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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-492
Drug Name:	Oxaliplatin for Injection (SR96669)
Indication(s):	Pediatric cancer
Applicant:	Sanofi-Aventis U.S. Inc.
Date(s):	Submission Date: July 10, 2006
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Review Priority:	Priority
Biometrics Division:	Division of Biometrics V (HFD-711)
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Keywords: Overall Survivor, Median PFS and Confidence Limit

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This supplemental NDA includes final study reports in fulfillment of the Pediatric Written Request (PWR) of 9 December 2004. In this NDA, the sponsor included two phase II studies: the pivotal Phase II study ARD5021 and a supportive study ARD5530. Study ARD 5021 is completed and study ARD5530 is ongoing. The sponsor also included one combined phase I/II study, study ARD5531 and one phase I study, study ARD DF17434. All of the studies were conducted in pediatric cancer patients. No statistical comparison was conducted in the completed phase II studies and therefore no statistical inference will be drawn from the studies.

1.2 Brief Overview of Clinical Studies

In this NDA submission, efficacy and safety data are collected for one phase I study, one Phase I/II dose finding trial (to establish the maximum tolerated dose MTD) and two phase II studies. These studies were conducted to determine the efficacy and safety of oxaliplatin in pediatric cancer patients. This reviewer focuses on the pivotal study ARD5021 and briefly summarize the results of the other studies.

Oxaliplatin as a single agent infusion has been administrated to a total of 159 pediatric patients (7 months-22 years of age) with solid tumors.

In the Phase I/II study (study ARD5531), oxaliplatin was administered as a 2-hour IV infusion on days 1, 8 and 15 q4w (1 cycle), for a maximum of 6 cycles, to 43 patients with refractory or relapsed malignant solid tumors. While 28 pediatric patients were treated in the Phase I study at 6 dose levels starting at 40 mg/m² and up to 110 mg/m², the recommended dose (RD) as 90mg/ m² IV was administered on days 1, 8 and 15 q4w to 15 patients in Phase II study.

In a second Phase I study (study DF17434), oxaliplatin was administered to 26 pediatric patients as a 2-hour IV infusion on day 1 q3w (1 cycle) at 5 dose levels starting at 100 mg/m² and up to 160 mg/m², for a maximum of 6 cycles. At the last dose level, oxaliplatin 85 mg/m² was administered on day 1 q2w, for a maximum of 9 doses.

Based on these studies, oxaliplatin 130 mg/m² as a 2-hour IV infusion on day 1 q3w (1 cycle) was further used in Phase II studies. In the pivotal Phase II study (study ARD5021), 43 pediatric patients were treated for recurrent or refractory embryonal CNS tumors for a maximum of 12 months in absence of progressive disease or unacceptable toxicity. In patients < 10kg the oxaliplatin dose used was 4.3 mg/kg. In a second Phase II study (study ARD5530), 47 pediatric patients were treated for recurrent solid tumors, for a maximum of 12 months or 17 cycles.

1.3 Statistical Issues and Findings

This supplemental NDA is to study oxaliplatin as a single agent in pediatric patients with medulloblastoma, supratentorial primitive neuroectodermal tumors and atypical teratoid rhaboid tumors after failure of initial therapy (study ARD5021), refractory or relapsed malignant solid tumors (study ARD5531) and with recurrent solid tumors (study ARD5530). The pivotal study ARD5021 was an open-label, single-agent Phase II study of oxaliplatin in pediatric patients with recurrent or refractory embryonal CNS tumors. 43 patients were enrolled in the study. The primary objectives were: 1) to estimate the objective response rate (complete response CR plus partial response PR) to oxaliplayin in patients with recurrent or refractory medulloblastoma at first progression; and 2) to estimate the objective response (CR plus PR) rate to oxaliplayin in patients with recurrent or refractory medulloblastoma at second or later relapse.

Statistical Issues:

1. All of the phase II trials are non-randomized trials. No statistical comparisons were conducted in these phase II studies and therefore no statistical inference will be drawn from the studies.

2. The sponsor provided results of progression-free survival in study ARD5021 and ARD5531. PFS is not interpretable in single arm studies. The descriptive statistics of PFS may be used only as supportive data.

Findings:

Study ARD5021: Study ARD5021 was an open-label, single-agent Phase 2 study of oxaliplatin in pediatric patients with recurrent or refractory embryonal CNS tumors. Simon's two-stage Phase II minimax design was to be used to stop accrual to this study as soon as the data suggested that the drug did not warrant further investigation. Based on the aforementioned design parameters, the two-stage design yielded a maximum sample size of 28 patients with medulloblastoma. Sponsor stated that one patient had partial response.

Study ARD5531: This was a multi-center, open-label, non-comparative, non-randomized Phase I/II study with direct individual benefit in children and adolescents with solid tumors, with the Phase II portion being used to provide information on the recommended dose (RD). No tumor responses were observed.

Study ARD5530: The study ARD5530 was an open-label single agent, Phase II study in patients ≤ 21 years of age that evaluated the response of relapsed/recurrent childhood solid tumors to oxalplatin. This study was to provide efficacy data to evaluate other agents in combination with oxaliplatin. The clinical benefit will be tumor control and improvement in disease related symptoms. This is an ongoing study. No tumor responses have been observed to date.

2. INTRODUCTION

2.1 Overview

This NDA was submitted in fulfillment of the Pediatric Written Request (PWR) of 9 December 2004. The sponsor studied the drug oxpliplatatin as a single agent in pediatric patients with medulloblastoma, supratentorial primitive neuroectodermal tumors and atypical teratoid rhaboid tumors after failure of initial therapy (study ARD5021), refractory or relapsed malignant solid tumors (study ARD5531) and with recurrent solid tumors (study ARD5530).

The pivotal study ARD5021 was an open-label, single-agent Phase II study of oxaliplatin in pediatric patients with recurrent or refractory embryonal CNS tumors. Forty three patients were enrolled in the study. The goals of this Phase II study were to estimate the response rate and further assess the toxicity of oxaliplatin in patients with recurrent or refractory embryonal tumors.

Study ARD5531 was a multi-center, open-label, non-comparative, non-randomized Phase I/2II study in children and adolescents with solid tumors, with the phase II portion being the part of the study that evaluated the recommended dose (RD). While 29 patients were included in phase I study, 15 subjects were enrolled in Phase II trial. Study ARD5531 was designed to establish the MTD of single agent weekly oxaliplatin, and thus an RD for phase II trials.

Study ARD5530 was an open-label single agent, Phase II study in patients ≤ 21 years of age that evaluated the response of relapsed/recurrent childhood solid tumors to oxalplatin. This study was to provide efficacy data to evaluate other agents in combination with oxaliplatin. The clinical benefit will be tumor control and improvement in disease related symptoms. This is an ongoing study.

2.1.1 Background

Oxaliplatin, trans-l-1,2-diaminocyclohexane (DACH) oxalatoplatinum, is a novel platinum agent, with similar potency to cisplatin. Oxaliplatin has demonstrated efficacy in preclinical and clinical studies against many tumors types, including those that are cisplatin resistant. Unlike cisplatin, oxaliplatin has caused little or no nephrotoxicity or ototoxicity in clinical trials. Oxaliplatin has demonstrated additive and/or synergistic cytotoxic activity in combination with many other chemotherapeutic agents, including CPT-11, carboplatin, cisplatin, cyclophosphamide, and 5-FU. Although significant progress has been made in the treatment of children with intracranial embryonal tumors such as medulloblastomas and primitive neuroectodermal tumor (PNET)s, the prognosis is poor for patients who have recurrent disease following radiotherapy. Phase II studies evaluating oxaliplatin in adults as a single agent in advanced colorectal cancer reported an 18% response rate as a first line therapy and 10% as second line therapy. Cisplatin and carboplatin used as single agents against metastatic colorectal cancer resulted in 3 and 2.4% response rates, respectively. The two major reactions to oxaliplatin are idiosyncratic and classical hypersensitivity responsive to steroid and histamine receptor antagonists. The Food and Drug Administration (FDA) approved the combination of oxaliplatin

with 5-fluorouracil and leucovorin for recurrent or progressive colorectal cancer within 6 months of first line therapy based on improved median time to tumor progression and tumor response.

In a phase I trial at St Jude Children's Research Hospital, 17 children with recurrent solid tumors have received oxaliplatin administered as a 2-hour IV infusion every 3 weeks. The starting dose was 100 mg/m^2 (3 patients), with subsequent escalation to 130 mg/m^2 (6 patients), 160 mg/m^2 (2 patients) and 160 mg/ m^2 with carbamazepine (6 patients). Diagnoses included neuroblastoma/ ganglioneuroblatoma (n=5), medulloblastoma (n=4), mucinous adenocarcinoma of colon (n=2), hepatocellular carcinoma (n=2), Ewing's sarcoma family tumor, rhabdomyosarcoma, anaplastic Wilm's tumor and chondrosarcoma (n=1 each). No objective antitumor responses were observed. However, stable disease was noted in one patient with medulloblastoma for 11 months and one patient with hepatocellular carcinoma for 5 months. Dose limiting toxicities (DLT) consisted of grade 3 paresthesias/ dysesthesias after completion of the oxaliplatin infusion in 2 patients receiving 160 mg/ m^2. In addition, one patient had grade 3 neutropenia, and the other patient had grade 3 thrombocytopenia. The MTD was 130 mg/ m^2 every 3 weeks.

In this NDA, the pivotal phase II study ARD5021 evaluated the response of relapsed/recurrent childhood solid tumors to oxaliplatin (130 mg/ m^2 intravenously as a two hour infusion every 3 weeks). This study provided efficacy data to evaluate other agents in combination with oxaliplatin. The sponsor had planned that the clinical benefit was tumor control and improvement in disease related symptoms.

2.1.2 Statistical Issues

1. All of the phase II trials are non-randomized trials. No statistical comparison was conducted in these phase II studies and therefore no statistical inference will be drawn from the study.

2. The sponsor provided results of progression-free survival in study ARD5021 and ARD5531. PFS is not interpretable in single arm studies. The descriptive statistics of PFS may be used only as supportive data.

2.2 Data Sources

Data and electronic documents used for this review are located on the network with the path "CDSESUB1\N21492\S_008\2006-07-10\crt\datasets"in the EDR. Submission to this file occurred on July 10, 2006.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

Study ARD5531 was a combination of phase I/II trials with phase II trial with the phase II portion being the part of the study that evaluate the recommended dose (RD). The study

ARD5530 is an on going study. This review will focus on the efficacy aspect of the pivotal phase II study ARD5201.

3.1.1 Study ARD5021

Study ARD5021 was an open-label, single-agent phase II study of oxaliplatin in pediatric patients with recurrent or refractory embryonal central nervous systerm (CNS) tumors. The first patient was enrolled on December 6, 2002 and the last patient was enrolled on May 20, 2005. A total of 43 pediatric patients were enrolled into study and all 43 patients were completed study.

3.1.1.1 Study Design

Study ARD5201 was an open-label, single-agent phase II study of oxaliplatin in patients with recurrent or refractory embryonal central nervous systerm (CNS) tumors. The study was conducted at 10 centers in the United States. Patients were stratified according to histology and prior recurrences (see table 1). ***Stratum IA*** included medulloblastoma patients with measurable disease after failure of initial therapy; ***Stratum IB*** included recurrent or refractory medulloblastoma patients with only positive CSF cytology or with linear leptomeningeal disease; ***Stratum 1C*** included medulloblastoma patients with measurable residual disease at second or later relapse; ***Stratum II*** included patients with recurrent or refractory S-PNET including pineoblastomas, and ependymoblastomas; ***Stratum III*** included patients with recurrent or refractory ATRT.

Table 1: Summary of the Stratums (Sponsor's Table)

Stratum I Medulloblastoma	**Stratum IA** Medulloblastoma with measurable disease at first relapse
	Stratum IB Recurrent or refractory medulloblastoma with only CSF (+) or linear leptomeningeal disease
	Stratum IC Medulloblastoma at second or later progression with measurable residual disease
Stratum II Recurrent S-PNET	
Stratum III Recurrent ATRT	

Simon's two-stage Phase 2 minimax design was to be used to stop accrual to this study as soon as the data suggested that the drug did not warrant further investigation. Based on the aforementioned design parameters, the two-stage design yielded a maximum sample size of 28 patients with medulloblastoma.

Oxaliplatin, 130 mg/m^2, was to be administered intravenously over 2 hours, every 21 days (one course) and could be continued for one year in the absence of disease progression or unacceptable toxicity. Please refer to FDA clinical review, Dr. Senderowicz for more details of inclusion and exclusion criterion for the study populations in this pivotal study.

3.1.1.2 Study Objectives

The primary objectives were: 1) to estimate the objective response rate (complete response medulloblastoma at first progression); and 2) to estimate the objective response (CR plus PR) rate to oxaliplayin in patients with recurrent or refractory medulloblastoma at second or later relapse.

The secondary objectives were: 1) to estimate the objective response rate to oxaliplatin in patients with recurrent or refractory supratentorial primitive neuroectodermal tumor (S-PNET) (including pineoblastomas and ependymoblastomas) or atypical teraoid rhabdoid tumor (ATRT); 2) to test for functional mismatch repair (MMR) system in tumor samples and patients' peripheral white blood cells; and)3) to evaluate the pharmcokinetics of oxaliplatin in the serum and cerebrospinal fluid (CSF) using a limited sampling strategy.

3.1.1.3 Efficacy Endpoints

Primary efficacy endpoint: Confirmed response rate, defined as complete response (CR) plus partial response (PR) to oxaliplatin in patients with recurrent or refractory medulloblastoma at first progression.

Objective response must have been sustained for at least one additional course. Any patient who received at least two courses of oxaliplatin was considered evaluable for the primary estimate of response. Patients who received only one course of oxaliplatin were not invaluable for response unless they died or experienced progressive disease prior to the second course. These patients were included in the analysis as having failed on the date of their event. Patients taken off the trial for toxicity after one course of oxaliplatin were considered non-evaluable for response, but were included in the description of toxicity. Patients taken off treatment for toxicity after two courses were considered to have had a competing event (failure). This design recognizes that most, if not all patients, will progress on treatment; even those patients who initially respond Patients were taken off therapy on the date progressive disease was not noted.

Secondary endpoints: The secondary endpoints are as follows: 1) the objective response rate (CR plus PR) to oxaliplatin in patients with recurrent or refractory supratentorial primitive neuroectodermal tumor (S-PNET) (including pineoblastomas and ependymoblastomas) or atypical teratoidrhabdoid tumor (ATRT); 2) functional mismatch repair (MMR) system in tumor samples and patient peripheral white blood cells; and 3) the pharmacokinetics of oxaliplatin in the serum and cerebrospinal fluid (CSF) using a limited sampling strategy.

3.1.1.4 Sample Size Considerations

In study ARD 5201, per protocol, a two-staged design was used to terminate the trial early for lack of evidence of adequate activity of oxaliplatin. This monitoring was performed separately for Stratums 1A and 1C, with accrual to 1C being conditional on accrual to 1A. In the binomial analysis only confirmed sustained objective responses were considered a success. Progressive disease, failure for any reason to have a confirmed response, unacceptable toxicity after two courses of therapy, and death were considered a failure. In the rest of the stratums, namely stratums IB, II and III, the sponsor stated that the small number of the patients were expected, the results of the study were reported descriptively in terms of estimates of cumulative incidence function to time to confirmed sustained objective response after treatment with 2 to 7 courses (one year) of oxaliplatin.

Stratum IA : Medulloblastomas at initial progression or refractory to initial therapy who have measurable disease

Assuming a binomial distribution for the number of objective responses, a group sequential monitoring rule that was based on Simon's two-stage Phase II minimax design was used. The sequential monitoring rule is described in following table.

Table 2 Two-Stage Group Sequential Rule (Sponsor's Table)

(b) (4)

Stratum IC: Medulloblastoma patients at second or later progression with measurable residual disease

Per Protocol Amendment 3, similar to Stratum IA, medulloblastoma patients who had measurable residual disease at second or later progression were treated. Patients were only treated on protocol once. The sponsor stated that it was expected that a sufficient number of patients in this stratum would be accrued to assess tumor response to oxaliplatin. In addition, patients at initial progression (Stratum IA) and those more heavily pre-treated (Stratum IC) may have similar response rates. Therefore, sponsor used the same design parameters and Simon's two-staged design to assess tumor response in Stratum IC. Continuing accrual to Stratum IC was conditional on what happened in Stratum IA, the sponsor claimed that if sufficient tumor response was observed in Stratum IA based on the sequential rule, then accrual to Stratum IC continued, assuming that sufficient response was observed here as well. Otherwise, accrual to Stratum IC ceased as soon as Stratum IA's accrual stopped. This was based on the assumption

that if the drug did not show sufficient activity in patients at first progression, then it probably would not be sufficient for patients at second or later progression.

3.1.1.5 Efficacy Analysis Methods

Per sponsor, efficacy in all three phase II studies, platinum concentrations in PUF were determined using a validated Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method with a limit of quantification (LOQ) of 1 ng/mL under the responsibility of the Clinical Metabolism and Pharmacokinetics department of Sanofi-Synthelabo Research, Alnwick, UK, a division of sanofi-aventis.

All raw data from the bioanalytical study for platinum in PUF are stored at the Sanofi-Synthelabo Research Scientific Records Center, Alnwick, UK, a division of Sanofi-Aventis.

Descriptive statistics, tables, and listings were used to describe the results of these studies. No formal statistical testing was planned.

3.1.1.6 Summary of the results of study ARD5201

This section presents the results of study ARD5201 of single agent oxaliplatin in pediatric patients with recurrent or refractory embryonal CNS tumors. The primary objective was to measure objective response rate.

A total of 43 patients, ranging in age from 7 months to 18 years, were treated with 47cycles of oxaliplatin. The median number of cycles was 2 with a range of 1 to 17 cycles administered. Per sponsor, a partial response was observed in 1 patient with medulloblastoma. This study was conducted to evaluate the efficacy of single agent oxaliplatin at dose of 130 mg/m2 in pediatric patients with recurrent or refractory embryonal CNS tumors. There were 3 **primary** strata: **Stratum I** included three substrata of patients with recurrent medulloblastoma; **Stratum II** included patients with recurrent or refractory S-PNET's and **Stratum III** included patients with recurrent or refractory ATRT's. The 3 **sub-strata in Stratum I** were: **Stratum IA** that included patients with medulloblastoma with measurable disease after failure of initial therapy; **Stratum IB** that included patients with recurrent or refractory medulloblastoma patients with positive CSF cytology or linear leptomeningeal disease; and **Stratum IC** that included medulloblastoma patients at second or later relapse with measurable residual disease.

The main efficacy assessment was based on only 2 strata; **Stratum IA and IC**. The study used a Simon two-stage Phase II minmax design (b) (4)

Continuation of enrollment on **Stratum IC** was also conditional upon the observed response rate on Stratum IA with the assumption that the response rate on Stratum IC would be at best equal to that observed on **Stratum IA.**

Total Forty-three patients were evaluable for efficacy. The majority of patients were male (69.8%) and most patients had a performance score between 80 and 100%. Disease progression was the most common reason for stopping treatment (74.4%). All patients received prior anticancer therapy; chemotherapy was received by all patients and prior radiotherapy was received by 74.4% of patients.

Tables 3 and 4 bellow are sponsors findings based on confirmed response rate by stratum and progression-free survival, respectively. The accuracy of sponsor's results has been confirmed by this reviewer.

Table 3: Summary of Confirmed Response Rate by Stratum (Sponsor's Table)

Table 4: Summary of Progression-Free Survival (Sponsor's Table)

Note: Per sponsor, the following are the definitions of the stratums.
Stratum IA - Medulloblastoma with measurable disease at FIRST relapse

Stratum IB - Recurrent or refractory medulloblastoma with only CSF (+) or linear leptomeningeal disease
Stratum IC - Medulloblastoma at SECOND or LATER progression with Measurable residual disease
Stratum II - Recurrent Supratentorial primitive neuroectodermal tumors (PNET)
Stratum III- Recurrent Atypical Teratoid Rhabdoid Tumors (ATRT)

Confirmed response rates: Sponsor's results of the confirmed response rates are summarized in Table 3. (b) (4)

Progression free survival: The sponsor's results of the progression survival were listed in table 4. (b) (4)

Reviewer Comments:

1. Study ARD5021 is a non-randomized trial. No statistical comparison was conducted in these phase II studies and therefore no statistical inference will be drawn from the study.

2. PFS is not interpretable in single arm studies. The descriptive statistics of PFS can be used only as a supportive interpretation.

3. According to the FDA medical reviewer, the reported PR was not confirmed.

3.1.2 Other supportive studies

Study ARD5531: This was a multi-center, open-label, non-comparative, non-randomized Phase I/2II study in children and adolescents with solid tumors, with the phase II portion being the part of the study that evaluated the recommended dose (RD). While 29 patients were included in phase I study, 15 subjects were enrolled in Phase II trial.
Study ARD5531 was designed to establish the MTD of single agent weekly oxaliplatin, and thus an RD for phase II trials.

Tables 5, 6 and 7 are sponsors results based on best overall response rate, best overall response by initial diagnosis and progression -free survival, respectively.

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Table 7: Summary of Progression-Free Survival (Sponsor's Table)

Study ARD5530: This was an open-label, single agent, Phase 2 study in patients ≤21 years of age that evaluated the response of relapsed/recurrent childhood solid tumors to oxaliplatin. This study was to provide efficacy data to evaluate other agents in combination with oxaliplatin. The clinical benefit will be tumor control and improvement in disease related symptoms. Oxaliplatin was administered at a dose of 130 mg/ m^2 over 2 hours intravenously. Each cycle was administered every 3 weeks. Patients could receive study treatment for up to 12 months or 17 cycles. Patients ≤12 months of age received a dose of 4.3 mg/kg. Within each category, a two-stage design was employed. Entry was terminated to any particular diagnostic category if the stopping criteria for the multistage rule were met. The two stage design is summarized in table 8.

Table 8: Two Stage Study Design (Sponsor's Table)

Table 9 below provided the results of the study. Forty-seven patients were treated at the time of data-cut off. The majority of patients were male (72.9%) and Caucasian (81.3%) and most patients had a performance score between 90% and 100%. Disease progression was the most common reason for stopping treatment (66.7%). All patients received prior anticancer therapy; chemotherapy was received by all patients and prior radiotherapy was received by 41.7% of patients. Forty patients were evaluable for efficacy. There were no responses in the four strata

(Ewing sarcoma/peripheral PNET (n=11), Neuroblastoma (n=13), Ostesarcoma (n=13) and Rhabdomyosarcoma (n=10)).

Table 9: Summary of Confirmed Response Rate by Stratum (Sponsor's Table)

(b) (4)

Reviewer's Comment: Study ARD5530 was an ongoing study.

4. SUMMARY AND CONCLUSIONS

This NDA supplement is in fulfillment of the Pediatric Written Request (PWR) of 9 December 2004. The sponsor studied the administration of oxaliplatin as a single agent in pediatric patients with medulloblastoma, supratentorial primitive neuroectodermal tumors and atypical teratoid rhaboid tumors after failure of initial therapy (study ARD5021) , refractory or relapsed malignant solid tumors (study ARD5531) and with recurrent solid tumors (study ARD5530).

(b) (4)

Since sponsor presented the pivotal phase II trial designed as open labeled, uncontrolled, non-randomized study, no formal statistical testing or comparisons could be conducted.
The effectiveness of oxaliplatin single agent in the pediatric populations has not been established. (b) (4) The final recommendation should be based on clinical judgment.

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