cycles followed by radiation therapy of 61.2 Gy to the primary tumor and involved lymph nodes with additional radiation to other loco-regional sites. This regimen produced pre-radiation complete responses in 5/16 (31%) and partial responses in 10/16 (62.5%) patients with Stage III/IV disease. Following both chemotherapy and chemoradiation therapy, 11/16 (68.75%) of patients experienced a CR and 4/16 (25%) a PR. [3]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains the debarment certificate, sufficient datasets, and relevant CRFs. Overall quality and integrity of the submission is fair.

3.2 Compliance with Good Clinical Practices

According to the ethics sections of the submission:
1) The studies used as a basis for clinical data presented in the submission were conducted in compliance with Good Clinical Practices (GCP), as required by the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice.
2) The studies also meet the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Sponsor, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC.

3.3 Financial Disclosures

Financial disclosures for study EFC10339 are included in the submission. There were no clinical investigators with disclosable financial interests in this study. No investigators received significant payments of other sorts as defined in 21 CFR 54.2 (f). There were no clinical investigators whose financial disclosure information is missing or incomplete for the covered clinical study EFC 10339.

No financial disclosure is required for Study 1 ARD6005 (CCG-0927, CTEP T92-0084) or Study 2 ARD6006 (CCG-0962) as neither study is a covered clinical study under 21 CFR Part 54.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable.

4.2 Preclinical Pharmacology/Toxicology

Not applicable.

4.3 Clinical Pharmacology in Pediatric Patients

4.3.1 Mechanism of Action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

The following is excerpted from clinical pharmacologist's review:

"The pharmacokinetics of docetaxel in pediatrics was characterized from data collected in the phase 1 (docetaxel monotherapy) and randomized phase 2 (TCF combination) studies using PK modeling approach. The 3 pharmacokinetic parameters in pediatrics (AUC = 4.3 ug•hr/mL, CL=17 L/hr/m2) were comparable to those in adults. (AUC = 3.6 ug•hr/mL, CL=20 L/hr/m2)

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)."

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies submitted in support of NDA 20449 s-059 are shown in Table 2.

Table 2: TAXOTERE Pediatric Clinical Studies

Study **-Coordinating investigator (and center)** **-Number of centers**	**Objectives**	**Test product(s)** **-formulation** **-Dosage regimen** **-Route of administration**	**Number of patients** **-Total[a b c]** **-Gender[b] (M/F)** **-Race[b] (C/B/O)** **-Age[b] median (range)** **-Treatment group[b]**	**Diagnosis of patients**	**Duration of treatment**
ARD6005 National Cancer Institute 16 active centers Safety, efficacy, PK	To determine: - the maximum tolerated dose (MTD) and the dose-limiting toxicity of docetaxel -the incidence and severity of other toxicities -a safe and tolerable dose to be used in Phase 2 trials -a safe and tolerable dose for docetaxel when administered with granulocyte colony stimulating factor (G-CSF) -the pharmacokinetics (PK) of docetaxel -Open label study	-Docetaxel as a 1-hour intravenous (IV) infusion every 21 days - Heavily pretreated patients (3 or more prior chemotherapy regimens) - 55, 65, or 75 mg/m2. - Less heavily pretreated patients (did not receive prior central axis radiation therapy [skull, spine, pelvis, or ribs] and received ≤2 prior chemotherapy regimens) - 75, 100, 125 or 150 mg/m2. -Once the MTD was established in the less heavily pretreated patients, there was further dose escalation with the use of G-CSF. Patients in this arm were treated with 150, 185, or 235 mg/m2 docetaxel.	- 61 / 61 / 61 - 31 / 28 / 2 missing - not reported - 12.5 years (1-22) - Heavily pretreated group: 23 patients - Less heavily pretreated group: 21 patients - G-CSF group: 17 patients	Children with refractory malignancies	Doses were repeated every 21 days in the absence of dose related toxicity

		G-CSF was administered subcutaneously at a dose of 5 µg/kg/day starting ≥48 hours after the dose of docetaxel.			
BAY0008 (PK portion of ARD6005) National Cancer Institute PK	Same as ARD6005	Same as ARD6005	- 29 with PK data / 26 evaluable - 10 / 18 - not reported - 11 years (1-20) - Heavily pretreated group: 6 patients - Less heavily pretreated group: 9 patients - G-CSF group: 14 patients	Same as ARD6005	Same as ARD6005
ARD6006 Safety, efficacy	- To determine the response rate of docetaxel in various strata of recurrent solid tumors of childhood and to assess the toxicity of docetaxel in a larger group of patients treated at the currently defined MTD - Open-label Phase 2 study in pediatric patients with advanced neoplastic disease	Docetaxel 125 mg/m2 as a 1-hour IV infusion every 21 days	- 178 / 174 / 174 - 110/68 - 110/24/44 - 12 years (1-26) - Not applicable	Patients ≤21 years of age at first diagnosis, with measurable recurrent or refractory solid tumors in target disease categories with no more than 2 prior therapies, and not previously treated with paclitaxel or docetaxel	Doses were Repeated every 21 days as tolerated, up to a total of 12 doses
EFC10339 26 active centers Safety, efficacy, PK	*Primary objective* - complete response (CR) rate of TCF compared to CF in the induction treatment of nasopharyngeal carcinoma (NPC); *Secondary objectives* - safety of TCF in comparison to CF after induction treatment of NPC - PK of docetaxel when added to CF; - overall response (OR) rate of TCF and CF on completion of consolidation (chemoradiotherapy) treatment of NPC; and, - overall survival of TCF and CF. - Randomized, international, multicenter, open label, 2:1 ratio	<u>Induction treatment</u> Docetaxel 75 mg/m2 IV over 1 hour on day 1 every 3 weeks in combination with: Cisplatin 75 mg/m2 IV day 1 over 6 hours every 3 weeks and 5-Fluorouracil 750 mg/m2/day IV continuous infusion (CI) day 1 to 4 every 3 weeks <u>Induction treatment</u> Cisplatin 80 mg/m2 IV day 1 over 6 hours every 3 weeks 5-Fluorouracil 1000 mg/m2/day IV CI day 1 to 4 every 3 weeks <u>Consolidation Treatment (all patients)</u> RT for 7-8 weeks and 3 cycles of cisplatin 100 mg/m2 every 21 days.	- 75 / 75 / 75 (induction) - 54 / 21 - 48 / 2 / 25 - 16 years (9-21) - TCF: 50 patients - CF: 25 patients	Children and adolescents newly diagnosed with NPC Stage IIB-IV with measurable disease, >1 month to ≤21 years of age at the time of diagnosis	9 weeks of induction 9 weeks of chemoradiation Follow up of 3 years

a: enrolled; b: treated; c: completed study drug according to Investigator (end-of-treatment form).
M = male; F = female; C = Caucasian; B = Black; O = other; SD = standard deviation

5.2 Review Strategy

The main focus of this review is to evaluate whether the Applicant has successfully fulfilled the requirement set forth in the issued PWR for the eligibility determination on the pediatric exclusivity. To that end, all studies submitted in this supplement, ECF10339, ARD6005, BAY008, and ARD6006, were fully reviewed with an emphasis on the randomized trial ECF 10339 for TAXOTERE's efficacy in the pediatric patients with NPC. To perform this review, the dossier, previous meeting minutes, the Proposed Pediatric Study Request (PPSR), PWR, and published literature were reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study Protocol EFC10339

Study EFC10339 is the efficacy trial to evaluate the TAXOTERE's efficacy in the pediatric patients with NPC.

Study Title
"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"

Protocol Milestones (Table 3)

- First patient enrolled on November 22, 2007
- Additional protocol amendments introduced December 2007 (following the initiation of enrollment).
- Study cut-off dates
    - March 17, 2009 (efficacy and safety in the induction period)
    - Data cut-off for dosing March 17, 2009
    - April 22, 2009 (serious adverse events)

Table 3: Protocol Milestones

Date	Milestone
March 23, 2007	Clinical Trial Protocol (original)
July 12, 2007	Protocol Amendment 1
November 14, 2007	Protocl Amendment 2
November 22, 2007	First patient enrolled
December 3, 2007	Protocol Amendment 3
March 17, 2009	Data cutoff (dosing)
April 22, 2009	Date of Database lock
November 12, 2009	Submission of NDA 20449 s-059
November 12, 2009	Clinical study report and datasets submission

Protocol Amendments

Amendment 1 – July 12, 2007 (no subjects were yet enrolled)
Several major and minor changes were made to improve protocol clarity.
The following were the major changes:

- Changed the total number of patients to be randomized from 51 to 72.
- Modified the inclusion criteria to include patients ≤ 21 years of age.
- Revised Sections 7, 9, and 12 to clarify study procedures.
- Added Appendix G: Radiation guidelines for both arms of the study

Amendment 2 – November 14, 2007 (no subjects were yet enrolled)

- Added regular cardiac surveillance during each visit for administration of chemotherapies that included vital signs as: heart rate, blood pressure and electrocardiogram (ECG) as medically indicated to now mandatory clinical examinations at induction phase and reflected in Study Flowchart.
- Added the following exclusion criterion: “Hypersensitivity to one of the drugs or their excipients”.
- Made administrative changes to reflect changes in study personnel.

Amendment 3 – December 3, 2007

- Revised the radiation rules for consolidation therapy including recommended dose for consolidation therapy allowing for determination fo target volume, the dose and schedule by local standards rather than protocol mandated.
- Clarified inclusion criterion on age required for study entry to >1 month to ≤ 21 years of age at the time of diagnosis.
- Added a description of how to calculate glomerular filtration rate (GFR).
- Revised hydration regimen by allowing magnesium sulfate.
- Clarified that the RECIST criteria used for CR evaluation were modified by employing volumetric assessment of the primary NPC tumor and associated adenopathy.
- Clarified that the MRI scan required at screening was to the head and neck area.
- Added CT/MRI scan of chest, abdomen and/or pelvis as well as a bone scan if the presence of distant metastases was suspected.
- Added hematology and biochemistry analyses at the screening visit to serve as baseline and removed the requirement for these tests prior to Cycle 1.
- Added recommendations regarding audiology, oral, and dental examinations.
- Clarified times of disease assessment.
- Increased the number of PK samples from 20 to 25.
- Introduced the potential analysis of response based on disease staging.
- Revised study flow chart.

Letters serving as clarification intended to be used in Amendment 4
The following letters were sent to study sites and later intended to be incorporated into Amendment 4. However, due to rapid enrollment of patients a fourth amendment was never incorporated.

- January 28, 2008: provides clarification on overdose reporting of TAXOTERE and/or other study agents
- February 25, 2008: contains the age eligibility for this study in France and revised ECG monitoring due to potential cardiovascular toxicity of TAXOTERE, 5-FU, and Cisplatin.
- January 20, 2009: clarification of histology reporting in the CRF

Study Objectives

The *primary objective* was :

- to estimate the complete response (CR) rate of TAXOTERE, Cisplatin, and 5-Fluorouracil (TCF) compared to Cisplatin and 5-Fluorouracil (CF) in the Induction treatment of nasopharyngeal carcinoma (NPC).

The *secondary objectives* were :

- to determine the safety of TCF in comparison to CF after induction treatment of NPC
- to determine pharmacokinetics (PK) of docetaxel when added to CF
- to determine the overall response (OR) rate of TCF and CF on completion of consolidation (chemo-radiotherapy) treatment of NPC
- to compare overall survival between TCF and CF treatments

The *tertiary objective* was:

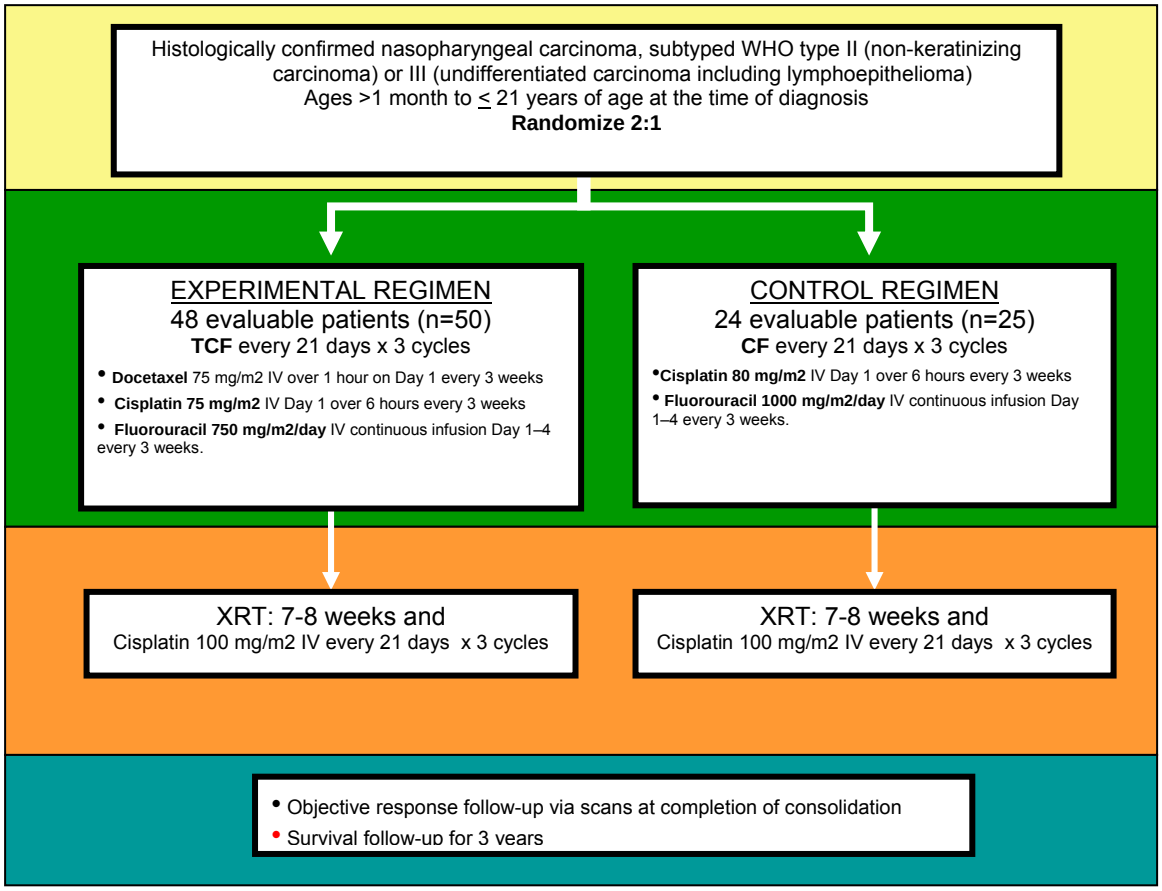
- to characterization of the role of EBV in the pathogenesis of NPC and to investigate the predictive value of the detection of the EBV-DNA in the peripheral blood of children with NPC

Study Design

Study EFC10339 was a randomized (2:1 ratio), international, multicenter, open label study designed to estimate the CR rate of TAXOTERE, 75 mg/m^2, administered as a 60-minute intravenous infusion on day 1 followed by Cisplatin, 75 mg/m^2/dose (2.7 mg/kg/dose if < 1 year of age), administered as a 6-hour intravenous infusion on day 1, and 5-Fluorouracil, 750 mg/m^2/dose (33 mg/kg/day if <1 year of age), administered as a 96-hour continuous infusion on days 1-4 every 3 weeks compared to Cisplatin, 80 mg/m^2/dose (2.7 mg/kg/dose if < 1 year of age), administered as a 6-hour intravenous infusion on day 1, and 5-Fluorouracil, 1000 mg/m^2/dose (33 mg/kg/day if <1 year of age), administered as a 96-hour continuous infusion on days 1-4 every 3 weeks in the induction treatment of NPC. The study schema is presented in

Figure 1. Approximately 72 patients, >1 month to ≤ 21 years of age with newly diagnosed, measurable, Stage IIB-IV, histologically confirmed NPC, subtypes WHO type II (undifferentiated carcinoma) or III (undifferentiated carcinoma includinglymphoepitheliomas) were to be enrolled.

Figure 1: EFC10339 Study Schema



The protocol primary endpoint was CR. Safety, pharmacokinetics of TAXOTERE added to CF, overall reponse rate following completion of consolidation therapy, and overall survival were secondary endpoints. The analysis of the primary endpoint, CR, was to be conducted 30 days after the last dose of TCF or CF (the end of the induction period) using MRI to determination of response. Patients were to also be followed for frequency and severity of hematological and non-hematological Adverse Events (AE) over the induction period. Pharmacokinetics analysis was to be performed in at least 25 pediatric patients in the TCF arm with analysis focused on TAXOTERE plasma clearance and area under the curve using the Bayesian approach. There was no planned interim analysis.

Treatment was to be continued through the consolidation period which consisted of 7-8 weeks of radiation therapy and Cisplatin 100 mg/m^2 given intavenously over 6 hours every 21 days for 3 cycles for all patients. As part of the secondary endpoints of the study patients were to complete consolidation treatment (9

weeks) and be evaluated by MRI for overall response (OR) and followed up for survival for 3 additional years.

Eligibility Criteria

The study population was comprised of children and adolescents >1 month and ≤ 21 years of age at the time of diagnosis with newly diagnosed NPC with measurable disease T2-T4 any NM status.

Additional Inclusion Criteria

- Histological confirmed nasopharyngeal carcinoma, subtypes WHO type II (non-keratinizing carcinoma) or III (undifferentiated carcinoma including lymphoepitheliomas)
- Genders eligible for study: Both
- All patients and/or their parents or legal guardians must sign a written informed consent and assent.

Exclusion Criteria

Subjects who met any of the following were excluded from study participation:

- Patients with short (less than 12 weeks) of life expectancy
- Prior chemotherapy or radiotherapy to the nasopharynx or neck for the treatment of nasopharyngeal carcinoma
- Performance status
    - Patients ≤ 16 years of age: Lansky <60%
    - Patients > 16 years of age: Karnofsky <60%
- Creatinine clearance or radioisotope glomerular filtration rate (GFR) <70 mL/min OR Serum creatinine based on age as follows for the calculation of GFR:
    - Greater than 0.8 mg/dL (for patients ≤ 5 years of age)
    - Greater than 1.0 mg/dL (for patients 6-10 years of age)
    - Greater than 1.2 mg/dL (for patients 11-15 years of age)
    - Greater than 1.5 mg/dL (for patients > 15 years of age)
- Bilirubin > 1.5 times upper limit of normal (ULN) for age
- AST or ALT > 2.5 times ULN for age
- Pregnant or breast feeding females
- Females of child bearing potential who are unwilling or unable to be tested for pregnancy
- Females of child bearing potential who are unwilling or unable to use effective contraception
- Hypersensitivity to one of the drugs or their excipients

Randomization and Blinding

Eligible patients were to be randomly assigned in a 2:1 fashion to one of the two treatment arms (TCF:CF) by means of a telephone call to an interactive voice response system (IVRS) at least 24 hours prior to their first dose of TAXOTERE.

Study Treatments, Concomitant Medications, and Dose Modifications

Study Treatments

Induction Treatment

Experimental regimen (TCF):

- Docetaxel 75 mg/m2 intravenously (IV) over 1 hour on Day 1 every 3 weeks
- Cisplatin 75 mg/m2 IV Day 1 over 6 hours (hours 1-7) every 3 weeks
- Fluorouracil 750 mg/m2/day IV continuous infusion (CI) Day 1–4 every 3 weeks (hours 7-103).
- Dexamethasone 2 doses of oral or intravenous dexamethasone, at a dose of 3 mg/m^2, every 6 hours beginning 12 hours before TAXOTERE to prevent the onset of hypersensitivity reaction (HSR) and to reduce and/or delay the occurrence of skin toxicity and fluid retention related to TAXOTERE. For those countries where dexamethasone was not marketed or if the dosage form was too low, investigators were to us methylprednisolone orally or prednisone or prednisolone orally.
- Prehydration for cisplatin treatment, D5W 0.45NS 500 ml/m^2 + mannitol 10 g/m^2 intravenously over hours -2 to 0 at 250 mL/m^2/hour.
- Posthydration following cisplatin treatment of D5W 0.45NS + KCL 20 mEq/L (addition of $MgSO_4$ 2 g/L was permitted) at 125 mL/m^2/hour for 24 hours (hours 7-31).

Control regimen (CF):

- Cisplatin 80 mg/m2 IV Day 1 over 6 hours (hours 0-6) every 3 weeks
- Fluorouracil 1000 mg/m2/day IV continuous infusion Day 1-4 (hours 6-102) every 3 weeks
- Prehydration for cisplatin treatment, D5W 0.45NS 500 ml/m^2 + mannitol 10 g/m^2 intravenously over hours -2 to 0 at 250 mL/m^2/hour.
- Posthydration following cisplatin treatment of D5W 0.45NS + KCL 20 mEq/L (addition of $MgSO_4$ 2 g/L was permitted) at 125 mL/m^2/hour for 24 hours (hours 6-30).

Consolidation Treatment

- Radiation therapy (RT) lasting 7 to 8 weeks
- Cisplatin 100 mg/m2 IV over 6 hours (hours 0-6) on day 1 every 21 days for 3 cycles
- Prehydration for cisplatin treatment, D5W 0.45 % NS 500 ml/m^2 + mannitol 10 g/m^2 intravenously over hours -2 to 0 at 250 mL/m^2/hour.
- Posthydration following cisplatin treatment of D5W 0.45NS + KCL 20 mEq/L (addition of $MgSO_4$ 2 g/L was permitted) at 125 mL/m^2/hour for 24 hours (hours 6-30).

Prophylactic and Concomitant Medications

Antiemetic premedication

Antiemetic premedication was to be given to all patients which included a 5-HT3 antagonist (i.e. ondansetron or granisetron) prior to and after cisplatin dosing.

Prophylactic antibiotic therapy
Receipt of prophylatic antibiotic therapy was recommended for all patients in the form of ciprofloxacin or alternate at 500 mg (or age related dose equivalent) orally twice a day for 10 days starting on day 5 of each cycle.

Granulocyte Colony Stimulating Factor (G-CSF)
Filgrastim (Neupogen) or Lenograstim was planned to be administered prophylactically during the second and/or subsequent cycles if patients had a prior episode of febrile neutropenia or infection, delayed recovery of absolute neutrophil count (ANC) at day 28, or Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) which persisted for > 7 days. No primary prophylactic administration for the first cycle was permitted.

The following were the recommended doses:

Lenograstim: 150 µg/m^2/day or
Filgrastim: 5 µg/m^2/day or
Pegfilgrastim (long acting GCSF): 6 mg (in patients >40kg)

All were to be given subcutaneously starting 24 hours after the completion of 5-FU infusion. GCSF was to be administered once daily for 10 days or until the ANC $> 1.5 \times 10^9$/L for 2 consecutive measurements. Pegfilgrastim was not to be administered within 14 days prior to the next chemotherapy cycle. Continuing G-CSF therapy during chemoradiation for those starting during the neoadjuvant chemotherapy was left to the discretion of the treating physician.

Dose Modifications

Myelosuppression
Treatment could commence if the ANC ≥ 750/ µL and platelets ≥ 75,000/ µL. For patients whose chemotherapy was delayed > 1 week for prolonged neutropenia, G-CSF was to be added for subsequent chemotherapy cycles as noted above. For > 1 week delays due to thrombocytopenia the involved agents were all to be dose reduced by 20% for the remainder of the treatment.

Ototoxicity
The investigators expected a decrease in auditory acuity at frequencies above the normal hearing level (4000-8000 Hz). Monitoring for ototoxicity was recommended to occur after every cycle. Dose modificiations for ototoxicity according to CTCAE version 3 were as follows:

Table 4: Dose modification of cisplatin for ototoxicity

Grade 1	Grade 2	Grade 3	Grade 4
No dose modificiation	No dose modification	Reduce the dose of cisplatin by 50% for all subsequent cycles	Hold cisplatin dose and do not restart unless follow-up audiograms show improvement in hearing function

Nephrotoxicity
Cisplatin was to be held for a creatinine clearance or GFR <50% of baseline value until the the creatinine clearance rose above 50% of the baseline value. Once the repeat GFR was >50% but <75% of baseline the dose was to be reduced by 50% and the creatinine clearance repeated after 2 cycles at that dose. If the GFR rose to ≥ 75% cisplatin was to be resumed at full dose.

For a creatinine clearance or GFR <75% of baseline value the cisplatin was to be reduced by 50% until the GFR returned to ≥75% of baseline value when the full dose could then be resumed.

Mucositis
For Grade 4 mucositis following fluorouracil administration the dose of fluorouracil was to be decreased by 25% by reducing the total duration of the infusion.

Hepatotoxicity
For a direct bilirubin >3 mg/dL prior to a cycle containing fluorouracil, the chemotherapy was to be held until the bilirubin normalized. If, within 1 week, the bilirubin failed to normalize fluorouracil was to be omitted. Further, if pilocarpine was instituted and the direct bilirubin was > 3mg/dL, the pilocarpine was to be held.

Discontinuation/Withdrawal from Study
Reasons for discontinuation from study treatment include the following:

- Documented progressive disease (PD)
- Diagnosis of a second malignant neoplasm
- Refusal of further protocol therapy by patient/parent/guardian
- Completion of planned therapy (Induction and Consolidation)
- Physician determined it to be in the patient's best interest

If a subject completely withdrew consent (no further treatment or follow-up), was lost to follow-up, or died before 3 year follow-up the subject was discontinued from therapy and withdrawn from the study.

Treatment Compliance
The administration of the correct dose according to assigned schedule was documented in hospital charts or notes and assessed on the basis of completed treatment page of the CRF, Discrepancy Resolution Form (DRF), or other appropriate instrument. The investigator was required and agreed to provide reliable data in an accurate and legible manner and to ensure direct access to source documents by Sponsor representatives. The investigator was required to maintain an adequate record of the receipt and distribution of all study medication using the CRF/Drug Accountability Form.

Concomitant Medications and Treatments

Prophylactic and therapeutic antiemetics were allowed prior to and after cisplatin dosing.

Prophylactic antibiotic therapy was recommended for all patients in the form of ciprofloxacin or alternate orally, twice a day for 10 days starting on day 5 of each cycle.

Premedication with dexamethasone was required for the TCF (expiremental arm). An equivalent could be administered if dexamethasone was not available.

Prophylactic G-CSF was not permitted during cycle 1, but was permitted for subsequent cycles if a prior episode of febrile neutropenia or infection, delayed recovery of absolute neutrophil count (ANC) at day 28, or Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) which persisted for > 7 days occurred.

Dose Delays
An ANC of ≥ 750 and a platelet count of ≥ 75,000 were required to receive chemotherapy. For delays greater than one week, G-CSF would be added for subsequent cycles. For delays greater than one week for thrombocytopenia, chemotherapy agents would be decreased by 20% for the remainder of the treatment.

For a creatinine clearance or GFR <50%, cisplatin therapy was to be withheld until the creatinine clearance rose above 50% of the baseline value.

Doses of chemotherapy were to be delayed for a direct bilirubin >3 mg/dL prior to a cycle of therapy containing fluorouracil until the bilirubin normalized.

Patient Evaluations

The study had screening, treatment, and post-treatment phases. The study calendars for each arm are shown in Table 5 and Table 6.

Screening Phase
All evaluations had to occur within 7 days before the subject's first dose of study medication, and included the following: obtain informed consent, determine eligibility, review prior medication history, obtain complete history (medical and surgical) and perform physical examination, obtain oral and dental evaluation including dental X-rays, recommended sialometry, obtain MRI scan of the head and neck and CT/MRI of the chest, abdomen, and/or pelvis if distant metastases were suspected, bone scan (required if symptomatic bone marrow metastases), randomization within 24 hours of treatment, labs including hematology, chemistry, INR, and APTT, creatinine clearance calculated using the Schwartz/Cockcroft-Gault formula according to age and if low a radioisotope GFR, EBV serology (optional), EBV-DNA level, and pregnancy test.

Treatment Phase
Induction Period
Studies during this phase were to include laboratory tests, physical exam, neurological exam, performance status, routine audiology exam was recommended prior to each cycle or if clinically indicated, AE/SAE recording, EBV-DNA level at cycle 2 week 4, administration of TCF or CF, and pharmacokinetic sampling for at least 25 patients randomized to TCF (first cycle only).

Follow-up Post Induction
Follow-up post induction was to occur 30 days ± 2 days post day 1 cycle 3 and may overlap with the Consolidation period. Studies during this phase were to include laboratory tests, physical exam, neurological exam, performance status, routine audiology exam was recommended prior to each cycle or if clinically indicated, AE/SAE recording, EBV-DNA level, and radiological examination using the same means as the initial assessment to be performed within 7 days prior to starting the consolidation phase and preferably as close to day 1 of cycle 4 as possible.

Consolidation Period
Studies during this phase were to include laboratory tests, physical exam, neurological exam, performance status, oral and dental evaluation and dental x-rays to be performed at the end of therapy, sialometry was recommended prior to starting and at the completion of radiation therapy, routine audiology exam was recommended at the end of therapy, AE/SAE recording, EBV-DNA level, and radiological examination using the same means as the initial assessment to occur 30 ± 2 days post day 1 of last cycle of chemoradiation during consolidation.

Post-Treatment Phase

In the post-treatment phase, patients were to be assessed for progression and followed for survival every 3 months for the first year post consolidation (week 16) and thereafter every 6 months for the 2nd and 3rd year post consolidation (week 16). During this time the following studies were to include laboratory tests, physical exam, neurological exam, performance status, sialometry was recommended at 3, 6, and 12 months after completion of radiation therapy.

Table 5: Assessment for TCF Arm A

Evaluation	Screening	Induction Period			Follow-up post Induction	Consolidation Period			Follow-up post consolidation		
Arm A (TCF)	**Day - 7 to -1**	**Day1/ Week 1 Cycle 1**	**Week 4 Cycle 2**	**Week 7 Cycle 3**	**30 days ±2 days post day 1 cycle 3[1]**	**Week 10 Cycle 4**	**Week 13 Cycle 5**	**Week 16 Cycle 6**	**1 Year post Week 16 visit to occur every 3 months**	**2nd Year post Week 16 visit to occur every 6 months**	**3rd Year post Week 16 visit to occur every 6 months**
Requirements											
Inclusion/Exclusion Criteria	X										
Previous Medical/Surgical History	X										
Informed Consent /Patient Demography	X										
Prior Medication History	X										
Clinical Examination	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]
BSA (body surface area)[3]		X	X	X		X	X	X			
Radiological Examination	X[4]				X[5]			X[6]			
Randomization	X[7]										
Test regimen Docetaxel		X	X	X							
Cisplatin		X	X	X		X	X	X			
Fluorouracil		X	X	X							
Radiotherapy + (Cisplatin concomitantly every 21 days)						X	X				
Safety:											
AE /SAE recording		X	X	X	X	X	X	X			

Evaluation	**Screening**	**Induction Period**			**Follow-up post Induction**	**Consolidation Period**			**Follow-up post consolidation**		
Arm A (TCF)	**Day - 7 to -1**	**Day1/ Week 1 Cycle 1**	**Week 4 Cycle 2**	**Week 7 Cycle 3**	**30 days ±2 days post day 1 cycle 3**[1]	**Week 10 Cycle 4**	**Week 13 Cycle 5**	**Week 16 Cycle 6**	**1 Year post Week 16 visit to occur every 3 months**	**2nd Year post Week 16 visit to occur every 6 months**	**3rd Year post Week 16 visit to occur every 6 months**
Laboratory Testing:											
Hematology (CBC)	X		X	X	X	X	X	X	X	X	X
Biochemistry (SBP)	X		X	X	X	X	X	X	X	X	X
Creatinine Clearance [8]	X		X	X	X	X	X	X			
EBV (EBV NA, VCA and EA antibodies) serology[9]	X										
EBV-DNA level[10]	X		X		X	X	X	X			
Oral And Dental Evaluation[11]	X							X			
Sialometry[12]	X				X			X	X		
Pregnancy test (for women of childbearing potential)	X										
Pharmacokinetics											
1st cycle only 25 patients in TCF arm[13]		X									

[1] Follow-up post induction visit may overlap with the Consolidation period.

[2] To cover the clinical standards within all countries the clinical exam may occur more frequently

[3] BSA calculated using Gehan-George or Mosteller Formulas (Appendix F)

[4] Radiogical examination (MRI scan of head and neck). In addition CT/MRI scan of chest, abdomen and/or pelvis might be required if the presence of distant metastases is suspected. Bone scan(is required for symptomatic bone marrow metastases)

[5] Radiological examination (response assessment using the same means as the initial assessment) should be performed within 7 days prior starting the consolidation phase (cycle 4), but preferably as close to day 1 of cycle 4 as possible.

[6] Radiological examination (response assessment using the same means as the initial assessment) to occur 30 days + or – 2 days post day 1 of last cycle of chemoradiation during consolidation.

[7] 24 hours prior to treatment

[8] To be calculated using the Schwartz formula (Appendix D). Low results will require the measurement to be done by isotope GFR

[9] Optional biology studies

[10] Quantitative determination of EBV -DNA in peripheral blood

[11] Oral and Dental Evaluation is recommended at screening and at the end of therapy

[12] Sialometery (if possible) should be performed at screening, before radiation and at completion of radiation and approximately 3, 6 and 12 months after completion of radiation

[13] Just before the End of Infusion EOI, EOI + 45 min, 5h

Table 6: Assessment for CF Arm B

Evaluation	Screening	Induction Period			Follow-up post Induction	Consolidation Period			Follow-up post consolidation		
Arm B (CF)	**Day - 7 to -1**	**Day1/ Week 1 Cycle 1**	**Week 4 Cycle 2**	**Week 7 Cycle 3**	**30 days ±2 days post day 1 cycle 3[1]**	**Week 10 Cycle 4**	**Week 13 Cycle 5**	**Week 16 Cycle 6**	**1 Year post Week 16 every 3 months**	**2 Years post Week 16 every 6 months**	**3 Years post Week 16 every 6 months**
Requirements											
Inclusion/Exclusion Criteria	X										
Previous Medical/Surgical History	X										
Informed Consent /Patient Demography	X										
Prior Medication History	X										
Clinical Examination	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]
BSA (body surface area)[3]		X	X	X		X	X	X			
Radiological Examination (MRI scan)	X[4]				X[5]			X[6]			
Randomization	X[7]										
Treatment Cisplatin		X	X	X		X	X	X			
Fluorouracil		X	X	X							
Radiotherapy + (Cisplatin concomitantly every 21 days)						X	X				
Safety:											
AE /SAE recording		X	X	X	X	X	X	X			

Evaluation	Screening	Induction Period			Follow-up post Induction	Consolidation Period			Follow-up post consolidation		
Arm B (CF)	**Day - 7 to -1**	**Day1/ Week 1 Cycle 1**	**Week 4 Cycle 2**	**Week 7 Cycle 3**	**30 days ±2 days post day 1 cycle 3[1]**	**Week 10 Cycle 4**	**Week 13 Cycle 5**	**Week 16 Cycle 6**	**1 Year post Week 16 every 3 months**	**2 Years post Week 16 every 6 months**	**3 Years post Week 16 every 6 months**
Laboratory Testing:											
Hematology (CBC)	X		X	X	X	X	X	X	X	X	X
Biochemistry (SBP)	X		X	X	X	X	X	X	X	X	X
Creatinine Clearance [8]	X		X	X	X	X	X				
EBV (EBV NA, VCA and EA antibodies) serology[9]	X										
EBV-DNA level [10]	X		X		X	X	X				
Oral And Dental Evaluation[11]	X							X			
Sialometry[12]	X				X			X	X		
Pregnancy test (for women of childbearing potential)	X										

[1] Follow-up post induction visit may overlap with the Consolidation period.

[2] To cover the clinical standards within all countries the clinical exam may occur more frequently

[3] BSA calculated using Gehan-George or Mosteller Formulas (Appendix F)

[4] Radiogical examination (MRI scan of head and neck). In addition CT/MRI scan of chest, abdomen and/or pelvis might be required if the presence of distant metastases is suspected. Bone scan(is required for symptomatic bone marrow metastases)

[5] Radiological examination (response assessment using the same means as the initial assessment) should be performed within 7 days prior starting the consolidation phase (cycle 4), but preferably as close to day 1 of cycle 4 as possible.

[6] Radiological examination (response assessment using the same means as the initial assessment) to occur 30 days + or – 2 days post day 1 of last cycle of chemoradiation during consolidation.

[7] 24 hours prior to treatment

[8] To be calculated using the Schwartz formula (Appendix D). Low results will require the measurement to be done by isotope GFR

[9] Optional biology studies

[10] Quantitative determination of EBV -DNA in peripheral blood

[11] Oral and Dental Evaluation is recommended at screening and at the end of therapy

[12] Sialometery (if possible) should be performed at screening, before radiation and at completion of radiation and approximately 3, 6 and 12 months after completion of radiation

Criteria for Efficacy Assessment

Primary Efficacy Endpoint

The assessment of complete response (CR) was to be performed according to the modified guidelines of RECIST which incorporate the combination of volumetric assessment (primary NPC, associated adenopathy) and measureable and non-measurable metastatic foci as per RECIST. CR was defined as the complete disappearance of the target and non-target lesion(s) after radiological evaluation and on completion of Induction therapy. The highest observed CR rate of the two arms was to be considered the best treatment for induction therapy from this randomized phase II study. The CR rate was to be calculated by treatment arm in the intention to treat (ITT) and evaluable population. Patients without tumor assessments or those who did not complete the induction treatment were to be considered treatment failures. The study provided an 85% probability to correctly select a treatment arm with the best CR rate by assuming a CR of 31% after 3 cycles of induction therapy for the experimental arm (TCF) and expecting a 20% CR for the control arm (CF) after randomizing 72 patients 2:1 (TCF:CF). The analysis of the primary efficacy variable was to be performed approximately within 12 weeks after the date of the last patient randomized.

An additional analysis of CR based on stratification by disease stage (stage III, IV versus stage IIb) was to be performed dependent on the number of stage IIb patients enrolled in the study to demonstrate the impact of disease stage on the CR if the distribution of disease stage were to be imbalanced between the two groups.

Independent Review Committee

An independent panel of experts (composed of neuroradiologists) were to review the MRI scans of patients treated in both arms and will assigned the appropriate objective response for all randomized and evaluable patients on completion of the Induction treatment period.

Handling of missing assessments and Censoring rules

In the case of missing data, which may cause inaccurate presentation of the study result, sensitivity analyses will be conducted to show the impact of missing data.

Unplanned imaging assessments

No provisions for unplanned imaging assessments were made.

Secondary Efficacy Endpoints

Overall Response

Overall response (CR, PR, SD, PD) was to be based on completion of both Induction and Consolidation (radiation and Cisplatin) therapy in the ITT and Evaluable population by treatment arm. The chi-square test (replaced by Fisher's exact test if the expected frequency in any one of the cells of the contingency table is <5) was to be used to compare proportions although the study was not designed to prove the difference is statistically significan.

Overall Survival

The Kaplan-Meier method was to be used to analyze overall survival and to estimate the median survival time. Time-to-event distributions will be compared using the log rank test. Hazard ratios and their 95% confidence intervals will be estimated from Cox proportional hazards models. All these analyses will be performed at the time of last follow up visit defined in the protocol to assess long-term benefit of docetaxel in combination of cisplatin and 5FU as the induction chemotherapy.

Other Variables

Safety Variables

Safety of TAXOTERE in combination with CF will include adverse events, vital signs (blood pressure, heart rate, and temperature) and laboratory data. The planned safety population was to include all patients who received at least one cycle of study drug.

Pharmacokinetic Variables

A pharmacokinetic analysis is to be performed in at least 25 patients randomized to receive Arm A (TCF) to assess TAXOTERE PK in combination with CF. Pharmacokinetic parameters are to focus on TAXOTERE plasma clearance and area under the curve.

Pharmacodynamic/genomics Variables

EBV and the predictive value of EBV-DNA in the peripheral blood on disease progression will be analyzed in patients tested at baseline (screening).

5.3.2 Supportive Studies

Two supportive trials were included in this submission: ARD6005 and AR6006, conducted by the Children's Cancer Group. These two trials were completed, data were collected, and published prior to the FDA's issuance of PWR.

Study ARD6005 was a dose-finding phase 1 study of TAXOTERE® monotherapy in patients with relapsed and/or refractory solid tumors. This study was opened in 16 centers in the United States and enrolled 61 patients. The objective of the study was to establish the maximum tolerated dose, dose limiting toxicity(ies), safety and pharmacokinetics of escalating doses of TAXOTERE® monotherapy in this patient population. The study was conducted from January 7, 1993 to September 17, 1996.

Reviewer's Comment: The study was conducted from January 7, 1993 to September 17, 1996 by the Pediatric Oncology Branch at the NCI and limited institutions of the Children's Cancer Study Group There was no data collected regarding race or ethnicity of the enrolled patients. Because this study closed nearly eleven years prior to issuance of the PWR, the Applicant was unable to comply with this request for collecting race and ethnicity data. However, the Applicant had not submitted subsequent requests to FDA to amend the PWR after its initial issuance.

Study ARD6006 was an efficacy and safety study of TAXOTERE® monotherapy in pediatric patients with recurrent and/or refractory solid tumors including Ewing sarcoma, rhabdomyosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma. This study was conducted February 28, 1997 to July 3, 2001.

Reviewer's Comment: This study was conducted in 46 centers in the United States, Canada, and Australia from February 28, 1997 to July 3, 2001. One-hundred-seventy-eight patients were enrolled. According to the PWR, at least 10 patients with each of the following tumors were to be enrolled: Ewing sarcoma, rhabdomyosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma.

6 Evaluation on the Applicant's Fulfillment of the PWR Requirement

Table 7 lists each item as requested in the PWR and this reviewer's conclusion as to whether it has been fulfilled or not.

As seen in Tables 7 and 8, four deficiencies were identified in which the Applicant did not completely meet the requirements set forth in the PWR

- Lack of data regarding race of the patients enrolled on Study 1 (ARD6005)
- Failure to enroll an adequate number of patients within neuroblastoma category and undifferentiated sarcoma and rhabdomyosarcoma category in Study 2 (ARD6006) as stated in the PWR.
- Failure in collecting time to toxicity resolution data for Study 2 (ARD6006)
- Failure of submission to include all Study 3 (EFC10339) data

However, the randomized trial (EFC10339) conducted according to the PWR demonstrated the lack of efficacy of adding TAXOTERE to the induction regimen with cisplatin and 5-FU in the treatment of pediatric patients with nasopharyngeal carcinoma. This information contained in the revised TAXOTERE labeling will be helpful to physicians and should be made available to the healthcare community. Thus, the deficiencies listed above would not change the overall conclusion that TAXOTERE did

not have overall benefits in the treatment of pediatric population including a variety of different solid tumors.

Therefore, this reviewer found that the Applicant has fairly, albeit incompletely, fulfilled the requirement set forth in the PWR.

Table 7: the Applicant's Fulfillment of the PWR Requirement (Reviewer's Table)

Written Request Items	**Information Submitted/ Sponsor's response**
Types of studies needed: Study 1: A dose-finding Phase 1 study of TAXOTERE® monotherapy in patients with relapsed refractory solid tumors, including pharmacokinetics, with doses determined for all appropriate age groups. Study 2: A Phase 2 single-arm study to determine the response rate and safety of TAXOTERE® monotherapy in patients with relapsed/refractory Ewing sarcoma, rhabdomyosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma. Study 3: A randomized study to evaluate the addition of TAXOTERE® to the combination of cisplatin-5-fluorouracil (CF) versus CF in the induction treatment of nasopharyngeal carcinoma (NPC).	**Types of studies:** ARD6005 (Study 1) : A dose-finding Phase 1 study of TAXOTERE® monotherapy in patients with relapsed refractory solid tumors, including pharmacokinetics, with doses determined for all appropriate age groups. ARD6006 (Study 2) : A Phase 2 single-arm study to determine the response rate and safety of TAXOTERE® monotherapy in patients with relapsed/refractory Ewing sarcoma, rhabdomyosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma. ARD6005 (Study 1) and ARD6006 (Study 2) were collaborations of the Pediatric Branch of the National Cancer Institute and the Children's Cancer Study Group, now the Children's Oncology Group (COG), and were conducted prior to the issuance of the TAXOTERE® Pediatric Written Request. EFC10339 (Study 3) : A randomized study to evaluate the addition of TAXOTERE® to the combination of cisplatin-5-fluorouracil (TCF) versus CF in the induction treatment of nasopharyngeal carcinoma (NPC).

Indications to be studied:	**Indications studied:**
Study 1: Refractory or relapsed pediatric solid tumors. Study 2: Refractory or relapsed Ewing sarcoma, rhabdomyosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma. Study 3: Newly diagnosed NPC stage T2-4	ARD6005 (Study 1): Refractory or relapsed pediatric solid tumors. ARD6006 (Study 2): Refractory or relapsed Ewing sarcoma, rhabdomyosarcoma and undifferentiated sarcoma, osteosarcoma, neuroblastoma, medulloblastoma, and astrocytoma. EFC10339 (Study 3) : Newly diagnosed NPC stage T2-4
Age group in which study(ies) will be performed:	**Age groups in which studies were performed:**
Study 1: Infants >1 month of age to adolescents up to 21 years of age, with a distribution of patients that reflects the demographics of the diseases under study. Study 2: Infants >1 month of age to adolescents up to 21 years of age, with a distribution of patients that reflects the demographics of the diseases under study. Study 3: Infants >1 month of age to adolescents up to 21 years of age	ARD6005 (Study 1): The study enrolled 61 patients distributed among the following age groups: infants 28 days - 23 mos (n=3), children 2 yrs - <12 yrs (n=25), adolescents 12 yrs - <16 yrs (n=15), >=16 yrs (n=17), missing age (n=1) ARD6006 (Study 2) : The study enrolled 178 patients distributed among the following age groups: infants 28 days - 23 mos (n=7), children 2 yrs - <12 yrs (n=79), adolescents 12 yrs - <16 yrs (n=45), >=16 yrs (n=47) EFC10339 (Study 3) : The study enrolled 75 patients in 2 treatment arms distributed among the following age groups: children 2 yrs - <12 yrs (TCF=4; CF=1), adolescents 12 yrs - <16 yrs (TCF=20; CF=10), >=16 yrs (TCF=26; CF=14)

Study endpoints*:*	**Study endpoints used:**
Study 1: primary endpoint - determination of maximum tolerated dose Secondary endpoints - PK, and response rate by RECIST criteria.	ARD6005 (Study 1): The determination of maximum tolerated dose and of dose limiting toxicities were the primary endpoints. Secondary endpoints were PK and response rate.
Study 2: primary endpoint - objective response rate defined by RECIST criteria Secondary endpoints - safety and tolerability	ARD6006 (Study 2): The determination of response rate was the primary endpoint. Secondary endpoints were safety and tolerability.
Data from studies 1 and 2 should be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.	PK data were collected in ARD6005 (Study 1) and EFC10339 (Study 3), but not in ARD6006 (Study 2). Minimal efficacy was seen in study 1 and study 2. Therefore a PK-PD model for effectiveness based on studies 1 and 2 was not developed. The sponsor collected the required data to develop the PK/PD models to explore exposure-response relationships for both effectiveness and safety but the outcome of the PK modeling limited a combined analysis using studies 1 and 2. Reporting a meaningful exposure-response model is not feasible given the following limitations in study 2: 1) No PK data was available. However, it was not required. 2) The sponsor could not predict exposures for patients in study 2 because no covariates were identified in their population PK model. 3) There was only one dose level administered in study 2; therefore, dose-response analysis could not be conducted.

	Exposure-safety was reported for 4 patients in study 1 with grade 4 neutropenia. Exposure-efficacy was not performed because minimal efficacy was observed in studies 1 and 2.
Study 3: Primary endpoint - Complete response rate (CR) following 3 cycles of induction chemotherapy according to RECIST criteria Secondary endpoints - pharmacokinetic analysis based on sparse PK sampling, overall response rate on completion of radiotherapy, overall survival, predictive value of EBV-DNA in peripheral blood	EFC10339 (Study 3): Primary endpoint - Complete response rate (CR) following 3 cycles of induction chemotherapy according to RECIST criteria. Secondary endpoints - Pharmacokinetic analysis based on sparse PK sampling, overall response rate on completion of radiotherapy, overall survival, predictive value of EBV-DNA in peripheral blood. Overall response rate on completion of radiotherapy, overall survival, and predictive value of EBV-DNA in peripheral blood will be reported in a revised study report once the study is completed.
Drug information: o *dosage form: IV* o *route of administration*: Intravenous o *regimen:* Study 1: dose escalation with a starting dose of 55 mg/m^2 of TAXOTERE® administered intravenously	**Drug information:** ARD6005 (Study 1): The heavily pretreated patients received intravenous docetaxel doses of 55, 65, or 75 mg/m^2 every 21

every 21 days. Study 2 TAXOTERE® 125 mg/m² administered intravenously every 21 days Study 3: • Experimental Regimen - TAXOTERE ® 75 mg/m² intravenously day 1 every 3 weeks - Cisplatin 75 mg/m ² intravenously over 6 hours day 1 every 3 weeks - Fluorouracil 750 mg/m ² intravenously as a continuous infusion days 1-4 every 3 weeks • Control Regimen - Cisplatin 80 mg/m ² intravenously over 6 hours day 1 every 3 weeks - Fluorouracil 1000 mg/m ² intravenously as a continuous infusion days 1-4 every 3 weeks	days. The less heavily pretreated patients received intravenous docetaxel doses of 75, 100, 125 or 150 mg/m^2 every 21 days. Once the MTD was established in the less heavily pretreated patients, there was further dose escalation with the use of G-CSF in an attempt to overcome the DLT of docetaxel, which was neutropenia. Patients in this arm were treated with 150, 185, or 235 mg/m^2 intravenous docetaxel every 21 days. G-CSF was administered subcutaneously at a dose of 5 µg/kg/day starting ≥48 hours after the dose of docetaxel. ARD6006 (Study 2) : TAXOTERE® 125 mg/m^2 administered intravenously every 21 days EFC10339 (Study 3) : Experimental Regimen - Docetaxel 75 mg/m^2 intravenously day 1 every 3 weeks - Cisplatin 75 mg/m ^{2} intravenously over 6 hours day 1 every 3 weeks - Fluorouracil 750 mg/m ^{2} intravenously as a continuous infusion days 1-4 every 3 weeks Control Regimen - Cisplatin 80 mg/m ^{2} intravenously over 6 hours day 1 every 3 weeks - Fluorouracil 1000 mg/m ^{2} intravenously as a continuous infusion days 1-4 every 3 weeks
Drug specific safety concerns: Neutropenia, leukopenia, thrombocytopenia; skin rashes,	**Drug specific safety concerns evaluated:** Neutropenia, leukopenia, thrombocytopenia; skin rashes,

mucositis, mild elevations of serum transaminases; neurotoxicity; peripheral edema and weight gain.	mucositis, mild elevations of serum transaminases; neurotoxicity; peripheral edema and weight gain. Safety was assessed by evaluating treatment exposure, adverse events, clinical laboratory results, and deaths.
Statistical information, including power of study and statistical assessments: Study 1: Descriptive statistics must be submitted. Descriptive statistics for the PK parameters, clearance, half-life, volume of distribution and area under the curve must be included. Study 2: Response to TAXOTERE® will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to protocol specified criteria. Preliminary evaluation of efficacy in terms of anti-tumor activity will be carried out in the procedure as follows. Within each category of tumors, 10 patients will be enrolled. If no patients with CR or PR responses, the trial will be terminated for this category because the agent is ineffective. If >=1 patient achieved a CR or PR, then another 10 patients will be enrolled. If <=2 of 20 evaluable patients with CR or PR responses, the trial for this category will be terminated because the agent is ineffective. If >=3 patients achieved a CR or PR, the trial will be terminated for this category because the agent is active. Response rate and overall survival should be described. Toxicity information including type, severity, time of onset,	**Statistical information, including power of study and statistical assessments:** ARD6005 (Study 1): Descriptive statistics on efficacy and safety were submitted. Descriptive statistics for the PK parameters, clearance, half-life, volume of distribution and area under the curve were included. ARD6006 (Study 2): Descriptive statistics on efficacy and safety were submitted. Analyses on response rate (responses were categorized as complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD] according to protocol specified criteria) and overall survival were submitted. Diseases requested to be studied in WR, number of patients enrolled per disease, and response see Table 8. According to the WR, if ≥ 1 patient achieved a CR or PR then another 10 patients will be enrolled. There were ≥ 1 CR or PR in the following disease subsets: Ewing Sarcoma, Undifferentiated Sarcoma, Osteosarcoma, and Neuroblastoma. Therefore, at least 20 patients should have been enrolled into each disease subset. However, only 4 patients with Undifferentiated Sarcoma and 13 patients with Neuroblastoma were enrolled.

time of resolution, and the probable association should be submitted.	Toxicity information including type, severity, time of onset, and the probable association were submitted. Time of resolution information was not collected.
Data from this study should be combined with data from Study 1 to develop PK-PD models to explore exposure-response relationships across age groups.	PK data were collected in ARD6005 (Study 1) and EFC10339 (Study 3), but not in ARD6006 (Study 2). Minimal efficacy was seen in study 1 and study 2. Therefore a PK-PD model for effectiveness based on studies 1 and 2 was not developed. The sponsor collected the required data to develop the PK/PD models to explore exposure-response relationships for both effectiveness and safety but the outcome of the PK modeling limited a combined analysis using studies 1 and 2. Reporting a meaningful exposure-response model is not feasible given the following limitations in study 2: 1) No PK data was available; however, it was not required. 2) The sponsor could not predict exposures for patients in study 2 because no covariates were identified in their population PK model. 3) There was only one dose level administered in study 2; therefore, dose-response analysis could not be conducted. Exposure-safety was reported for 4 patients in study 1 with grade 4 neutropenia. Exposure-efficacy was not performed because minimal efficacy was observed in studies 1 and 2.

Study 3: This trial should have 85% probability to correctly select a treatment group with the best complete response rate following the induction treatment. This requires a sample size of 72 patients in a 2:1 ratio of randomization to either the experimental group or the control group. Descriptive statistics for safety and efficacy of patients at the end of induction chemotherapy of the Phase 2 study must be submitted. Pharmacokinetic parameters should be estimated using a Bayesian estimation method and the existing adult population PK model as prior information. The analysis should focus on docetaxel plasma clearance and area under the curve as they are well estimated using the Bayesian approach.	EFC10339 (Study 3): Seventy-five patients in a 2:1 ratio of randomization to either the experimental group or the control group were included in the study. Descriptive statistics for safety and efficacy of patients at the end of induction chemotherapy were submitted. Pharmacokinetic parameters were estimated using a Bayesian estimation method and the existing adult population PK model as prior information. The analysis focused on docetaxel plasma clearance and area under the curve as they were well estimated using the Bayesian approach.
Labeling that may result from the study(ies): Appropriate sections of the label may be changed to incorporate the findings of the studies.	**Labeling that may result from the studies:** *Proposed changes to the 8.4 Pediatric Use and 12.3 Human Pharmacokinetics sections of the label were submitted to incorporate the findings of ARD6005 (Study 1), ARD6006 (Study 2), and EFC10339 (Study 3).*
Format of reports to be submitted: Full study reports (including data sets and individual data listings) not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. Even if the study fails, we need full study reports with data to support study conclusion. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial	**Format of reports submitted:** Full study reports (including data sets and individual data listings as well as CRFs) for all studies were submitted. All source documents for the creation of the ARD6005 (Study 1) database were submitted. All CRFs for ARD6006 (Study 2) (considered as source documents for the ARD6006 (Study 2) dataset) were submitted. ARD6005 (Study1) includes no information regarding ethnicity or race. ARD6006 (Study 2) includes information

minorities.	regarding race but categorizes it differently than as requested in the WR. The sponsor included Hispanic in race data and therefore collect no ethnicity data. EFC10339 (Study 3) includes information on the representation of pediatric patients of ethnic and racial minorities.
All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.	The reports for ARD6006 (Study 2) and EFC10339 (Study 3) include information on race. However, for ARD6006 (Study 2), race and ethnicity were categorized differently than specified in the WR. Race was categorized as Caucasian, African American, Hispanic, Oriental, Native American, Indian Subcontinent, or other. Neither race nor ethnicity data were collected in ARD6005 (Study 1).
Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before February 12, 2010. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.	Study reports were submitted on November 13, 2009. However, for EFC10339 (Study 3), overall response rate on completion of radiotherapy, overall survival, and predictive value of EBV-DNA in peripheral blood will be reported in a revised study report once the study is completed.

Table 8: Reviewer's analysis of tumor types as requested, number of patients enrolled per type, and tumor responses (ARD6006)

Disease requested in WR	# Enrolled	CR	PR	SD	PD	N/A	Expected # of enrollments per WR	Fulfill PWR
Ewing's Sarcoma	21		1	8	12		20	Yes
Rhabdomyosarcoma and Undifferentiated Sarcoma	9 4	 1		1 1	7 2	1	20	No
Osteosarcoma	22		1	9	9	3	20	Yes
Neuroblastoma	13		1	3	7	2	20	No
Medulloblastoma	12			4	7	1	10	Yes
Astrocytoma	11			3	6	2	10	Yes

Reviewer's Comment: The PWR stated that within each category of tumors, "if >=1 patient achieved a complete response or partial response, then another 10 patients will be enrolled." Based on the dataset, one patient in the category of rhabdomyosarcoma and undifferentiated sarcoma had a confirmed complete response. However, only 13 patients were enrolled into this tumor category instead of 20. Similarly, one patient with neuroblastoma experienced a partial tumor response, but only 13 patients with this tumor type had been enrolled instead of 20. To rule out the possibility that this inadequate enrollment to the above tumor categories was due to the tumor responses observed in subsequent patients after the enrollment of the initial 10 patients, this reviewer analyzed the time of enrollment for these two categories with regard to the observed tumor responses in patients with neuroblastoma, and undifferentiated sarcoma and rhabdomyosarcoma (Table 9).

Table 9: Reviewer's Table of Patients by Selected Disease, Enrollment, Response according to PWR requirements

Subject ID	Best Response Confirmed	Patients enrolled before responding patient (yyyy-mm-dd)		Responding Patient (yyyy-mm-dd)			Patients enrolled after responding patient (yyyy-mm-dd)	
		Date of first dose of TAXOTERE	End of Study Date	Date of enrollment	Date of response designation	End of study date	Date of first dose of TAXOTERE	End of Study Date
NEUROBLASTOMA								
58516	PD	1997-02-28	1997-03-20					
58030	PD	1997-04-26	1997-06-10					
65331	SD	1997-06-19	1997-10-22					
60412	PD	1998-03-03	1998-04-17					
59941	PD	1998-04-04	1998-05-03					
59551	SD	1998-08-03	1998-10-28					
67019	PD	1998-12-21	1999-01-28					
68170	NA	1999-04-09	1999-04-09					
65755	PD	1999-06-01	1999-07-20					
69615	*	1999-09-08	XXXX-XX-XX					
80787	**PR**			**1999-12-16**	**2000-03-10**	**2001-01-03**		
01210	SD						2001-02-28	2001-07-02
09209	PD						2001-05-22	2001-07-02
UNDIFFERENTIATED SARCOMAS								
55825	PD	1997-10-10	1997-12-05					
68374	SD	1997-09-26	1997-12-17					
49288	**CR**			**1997-11-28**	**1997-12-27**	**1999-01-04**		
08919	PD						2001-09-25	2001-10-31
RHABDOMYOSARCOMA								
78174	PD	1997-03-25	1997-04-04					
61808	PD	1997-03-27	1997-05-08					
65240	PD	1997-05-30	1997-07-07					
65409	PD	1997-06-24	1997-08-13					
77603	SD	1997-07-11	1997-09-11					
58381	PD	1997-08-26	1997-10-01					
79376	PD	1997-08-29	1997-10-30					
56956	NA						1998-07-30	1998-08-04
11698	PD						1998-09-30	1998-10-13

* Blank, NA= Not Available

Reviewer's comments: As shown in Table 9, patient enrollment continued after the 9th evaluable patient with neuroblastoma was reported to have a PR. In the undifferentiated sarcoma and rhabdomyosarcoma category, the enrollment continued after the 3rd enrolled patient with undifferentiated sarcoma experienced a CR. However, enrollment ceased before the required 20 patients were enrolled in each type of neuroblastoma, and undifferentiated and rhabdomyosarcoma. Therefore, this inadequate enrollment was not due to the tumor responses observed in subsequent patients after the enrollment of the initial 10 patients. The study was closed in November 2001. The Applicant had not submitted subsequent request to amend the PWR to correct this deficiency.

In addition, the submission failed to include data on time to toxicity resolution for Study 2 (ARD6006) as requested.

7 Review of Efficacy

Efficacy Summary

Overall, the data submitted in this supplement did not demonstrate any treatment benefits with TAXOTERE for pediatric patients with a variety of different solid tumor types. In the randomized trial EFC 10339, one patient experienced a complete response when treated with TCF in the induction therapy for pediatric patients with NPC. In phase 1 and phase 2 trials a total of 238 treatedpatients, the tumor response rate ranged from one CR (0.4%) in a patient with undifferentiated sarcoma to seven PRs (2.9%) seen in four patients with Ewing Sarcoma, and one each in neuroblastoma, osteosarcoma, and squamous cell carcinoma.

7.1 Indication

The applicant is not seeking a pediatric indication for TAXOTERE.

7.1.1 Methods

The primary efficacy analysis is based on a single randomized Phase 2 study (EFC 10339) in 75 pediatric patients with newly diagnosed NPC.

Enrollment began November 22, 2007. The data cut-off for dosing and therefore efficacy and safety in the induction period was March 17, 2009. Patients were followed for serious adverse events (SAEs), including those in the consolidation phase, up until April 22, 2009, the date of the database lock.

Table 10 shows the 26 study sites in 14 countries. All patients were enrolled outside of the U.S.

Table 10: Reviewer Enrollment by Country (EFC10339)

Country	Number of Subjects Enrolled n (%) TCF (N=50)	CF (N=25)	Country	Number of Subjects Enrolled n (%) TCF (N=50)	CF (N=25)
Algeria	1 (2%)	0	Korea	4 (8%)	0
Brazil	4 (8%)	0	Mexico	1 (2%)	0
China	2 (4%)	2 (8%)	Morocco	8 (16%)	8 (32%)
France	1 (2%)	0	Philippines	2 (4%)	2 (8%)
India	2 (4%)	3 (12%)	Thailand	3 (6%)	0
Indonesia	0	2 (8%)	Tunisia	8 (16%)	2 (8%)
Italy	5 (10%)	0	Turkey	9 (18%)	6 (24%)

Seventy-five patients were randomized (2:1) to receive either TCF or CF. As seen in Table 11, all 75 patients were treated, presenting the intention to treat population for efficacy analysis and the safety population as well. Pharmacokinetics were evaluated in 26 patients of the TCF group.

Table 11: Summary of Analysis of Enrolled Patients (EFC10339)

	Randomized	Treated	ITT pop.	Safety pop.	PK pop.
TCF	50	50	50	50	26
CF	25	25	25	25	--
Total	75	75	75	75	26

Major protocol deviations include violation of inclusion/exclusion criteria, use of prohibited therapies, overdose of treatment, and omission of key assessments.

Major deviations were defined as follows:

- Major deviations included deviations to inclusion criteria 1, 2, 3, and 5 and exclusion criteria 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11.
- Additional major deviations consisted of the following:
    - Patient had no labs done before first administration
    - Patients in the TCF group did not receive docetaxel
    - Patient did not receive 3 cycles of induction treatment for reasons other than safety
    - Patient actually received a ≥30% higher dose than the planned dose in a cycle, resulting in an overdose.

  - Patient had a delay between 2 cycles >35 days
  - Patient received a drug other than the investigational products or drug planned by protocol
- Adverse events were not summarized by cycle
- Four patients had major protocol deviations.
  - Three patients (1 patient in the TCF group [Patient No. 788002001]) and 2 patients in the CF group [Patient No. 504001005 and Patient No. 792002002]) did not have bilirubin measured during the patient selection process.
  - One patient in the CF group (Patient No. 156005001) received 5-floxuridine instead of 5-FU in Cycle 1.

Minor Deviations

A total of 37 patients had minor deviations; 28 patients in the TCF group and 9 patients in the CF group. Four patients in the TCF group and 1 patient in the CF group had deviations in multiple areas. These minor deviations consisted of the following:

- assessments done before the informed consent was signed (11 patients TCF, 2 patients CF)
- study treatment administration beginning more than 7 days after the informed consent was signed (8 patients TCF, 6 patients CF)
- dosing deviations (13 patients TCF, 2 patients CF)

The dosing deviations that were reported consisted of the following:

- a patient received a ≥ 30% higher dose than the planned dose in a cycle, resulting in an overdose
- a full dose of 5-FU that was not administered within a window of 96 hours ± 24 hours.

Randomization and dosing irregularities

The following 5-FU dosing abnormalities were reported:

- Patient No. 012001001(TCF) received the total 5-FU dose in Cycle 1 over 3 days instead of 4 days.
- Patient No. 156005001 (CF) received the total 5-FU dose in Cycle 2 and Cycle 3 over 8 hours instead of 24 hours. This event was reported as an adverse event of overdose.
- Patient No. 156005002 (TCF) received the total 5-FU dose in Cycle 1 over 8 hours instead of 24 hours. This event was reported as an adverse event of overdose. This patient discontinued treatment with 5-FU due to an adverse event (increased ALT/AST) during Cycle 1.
- Patient No. 156005004 (CF) received the total 5-FU dose in Cycle 1 over 8 hours instead of 24 hours. This event was reported as an adverse event of overdose.
- Patient No. 156005005 (TCF) received the total 5-FU dose in Cycle 1 and Cycle 2 over 8 hours instead of 24 hours. This event was reported as an adverse event of overdose.
- Patient No. 250001001 (TCF) received the total 5-FU dose in Cycle 2 over 2 days instead of over 4 days as defined by the protocol. This patient experienced vomiting

2 days after the last dose of 5-FU that progressed to a Grade 3 SAE 2 days later. This SAE resolved and the patient went on to receive Cycle 3. This event was reported as an adverse event of accidental overdose.

- Patient No. 356001001 (TCF) received 5-FU for 6 days in Cycle 1 instead of 4 days and received a total dose of 4500 mg.
- Patient No. 484001001 (TCF) received 5-FU for only 1 day in Cycle 1 due to the onset of convulsions.
- Patient No. 788003008 (TCF) received the total 5-FU dose in Cycle 1 over 5 days instead of 4 days because of a delay in dosing due to Mallory-Weiss syndrome.

7.1.2 Demographics

The sponsor's summary of baseline and demographic characteristics in the ITT population are depicted in Table 12. Fifty-four males and 21 females were enrolled and treated. Of those subjects 48 were Caucasian, 2 were Black, and 25 were other. Median age 16 years (9-21).

Table 12: Summary of Demographic Characteristis in ITT population (EFC10339)

	TCF Group (N=50)	CF Group (N=25)
Age, in years		
Median	16	16
Min	9	9
Max	21	21
Age		
Neonates (0-27 days)	0	0
Infants (28 days – 23 months)	0	0
Children (2 years - < 12 years)	4 (8%)	1 (4%)
Adolescents (12 years - <16 years)	20 (40%)	10 (40%)
≥ 16 years	26 (52%)	14 (56%)
Race		
Caucasian/white	32 (64%)	16 (64%)
Black	2 (4%)	0
Asian/oriental	13 (26%)	9 (36%)
Other	3 (6%)	0
Sex		
Male	35 (70%)	19 (76%)
Female	15 (30%)	6 (24%)
Ethnicity		
Hispanic	2 (4%)	0
Non Hispanic	48 (96%)	25 (100%)

The treatment groups were similar with regard to baseline disease characteristics (Table 13 and Table 14). In each group, the majority of the patients had Type III (undifferentiated carcinoma) (86% TCF and 96% CF). The majority of patients in each group had Stage IV disease (58% TCF and 52% CF).

Table 13: Summary of Baseline Disease Characteristics (EFC10339)

Disease Characteristic	TCF Group (N=50)	CF Group (N=25)
Months from initial diagnosis		
Median	0.7	0.6
Min	0	0
Max	4	3
WHO Classification		
Type II (non-keratinized)	7 (14%)	1 (4%)
Type III (undifferentiated carcinoma)	43 (86%)	24 (96%)
Differentiation grade tumor cell		
Well differentiated	1 (2%)	0
Poorly differentiated	6 (12%)	2 (8%)
Undifferentiated	42 (86%)	23 (92%)

Table 14: Summary of Baseline Disease Stage by Age Group (EFC 10339)

	TCF Group (N=50) Number (%)	CF Group (N=25) Number (%)
II B	3 (6%)	1 (4%)
Age ≥ 16	3 (6%)	1 (4%)
III	18 (36%)	11 (44%)
Children (2 years - < 12 years)	1 (2%)	1 (4%)
Adolescents (12 years - <16 years)	11 (22%)	5 (20%)
Age ≥ 16	6 (12%)	5 (20%)
IV	29 (58%)	13 (52%)
Children (2 years - < 12 years)	3 (6%)	0
Adolescents (12 years - <16 years)	9 (18%)	5 (20%)
Age ≥ 16	17 (34%)	8 (32%)

7.1.3 Subject Disposition

Table 15: Summary of Reason for End of Induction Chemotherapy, ITT (EFC 10339)

	CF GROUP (N=25)	TCF GROUP (N=50)
ADVERSE EVENT	2 (8.0%)	1 (2.0%)
COMPLETED STUDY TREATMENT PERIOD	23 (92.0%)	47 (94.0%)
DISEASE PROGRESSION	0	1 (2.0%)
OTHER REASON	0	1 (2.0%)

7.1.4 Analysis of Primary Endpoint(s)

The applicant's primary efficacy analysis for EFC10339 was to compare the CR rate of TCF compared to CF in the induction treatment of NPC according to modified guidelines of RECIST criteria. These modified guidelines incorporated the volumetric assessment of primary NPC and associated adenopathy as well as measurable and nonmeasurable metastatic foci as per RECIST. Complete response was defined as the complete disappearance of the target and non-target lesion(s) after completion of induction therapy by radiologic evaluation.

The data in Table 16 demonstrate the frequency of best overall response after completion of induction chemotherapy based on radiological assessment. An independent panel of experts reviewed the MRI scans of patients treated in both arms and assigned the appropriate objective response for all randomized and evaluable patients. There was a single CR in the TCF group (2%) while none of the patients in the CF group had a CR.

Table 16: EFC 10339 Primary Endpoint Results

	CF GROUP (N=25)	TCF GROUP (N=50)
Complete Response	0	1 (2.0%)
Partial Response	20 (80.0%)	38 (76.0%)
Stable Disease	2 (8.0%)	6 (12.0%)
Progressive Disease	0	2 (4.0%)
Unknown	0	1 (2.0%)
Missing	3 (12.0%)	2 (4.0%)

The following patients were considered missing as they did not have radiological assessments performed:

Patient No. 484001001 (TCF) withdrew from the study after Cycle 3 due to progressive disease.
Patient No. 788002001 (TCF) withdrew consent after receiving Cycle 1.
Patient No. 356002001 (CF) withdrew during Cycle 1 due to an adverse event.
Patient No. 356004001 (CF) withdrew consent after Cycle 3 due to an adverse event.
Patient No. 504002005 (CF) withdrew during Cycle 1 due to an adverse event.

One additional patient (Patient No. 792002003 [TCF]) had an efficacy response that was unknown due to an incorrect tumor assessment method.

7.1.5 Analysis of Secondary Endpoints(s)

Overall Response
Overall response (CR, PR, SD, PD) was to be based on completion of both Induction and Consolidation (radiation and Cisplatin) therapy in the ITT and Evaluable population by treatment arm. This analysis was not submitted with the current application.

Overall Survival
Follow-up was to occur for three years. The first patient was enrolled in November of 2007. The analysis of overall survival was not submitted with the current application.

7.1.6 Other Endpoints

Pharmacokinetic Variables
A pharmacokinetic analysis was to be performed in at least 25 patients randomized to receive Arm A (TCF) to assess TAXOTERE PK in combination with CF. Pharmacokinetic parameters were to focus on TAXOTERE plasma clearance and area under the curve.

Pharmacodynamic/genomics Variables
EBV and the predictive value of EBV-DNA in the peripheral blood on disease progression was to be analyzed in patients tested at baseline (screening).

Reviewer's Comment: EFC10339 was conducted in 26 centers in 14 countries. It was a randomized, study comparing docetaxel, cisplatin, and 5-fluorouracil in combination with cisplatin and 5-fluorouracil in the induction treatment of pediatric patients with newly diagnosed nasopharyngeal carcinoma. The study enrolled its first patient November 22, 2007 with a data cut off date for dosing of March 17, 2009. The planned follow-up for this study was three years. The applicant failed to report overall response rate on completion of radiotherapy, overall survival, and predictive value of EBV-DNA in peripheral blood. The Applicant stated in this current submission that above results will be provided "in a revised study report once the study is completed". However, the planned late submission does not completely fulfill the PWR which requested full study reports be submitted by February 12, 2010 (see section 6).

7.1.7 Subpopulations

No subpopulations were studied.

7.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

7.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

7.1.10 Additional Efficacy Issues/Analyses

7.2 Supportive Study Efficacy Results

7.2.1 Supportive Study ARD6005

A Phase I Study of TAXOTERE in Pediatric Patients With Advanced Neoplastic Disease:

In ARD6005, a dose-finding phase 1 study of TAXOTERE monotherapy with or without G-CSF in patients with relapse and/or refractory solid tumors who were both heavily treated and less heavily treated. The proportions of male (52.5%) and female (47.5%) subjects in the ITT population were similar (Table 17). The median age of the subjects treated was 12.5 years with a range of 1 to 22 years. There was one protocol violation. Patient No. 840055 was 22 years-old at the time of enrollment. Data on race was not collected.

Table 17: Summary Baseline Demographics in ITT population, ARD6005

	Heavily pretreated			Less heavily pretreated				G-CSF use			Overall
	55 mg/m² (N=7)	65 mg/m² (N=10)	75 mg/m² (N=6)	75 mg/m² (N=4)	100 mg/m² (N=6)	125 mg/m² (N=5)	150 mg/m² (N=6)	150 mg/m² (N=6)	185 mg/m² (N=6)	235 mg/m² (N=5)	Total (N=61)
Age[a]											
Number	7	10	6	3	6	5	6	6	6	5	60
Mean (SD)	14.7 (7.2)	8.7 (5.3)	14.3 (4.2)	11.7 (3.2)	9.7 (8.2)	7.2 (6.1)	9.8 (5.9)	13.0 (5.2)	9.3 (6.7)	15.0 (3.4)	11.2 (6.1)
Median	18.0	9.5	14.0	13.0	9.0	5.0	9.0	14.0	8.5	16.0	12.5
Min : Max	2 : 21	1 : 16	8 : 21	8 : 14	1 : 22	2 : 16	4 : 21	3 : 17	2 : 20	9 : 17	1 : 22
Age group											
missing	0	0	0	1 (25.0%)	0	0	0	0	0	0	1 (1.6%)
neonates (0 - 27 days)	0	0	0	0	0	0	0	0	0	0	0
infants (28 days - 23 months)	0	2 (20.0%)	0	0	1 (16.7%)	0	0	0	0	0	3 (4.9%)
children (2 years - <12 yrs)	2 (28.6%)	4 (40.0%)	1 (16.7%)	1 (25.0%)	2 (33.3%)	4 (80.0%)	5 (83.3%)	1 (16.7%)	4 (66.7%)	1 (20.0%)	25 (41.0%)
adolescents (12 years - <16 yrs)	1 (14.3%)	3 (30.0%)	3 (50.0%)	2 (50.0%)	2 (33.3%)	0	0	3 (50.0%)	1 (16.7%)	0	15 (24.6%)
>=16	4 (57.1%)	1 (10.0%)	2 (33.3%)	0	1 (16.7%)	1 (20.0%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	4 (80.0%)	17 (27.9%)
Sex											
Male	4 (57.1%)	6 (60.0%)	5 (83.3%)	2 (50.0%)	3 (60.0%)	2 (40.0%)	2 (33.3%)	3 (50.0%)	2 (33.3%)	2 (50.0%)	31 (52.5%)
Female	3 (42.9%)	4 (40.0%)	1 (16.7%)	2 (50.0%)	2 (40.0%)	3 (60.0%)	4 (66.7%)	3 (50.0%)	4 (66.7%)	2 (50.0%)	28 (47.5%)
Missing	0	0	0	0	1	0	0	0	0	1	2

[a] One patient (840013) had data missing for age

Table 18 provides a summary of the ITT population baseline disease characteristics in ARD6005. The most common tumor types were osteosarcoma (27.9%), Ewing's sarcoma/PNET (14.8%), desmoplastic small round cell tumor (6.6%), rhabdomyosarcoma (6.6%), hepatoblastoma (4.9%), wilms tumor (4.9%). Other, rare tumor types made up 19.7% of the ITT population (epidermoid carcinoma of salivary gland, metastatic peripheral neuroectodermal tumor, brain stem glioma (n=3), synovial cell sarcoma, adrenocortical carcinoma, alveolar soft part sarcoma, malignant Schwannoma, nasopharyngeal carcinoma, yolk sac tumor, and lung cancer)

Table 18: Sponsor's Summary of Baseline Disease Characteristics- Number (%) of Patients, ITT Population (ARD6005)

	Heavily pretreated			Less heavily pretreated				G-CSF use		Overall
	55 mg/m² (N=7)	65 mg/m² (N=10)	75 mg/m² (N=6)	75 mg/m² (N=4)	100 mg/m² (N=6)	125 mg/m² (N=5)	150 mg/m² (N=6)	150 mg/m² (N=6)	185 mg/m² (N=6)	235 mg/m² (N=5)	Total (N=61)
Disease diagnosis											
Osteosarcoma	1 (14.3%)	1 (10.0%)	3 (50.0%)	1 (25.0%)	0	1 (20.0%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	4 (80.0%)	17 (27.9%)
Other	3 (42.9%)	6 (60.0%)	0	1 (25.0%)	1 (16.7%)	0	0	0	0	1 (20.0%)	12 (19.7%)
Ewing's sarcoma/PNET	0	2 (20.0%)	1 (16.7%)	1 (25.0%)	1 (16.7%)	3 (60.0%)	1 (16.7%)	0	0	0	9 (14.8%)
Desmoplastic small round cell tumor	0	0	1 (16.7%)	0	0	1 (20.0%)	0	1 (16.7%)	1 (16.7%)	0	4 (6.6%)
Rhabdomyosarcoma	1 (14.3%)	0	0	0	2 (33.3%)	0	1 (16.7%)	0	0	0	4 (6.6%)
Hepatoblastoma	1 (14.3%)	1 (10.0%)	0	0	0	0	0	0	1 (16.7%)	0	3 (4.9%)
Unknown	1 (14.3%)	0	0	1 (25.0%)	0	0	0	0	1 (16.7%)	0	3 (4.9%)
Wilms tumor	0	0	1 (16.7%)	0	0	0	1 (16.7%)	0	1 (16.7%)	0	3 (4.9%)
Colon Cancer	0	0	0	0	1 (16.7%)	0	0	1 (16.7%)	0	0	2 (3.3%)
Neuroblastoma	0	0	0	0	1 (16.7%)	0	0	1 (16.7%)	0	0	2 (3.3%)
Missing	0	0	0	0	0	0	0	0	1 (16.7%)	0	1 (1.6%)
Undifferentiated sarcoma	0	0	0	0	0	0	0	1 (16.7%)	0	0	1 (1.6%)
Primary tumor site											
Bone	1 (14.3%)	1 (10.0%)	4 (66.7%)	1 (25.0%)	0	1 (20.0%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	2 (40.0%)	16 (26.2%)
Other	3 (42.9%)	4 (40.0%)	0	0	3 (50.0%)	2 (40.0%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	0	16 (26.2%)
Lung	1 (14.3%)	1 (10.0%)	0	2 (50.0%)	0	0	1 (16.7%)	0	0	3 (60.0%)	8 (13.1%)
Brain	1 (14.3%)	2 (20.0%)	0	0	0	2 (40.0%)	0	0	0	0	5 (8.2%)
Kidneys	0	0	1 (16.7%)	0	1 (16.7%)	0	1 (16.7%)	0	1 (16.7%)	0	4 (6.6%)
Liver	1 (14.3%)	1 (10.0%)	0	0	0	0	0	0	1 (16.7%)	0	3 (4.9%)
Adrenal glands	0	1 (10.0%)	0	0	0	0	0	1 (16.7%)	0	0	2 (3.3%)
Colon	0	0	0	0	1 (16.7%)	0	0	0	0	0	1 (1.6%)
Eye	0	0	0	0	1 (16.7%)	0	0	0	0	0	1 (1.6%)
Lymph node	0	0	0	0	0	0	0	1 (16.7%)	0	0	1 (1.6%)
Missing	0	0	0	0	0	0	0	0	1 (16.7%)	0	1 (1.6%)
Nasopharynx	0	0	0	0	0	0	0	1 (16.7%)	0	0	1 (1.6%)
Other head and neck	0	0	0	1 (25.0%)	0	0	0	0	0	0	1 (1.6%)
Retroperitoneum	0	0	1 (16.7%)	0	0	0	0	0	0	0	1 (1.6%)

Reviewer's Comment: Other tumors made up only 14.7% of total diseases at diagnosis given that subjects with brain stem gliomas made up 4.9% of the ITT population.

7.2.2 Supportive Study ARD6006

A Phase II study of docetaxel (TAXOTERE®) in children with recurrent solid tumors (CCG-0962):

One hundred-seventy eight patients were enrolled in ARD6006 an efficacy and safety study of TAXOTERE monotherapy in pediatric pateints with recurrent and/or refractory solid tumors. There were 110 male and 68 female subjects enrolled in the ITT population. The median age of subjects was 12 years of age and ranged from 1 year to 26 years. Forty-seven patients (26.4%) were 16 years of age or older. Race data was collected. The majority of subjects were white (61.8%), while 18% were Hispanic and 13.5% Black.

Table 19: Summary Baseline Demographics ITT population (ARD6006)

	Total (N=178)
Age, in years	
Number	178
Mean (SD)	11.3 (5.7)
Median	12
Min/Max	1 : 26
Age group	
Neonates (0-27 days)	0
Infants (28 days – 23 months)	7 (3.9%)
Children (2 years - < 12 years)	79 (44.4%)
Adolescents (12 years - <16 years)	45 (25.3%)
≥ 16 years	47 (26.4%)
Race	
Caucasian/white	110 (61.8%)
Hispanic	32 (18.0%)
Black	24 (13.5%)
Oriental	5 (2.8%)
Native American	4 (2.2%)
Indian Subcontinent	1 (0.6%)
Other	2 (1.1%)
Sex	
Male	110 (61.8%)
Female	68 (38.2%)

TAXOTERE monotherapy was evaluated in ARD6006, a phase 2 single-arm trial in 178 pediatric patients (median age 12 years, range 1-26 years) with a variety of recurrent/refractory solid tumors. Efficacy was not established with tumor response rates ranging from one complete response (CR) (0.6%) in a patient with undifferentiated sarcoma to four partial responses (2.2%) seen in one patient each with Ewing Sarcoma, neuroblastoma, osteosarcoma, and squamous cell carcinoma.

Reviewer's comment: Although one patient was 26 years old at the time of study enrollment, this subject made eligibility criteria of being < 21 years old at the time of diagnosis.

8 Review of Safety

The analysis of the safety of TAXOTERE in combination with cisplatin and 5-fluorouracil in pediatric patients was performed primarily by review of patients with newly diagnosed Nasopharyngeal Carcinoma on study EFC10399. The total number of patients enrolled and randomized in this study was 75. The safety analysis consisted of 75 patients assessed for treatment exposure, adverse events, clinical laboratory results, and deaths. Adverse events were analyzed by age, gender, and race.

Safety Summary
The overall safety profile of TAXOTERE in pediatric patients was found to be similar to that of adult population. Table 19 summarizes the most frequent Treatment-Emergent Adverse Events (TEAEs) observed in trial EFC10339.

Table 20: The Most Frequent Treatment-Emergent Adverse Events (EFC 10339)

Toxicity	TCF %		CF %	
	All Grades	Grade 3,4	All Grades	Grade 3,4
Vomiting	84%	16%	80%	12%
Nausea	62%	2%	32%	0%
Neutropenia/ neutrophil count abn.	30%	26%	28%	20%
Febrile Neutropenia	6%	6%	0	0

8.1 Methods

8.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data from 75 patients on trial EFC 10339 was used in the safety evaluation

8.1.2 Categorization of Adverse Events

MedRA terms (SOC and Preferred Terms) were used in the AE categorization.

8.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

None

8.2 Adequacy of Safety Assessments

8.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Patients in the TCF group were to receive 75 mg/m^2 of TAXOTERE per cycle (3 weeks) for a total of 225 mg/m^2 during 9 weeks. The reported cumulative dose was 221.8 mg/m^2 (range: 73 to 235 mg/m^2). The theoretical dose intensity was 225/9 = 25 mg/m^2/week. The median dose intensity was 24.6 mg/m^2/week (range 12 to 27 mg/m^2/week). Therefore, the median relative dose intensity was 98.4%. Most patients received TAXOTERE as specified in the protocol.

Table 21: TAXOTERE Dose in the Induction Period in TCF Treatment Group, Safety Population, EFC10339

	TCF GROUP (N=50)
Number of cycles	
Median	3.0
Min	1
Max	3
Total cumulative dose (mg/m^2)	
Median	221.8
Min	73
Max	235
Dose intensity (mg/m^2/week)	
Median	24.6
Min	12
Max	27
Relative dose intensity (%)	
Median	98.6
Min	47
Max	108

Similarly, cisplatin and 5-FU doses in the induction period for the safety population can be seen in Table 22 and Table 23.

Table 22: Cisplatin dose in the induction period, safety population (EFC 10339)

	CF GROUP (N=25)	TCF GROUP (N=50)
Number of cycles		
Median	3.0	3.0
Min	1	1
Max	3	3
Total cumulative dose (mg/m^2)		
Median	236.9	221.8
Min	78	73
Max	299	235
Dose intensity (mg/m^2/week)		
Median	26.3	24.6
Min	23	12
Max	33	27
Relative dose intensity (%)		
Median	98.6	98.6
Min	85	47
Max	124	108

Table 23: 5-fluorouracil dose in the induction period, safety population (EFC10339)

	CF GROUP (N=25)	TCF GROUP (N=50)
Number of cycles		
Median	3.0	3.0
Min	1	1
Max	3	3
Total cumulative dose (mg/m^2)		
Median	11820.5	8866.3
Min	3925	2935
Max	12072	9411
Dose intensity (mg/m^2/week)		
Median	1313.4	986.0
Min	901	359
Max	1360	1081
Relative dose intensity (%)		
Median	98.5	98.6
Min	68	36
Max	102	108

8.2.2 Explorations for Dose Response

This trial had only one CR in the experimental arm and no CR in the control arm. Therefore, there was not enough information to explore dose response.

8.2.3 Special Animal and/or In Vitro Testing

Not applicable.

8.2.4 Routine Clinical Testing

Not applicable.

8.3 Major Safety Results

8.3.1 Deaths

Three subject deaths were reported. Two of which were in the TCF group (subjects 484001001 and 504003001) ages 14 and 13 respectively. Both subjects died of disease progression and both deaths occurred later than 30 days after the last consolidation treatment. An additional subject (504002005) age 19, randomized to the CF group died during the induction period from febrile bone marrow aplasia and septic shock considered related to study treatment.

8.3.2 Nonfatal Serious Adverse Events

SAEs were demonstrated in 24% of patients in each treatment group (TCF and CF) see Table 24. The most common SAEs consisted of hematologic disorders (14% TCF, 16% CF). Neutropenia was the most frequently reported SAE during the induction period and was equal in both treatment groups (8% TCF, 8% CF). Gastrointestinal SAEs were more frequent in the TCF group (14% TCF. 0% CF).

Table 24: Number (%) of patients with an SAE in the induction period regardless of relationship to study treatment by SOC and preferred term, safety population

SOC	CF GROUP (N=25)		TCF GROUP (N=50)	
PREFERRED TERM	All Grades	Grade 3,4	All Grades	Grade 3,4
Any event	6 (24.0%)	6 (24.0%)	12 (24.0%)	10 (20.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4 (16.0%)	3 (12.0%)	7 (14.0%)	7 (14.0%)
NEUTROPENIA/NEUTROPHIL COUNT	2 (8.0%)	1 (4.0%)	4 (8.0%)	4 (8.0%)
FEBRILE NEUTROPENIA	0	0	3 (6.0%)	3 (6.0%)
FEBRILE BONE MARROW APLASIA	1 (4.0%)	1 (4.0%)	0	0
THROMBOCYTOPENIA	1 (4.0%)	1 (4.0%)	0	0
GASTROINTESTINAL DISORDERS	0	0	7 (14.0%)	3 (6.0%)
DIARRHOEA	0	0	3 (6.0%)	0
VOMITING	0	0	2 (4.0%)	2 (4.0%)
ABDOMINAL PAIN	0	0	1 (2.0%)	0
GASTRITIS	0	0	1 (2.0%)	1 (2.0%)
MALLORY-WEISS SYNDROME	0	0	1 (2.0%)	0
PROCTALGIA	0	0	1 (2.0%)	0
CARDIAC DISORDERS	0	0	1 (2.0%)	0
TACHYCARDIA	0	0	1 (2.0%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (4.0%)	1 (4.0%)	1 (2.0%)	0
PYREXIA	1 (4.0%)	1 (4.0%)	1 (2.0%)	0
IMMUNE SYSTEM DISORDERS	0	0	1 (2.0%)	1 (2.0%)
HYPERSENSITIVITY	0	0	1 (2.0%)	1 (2.0%)
INFECTIONS AND INFESTATIONS	3 (12.0%)	3 (12.0%)	1 (2.0%)	1 (2.0%)
POSTOPERATIVE WOUND INFECTION	0	0	1 (2.0%)	1 (2.0%)
CENTRAL LINE INFECTION	1 (4.0%)	1 (4.0%)	0	0
NEUTROPENIC INFECTION	1 (4.0%)	1 (4.0%)	0	0
PHARYNGITIS BACTERIAL	1 (4.0%)	1 (4.0%)	0	0
SEPTIC SHOCK	1 (4.0%)	1 (4.0%)	0	0
INVESTIGATIONS	0	0	1 (2.0%)	1 (2.0%)
ALANINE AMINOTRANSFERASE INCREASED	0	0	1 (2.0%)	1 (2.0%)
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	1 (2.0%)	1 (2.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	1 (2.0%)	0
TUMOUR HAEMORRHAGE	0	0	1 (2.0%)	0
NERVOUS SYSTEM DISORDERS	2 (8.0%)	2 (8.0%)	1 (2.0%)	1 (2.0%)
CONVULSION	2 (8.0%)	2 (8.0%)	1 (2.0%)	1 (2.0%)
VASCULAR DISORDERS	0	0	1 (2.0%)	0
HYPOTENSION	0	0	1 (2.0%)	0

8.3.3 Dropouts and/or Discontinuations

As depicted in Table 25, four patients (2 TCF group, 2 CF group) withdrew from treatment due to adverse events related to study treatment. Patient No. 156005002 treated on the TCF arm, discontinued 5-FU but continued therapy with TAXOTERE and cisplatin.

Table 25: Summary of TEAEs leading to withdrawal from treatment in the induction period, number (%) of patients, safety population (EFC10339)

	CF GROUP (N=25)		TCF GROUP* (N=50)	
PREFERRED TERM	All Grades	Grade 3,4	All Grades	Grade 3,4
Any event	2 (8.0%)	2 (8.0%)	2 (4.0%)	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	2 (4.0%)	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	2 (4.0%)	0
NEUTROPENIC INFECTION	1 (4.0%)	1 (4.0%)	0	0
SEPTIC SHOCK	1 (4.0%)	1 (4.0%)	0	0
THROMBOCYTOPENIA	1 (4.0%)	1 (4.0%)	0	0

*Patient No. 156005002 on TCF group discontinued 5-FU treatment but continued on docetaxel+cisplatin

8.3.4 Significant Adverse Events

Other significant adverse events are seen in Table 26. Two subjects who experienced convulsions, one from each treatment group, were noted to have Grade 4 hyponatremia at the time of their seizure.

Table 26: Reviewer analysis of significant adverse events, safety population (EFC1033)

Adverse Event	TCF Number	CF Number
Hypersensitivity	4	0
Convulsions	1	2

8.4 Supportive Safety Results

8.4.1 Common Adverse Events

The overall incidence and severity of TEAEs were similar in both induction treatment groups. The incidence of TEAEs was similar in both groups; 96% of patients in the TCF group and 100% of patients in the CF group experienced an adverse event. The most frequent TEAEs in each group, regardless of relationship to study treatment were gastrointestinal (90.0% TCF, 84.0% CF) and hematologic (44.0% TCF, 36.0% CF). Treatment emergent adverse events more common in the TCF group were cutaneous (66.0% TCF, 8.0% CF), general (38.0% TCF, 24.0% CF), investigations (32.0% TCF, 20.0% CF), metabolic and nutrition (28.0% TCF, 16.0% CF), nervous system (18.0%

TCF, 12.0% CF), psychiatric (8.0% TCF, 0% CF), respiratory (16.0% TCF, 0% CF), and vascular (14.0% TCF, 4.0% CF).

The most frequent TEAEs in the TCF group regardless of relationship to study treatment were vomiting (84.0%), nausea (62.0%), alopecia (56.0%), diarrhea (36.0%), and neutropenia (30.0%). The following TEAEs occurred at a rate ≥10 percentage points higher in the TCF group compared with the CF group: anemia, abdominal pain, abdominal pain upper, constipation, nausea, diarrhea, stomatitis, hyponatremia, and alopecia. The most frequent treatment-related TEAEs in the TCF group were vomiting (80.0%), nausea (60.0%), alopecia (56.0%), neutropenia/neutrophil count (30.0%), and diarrhea (26.0%).

The most frequent TEAEs in the CF group regardless of relationship to study treatment were vomiting (80.0%), nausea (32.0%), neutropenia/neutrophil count (28.0%), pyrexia (16.0%), anorexia (12.0%), and diarrhea (12.0%). The most frequent treatment-related TEAEs in the CF group were vomiting (80.0%), nausea (28.0%), neutropenia/neutrophil count (28.0%), anorexia (12.0%), and diarrhea (12.0%).

Thirteen patients (26%) in the TCF group and 6 patients (24%) in the CF group had dose delays of interruptions due to adverse events. These events were primarily neutropenia and hypersensitivity reactions.

8.4.2 Laboratory Findings

Laboratory parameters during the induction period were obtained and provided in the submission. Notably, there was an increased percentage of patients with Grade 1 ad 2 liver function abnormalities (ALT and AST) and Grade 1 and 2 hyperglycemia in the TCF group versus the CF group. There was no difference in AST, ALT, or hyperglycemia Grade 3, 4 between the groups. There was no difference in hematology parameters (all grades and Grade 3, 4) between the TCF and CF group.

8.4.3 Vital Signs

The listing of subject vital signs (systolic blood pressure, diastolic blood pressure, heart rate and temperature, height, weight, and performance status) and other procedures were included in the submission. No significant abnormalities were identified for the vital signs associated with TAXOTERE administration.

8.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not regularly done as part of this study.

8.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed as part of this study.

8.4.6 Immunogenicity

Not applicable.

8.5 Other Safety Explorations

8.5.1 Dose Dependency for Adverse Events

One dose of TAXOTERE was used in EFC 10339 and thus dose dependency for adverse events cannot be evaluated.

8.5.2 Time Dependency for Adverse Events

Not applicable

8.5.3 Drug-Demographic Interactions

Pharmcokinetic evaluation was performed in 28 patients and specimens received for 26 patients. Pharmacokinetic analysis was performed in 26 patients at Cycle 1. Of those patients evaluable, 18 were male, 8 were female, 19 were Caucasian/white, 1 Black, and 3 Asian/Oriental. The median age was 16 (range:10-21 years). Mean AUC in pediatric patients treated at 75 mg/m^2 was similar to that observed in adult patients with several tumor types treated with docetaxel monotherapy with mean values of 3.43 and 3.51 µg.h/mL respectively.

8.5.4 Drug-Disease Interactions

Not applicable.

8.5.5 Drug-Drug Interactions

Not applicable.

8.6 Additional Safety Evaluations

8.6.1 Human Carcinogenicity

Not applicable.

8.6.2 Human Reproduction and Pregnancy Data

Not applicable.

8.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric assessment of effects on growth was not performed.

8.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

8.7 Additional Submissions / Safety Issues

There was no 120-day safety update for this supplement because there was no additional safety data was collected after the original submission.

9 Postmarket Experience

Not applicable. TAXOTERE has not been marketed for any pediatric indication.

10 Appendices

10.1 Labeling Recommendations

The following labeling has been incorporated into the current prescribing information.

The efficacy of TAXOTERE in pediatric patients as monotherapy or in combination has not been established. The overall safety of TAXOTERE in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile in adults.

TAXOTERE has been studied in a total of 289 pediatric patients: 239 in 2 trials with monotherapy and 50 in combination treatment with cisplatin and 5-fluoruracil (TCF).

(b) (4)

TAXOTERE Monotherapy
TAXOTERE monotherapy was evaluated in a dose-finding phase 1 trial in 61 pediatric patients (median age 12.5 years, range 1-22 years) with a variety of refractory solid tumors. The recommended dose was 125 mg/m^2 as a 1-hour intravenous infusion every 21 days. The primary dose limiting toxicity was neutropenia.

The recommended dose for TAXOTERE monotherapy was evaluated in a phase 2 single-arm trial in 178 pediatric patients (median age 12 years, range 1-26 years) with a variety of recurrent/refractory solid tumors. Efficacy was not established with tumor response rates ranging from one complete response (CR) (0.6%) in a patient with undifferentiated sarcoma to four partial responses (2.2%) seen in one patient each with Ewing Sarcoma, neuroblastoma, osteosarcoma, and squamous cell carcinoma.

TAXOTERE in Combination
TAXOTERE was studied in combination with cisplatin and 5-fluorouracil (TCF) versus cisplatin and 5-fluorouracil (CF) for the induction treatment of nasopharyngeal carcinoma (NPC) 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.

10.3 Advisory Committee Meeting

None

10.4 Pediatric Exclusivity Board Meetings

This reviewer presented the review findings for pediatric exclusivity determination to the Pediatric Exclusivity Board (PEB) on 01-26-2010 and on 03-16-2010. Although the Applicant did not completely meet the requirements set forth in the PWR due to the deficiencies identified in section 1.1, they would not change the overall conclusion that TAXOTERE did not have overall benefits in the treatment of pediatric population including a variety of different solid tumors. The Applicant fairly responded to the Pediatric Written Request mainly due to the efforts made in conducting ARD6006 which treated 178 patients with a variety of tumor types and EFC10339, a randomized study of 75 patients in a rare tumor of NPC, despite the fact that ARD6006 was conducted and completed by the Children's Cancer Group before the PWR was issued and that there was a clear demonstration that TAXOTERE had no treatment benefit in the pediatric population. Discussion at the 2nd PEB meeting indicated that including these data in the labeling would be beneficial to physicians that currently use this product in pediatric patients so that they and patients can be better informed regarding TAXOTERE use in pediatric population. The Pediatric Exclusivity Board granted pediatric exclusivity for TAXOTERE, effective March 17, 2010.

10.5 Literature Review/References

[1] Pappo AS, Furman, WL. (2006).Management of infrequent cancers of childhood. In PA Pizzo, DG Poplack (Eds.), *Principles and practice of pediatric oncology* (1172-1177). Philadelphia: Lippincott Williams & Wilkins.

[2] Douglass EC, Fontanesi J, Ribeiro RC, Hawkins E. Improved long-term disease-free survival in nasopharyngeal carcinoma (NPC) in childhood and adolescnece: a multi-instituion treatment protocol [abstract]. *Proc Am Soc Clin Oncol.* 1996; 15:A1470.

[3] Rodriguez-Galindo C, Wofford M, Castleberry RP, et al. Preradiation Chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin for pediatric nasopharyngeal carcinoma: results of pediatric oncology group (now children's oncology group) Study 9486 *Cancer* 2005;103:850-857.

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

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/s/

KRISTEN M SNYDER
05/03/2010

KE LIU
05/04/2010