CLINICAL REVIEW

Application Type	NDA
Submission Number	CDSESUB1\N21492
Submission Code	S_008\
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Reviewer Name	Adrian M. Senderowicz
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Established Name	Oxaliplatin
(Proposed) Trade Name	Oxaliplatin
Therapeutic Class	Anticancer agent
Applicant	Sanofi-Aventis
Priority Designation	P
Formulation	(b) (4) powder
Dosing Regimen	130 mg/m IV every 21 days
Indication	Pediatric solid tumors
Intended Population	Pediatric

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of this sNDA supplement N21492\S008 for Eloxatin® (oxaliplatin for injection) to add information from the pediatric cancer trials to the label.

1.2 Recommendation on Postmarketing Actions

No new recommendations. Continue post-marketing surveillance

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

No new requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The oxaliplatin pediatric program consists of 4 studies – 2 Phase 1 studies (ARD5531 and DFI7434) and 2 Phase 2 studies (ARD5021 and ARD5530) involving 159 patients ages 7 months to 22 years with advanced and/or refractory solid tumors. Only 1 partial response was observed in the entire program (1/159 (b) (4)).

In a Phase 1-2 study (ARD5531), oxaliplatin was administered as a 2-hour IV infusion on days 1, 8 and 15 every 4 weeks (1 cycle), for a maximum of 6 cycles, to 43 patients with refractory or relapsed malignant solid tumors, mainly neuroblastoma and osteosarcoma. Twenty eight (28) pediatric patients in the Phase I study received oxaliplatin at 6 dose levels starting at 40 mg/m² with escalation to 110 mg/m². The dose limiting toxicity (DLT) was sensory neuropathy at the 110mg/m² dose. Fifteen (15) patients received oxaliplatin at a dose of 90 mg/m² IV in the Phase II portion of the study. At this dose,

paresthesia (60%, G3/4: 7%), fever (40%, G3/4: 7%) and thrombocytopenia (40%, G3/4: 27%) were the main adverse events. No responses were observed.

In a second Phase 1 study (DFI7434), oxaliplatin was administered to 26 pediatric patients as a 2-hour IV infusion on day 1 every 3 weeks (1 cycle) at 5 dose levels starting at 100 mg/m² with escalation to 160 mg/m², for a maximum of 6 cycles. In a separate cohort, oxaliplatin 85 mg/m² was administered on day 1 every 2 weeks, for a maximum of 9 doses. Patients had metastatic or unresectable solid tumors mainly neuroblastoma and ganglioneuroblastoma. The DLT was sensory neuropathy at the 160 mg/m² dose. Based on these studies, oxaliplatin 130 mg/m² as a 2-hour IV infusion on day 1 every 3 weeks (1 cycle) was used in subsequent Phase II studies. A dose of 85 mg/m^2 on day 1 every 2 weeks was also found to be tolerable. No responses were observed

In one Phase 2 study (ARD5021), 43 pediatric patients with recurrent or refractory embryonal CNS tumors received oxaliplatin 130 mg/m2 every 3 weeks for a maximum of 12 months in absence of progressive disease or unacceptable toxicity. In patients < 10 kg the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were leukopenia (67%, G3/4: 12%), anemia (65%, G3/4: 5%), thrombocytopenia (65%, G3/4: 26%), vomiting (65%, G3/4: 7%), neutropenia (58%, G3/4: 16%) and sensory neuropathy (40%, G3/4: 5%). One partial response was observed.

In a second Phase 2 study (ARD5530), 47 pediatric patients with recurrent solid tumors, including Ewing sarcoma or peripheral PNET, osteosarcoma, rhabdomyosarcoma and neuroblastoma, received oxaliplatin 130 mg/m2 every 3 weeks for a maximum of 12 months or 17 cycles. In patients $\leq$ 12 months old the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were sensory neuropathy (53%, G3/4: 15%), thrombocytopenia (40%, G3/4: 26%), anemia (40%, G3/4: 15%), vomiting (32%, G3/4: 0%), nausea (30%, G3/4: 2%) and AST increased (26%, G3/4: 4%). No responses were observed.

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 109 pediatric patients during the first cycle. The median clearance in pediatric patients estimated by the population pharmacokinetic analysis was 4.80 L/h. The inter-patient variability of platinum clearance in pediatric cancer patients was 40.9 %. Mean platinum pharmacokinetic parameters in ultrafiltrate were C_{max} of 754 $\pm$ 244 ng/mL, AUC_{0-48} of 7520 $\pm$ 5070 ng·h/mL and AUC of 8830 $\pm$ 1570 ng·h/mL at 85 mg/m² of oxaliplatin and C_{max} of 1100 $\pm$ 428 ng/mL, AUC_{0-48} of 9740 $\pm$ 2520 ng·h/mL and AUC of 17300 $\pm$ 5340 ng·h/mL at 130 mg/m² of oxaliplatin. PK parameters are similar to the ones observed in adults. No PK/PD was done due to low response rate in this population (< 1%)

(b) (4)

1.3.2 Efficacy:

Only 1 reported partial response out of 159 patients was observed [redacted] (b) (4)

1.3.3 Safety:

In general, the safety profile of oxaliplatin in the pediatric population was similar to the one observed in the adult population. A total of 98 deaths were reported in all trials. Two of them occurred during the trial (1 case associated with dehydration and the other due to SVC syndrome) and 13 occurred within 28 days after last dose. All deaths were clearly or likely due to disease progression. This is expected in a population with very advanced and refractory metastatic solid tumors. Assessment of cause of AEs is difficult in this end-stage population. SAEs occurred in ~ 20 % of patients. SAEs seen in 2 or more patients were: headache, hypersensitivity reactions, convulsions and sensory neuropathy. AEs leading to discontinuations were as follows: 3 cases of thrombocytopenia, 2 cases of hypersensitivity reactions and 1 each: pain, dehydration, bone pain, tumor pain, Horner's syndrome, urinary retention, pleural effusion, respiratory distress, hematoma and 1 SVC occlusion. Most common AEs were leukopenia, thrombocytopenia, anemia, vomiting and sensory neuropathy.

1.3.4 Dosing Regimen and Administration:

Based on study ARD5531, the recommended Phase 2 dose was 90 mg/m2 oxaliplatin administered IV over 2 hours. Sixteen patients were treated at this dose in this trial. However, in both Phase 2 trials ARD5021 and ARD5530, the dose was 130 mg/m2 oxaliplatin administered IV over 2 hours every 3 weeks. For patients < 10 kg, the dose was 4.3 mg/kg.

1.3.5 Drug-Drug Interactions

None reported in pediatric trials.

1.3.6 Special Populations

These studies were performed in kids, ages 7 months until 21 years of age.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Oxaliplatin is a derivative of cisplatin, a known effective antitumor agent.

2.2 Currently Available Treatment for Indications

Therapy of pediatric solid tumors involves very intensive combination chemotherapy regimens. For some indications, cisplatin (analog of oxaliplatin) is included in several combination chemotherapies (please see http://www.cancer.gov/cancertopics/ types/ childhoodcancers for more information)

2.3 Availability of Proposed Active Ingredient in the United States

It is available in the US since its approval for the treatment of refractory advanced colorectal cancer in August 2002, under subpart H. In January 2004, this agent received full approval for advanced colorectal carcinoma. In November 2004, oxaliplatin received accelerated approval for the adjuvant treatment (stage III) of colon cancer.

2.4 Important Issues With Pharmacologically Related Products

Not applicable

2.5 Presubmission Regulatory Activity

Oxaliplatin was approved under subpart H for the treatment of refractory advanced colorectal cancer on 8/02. In January 2004, oxaliplatin received full approval for advanced colorectal cancer. In November 2004, oxaliplatin received accelerated approval for the adjuvant treatment (stage III) of colon cancer.
On Dec 2004, the DDOP requested a Pediatric Written Request to the Sponsor. In the letter, the division requested that the sponsor study this agent in the pediatric oncological population. On 7/10/06, the sponsor submitted the clinical study report (see Appendix, Table 1 for the PWR and Companies' s response). On 9/27/06, the division presented the data to the Pediatric Board Review. The Board recommended extension of exclusivity.

2.6 Other Relevant Background Information

Not applicable

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable

3.2 Animal Pharmacology/Toxicology

Not applicable

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Application: N021492
Document: 2961201
Location: \\CDSESUB1\N21492\S_008\2006-07-10

4.2 Tables of Clinical Studies

Table 1 Oxaliplatin Pediatric studies

Study	Phase	Description of treatments	Na	Study Status
ARD5531	Phase 1	• 40, 50, 60, 75, 90, or 110 mg/m2 oxaliplatin administered IV over 2 hours on Days 1, 8, and 15 of each cycle • Children < 1 year had their dose calculated in mg/kg: 1.3, 1.7, 2.0, 2.5, 3.0, or 3.7 mg/kg • Cycle repeated every 4 weeks	29	Completed
	Phase 2 Recommended Dose cohort	• 90 mg/m2 oxaliplatin administered IV over 2 hours on Days 1, 8, and 15 of each cycle • Cycle repeated every 4 weeks	16	Completed
DFI7434	Phase 1	• 100, 130, 160 mg/m2 oxaliplatin or 160 mg/m2 oxaliplatin with carbamazepine administered IV over 2 hours every 3 weeks • 85 mg/m2 oxaliplatin administered IV over 2 hours every 2 weeks	26	Completed
ARD5021	Phase 2	• 130 mg/m2 oxaliplatin administered IV over 2 hours; patients <10 kg received oxaliplatin 4.3 mg/kg • Cycle repeated every 3 weeks	43	Completed
ARD5530	Phase 2	• 130 mg/m2 oxaliplatin administered IV over 2 hours; patients ≤ 12 months received oxaliplatin 4.3 mg/kg • Cycle repeated every 3 weeks • Four strata completed; 7 strata ongoing	48b	Completed

[a] Number of patients entered. [b] Number of patients enrolled in 4 completed strata of interest per the PWR. Source: Sponsor's Table (1.2)1

ARD5531

This was a multi-center, open-label, non-comparative, non-randomized Phase 1/2 study in children and adolescents with solid tumors, with the Phase 2 portion being the part of the study that evaluated the recommended dose (RD). The study was conducted at 8 centers in France. Patients had to be 6 months to 21 years of age with a life expectancy of more than 6 weeks. Patients must have had Histologically or cytologically confirmed malignant solid tumors and had an Eastern Cooperative Oncology Group (ECOG) Performance status ≤2 (Lansky scale was recommended in patient <12 years of age).

In Phase 1, 18 to 36 patients were to be included to assess the DLTs and the MTD with 3 to 6 patients at each dose level. Six dose levels were planned. The starting dose level was equal to 40 mg/m² (corresponding to 80% of the recommended dose in adults) with an approximate dose escalation of 20% per level. Children <1 year had their dose calculated in mg/kg: 1.3, 1.7, 2.0, 2.5, 3.0, or 3.7 mg/kg. Each cycle was repeated every 4 weeks. At least 10 patients were to be treated in the Phase 2 RD portion of the study at the recommended dose to evaluate toxicity over 4 cycles.

The treatment was continued as 1 cycle every 4 weeks for a maximum of 6 cycles. Treatment continuation beyond 6 cycles was discussed with the trial coordinator and the Sponsor.

Objectives
The primary objective of the study was to establish the maximum tolerated dose (MTD) of single agent weekly oxaliplatin, and thus an RD for Phase 2 trials. The secondary objectives were to 1) define dose limiting toxicity (DLT); 2) define the safety profile; 3) examine pharmacokinetic parameters; and 4) evaluate efficacy.

Efficacy, safety, and pharmacokinetic evaluations
Efficacy was not a primary objective of this study. Best overall response to treatment was summarized for all patients enrolled. Ninety-five percent confidence limits were calculated.
Exposure to oxaliplatin was summarized by number of cycles administered. Total number of cycles, median, minimum, and maximum were shown for each dose group and for the total population.

Dose limiting toxicities were summarized. The following toxicities were considered DLT if it was likely they were related to oxaliplatin:
• prolonged Grade 4 neutropenia (<0.5 x 109/L) lasting more than 7 days;
• prolonged Grade 4 thrombocytopenia (<10.0 x 109/L) lasting more than 7 days;
• any other non-hematological and Grade 4 toxicity including Grade 4 infection whatever the duration of neutropenia (except alopecia);
• any non-hematological toxicity ≥ Grade 3 except:
- Grade 3 AST/ALT that returned to baseline by the time of retreatment;
- Grade 3 fever without documented infection;
- Grade 3 nausea and vomiting in the absence of effective maximal antiemetic treatment;
- Grade 3 mucositis.
• Grade 2 peripheral neuropathy that does not resolve prior to initiation of the next cycle

of therapy;
• life-threatening toxicity.

Adverse events and clinical laboratory results were summarized by all grades and Grade 3 or 4. Specific neurological events were summarized separately. All deaths were listed and deaths within 28 days of the last dose of oxaliplatin were summarized. Serious adverse events (SAEs) and AEs leading to study medication discontinuation were summarized.
Plasma PK parameters were listed by patient and summarized using descriptive statistics by level.

DFI7434

This was an open-label non-randomized Phase 1 study that investigated several dose levels of oxaliplatin to define a dose level that was tolerable and could be used for future Phase 2 studies.

The study was conducted at 1 US center. Patients had to be under 21 years of age at the time treatment began and must have had histologically confirmed solid tumors that were metastatic or unresectable or for which standard curative or palliative measures do not exist or are no longer effective. Patients had to have an ECOG performance status = 2 (or Lansky Play-Performance Scale 50%) and adequate organ and marrow function.

Five dose levels were used. The starting dose level was 100 mg/m2. Successive cohorts were treated at increasing dose levels (depending on the occurrence of DLTs) up to the MTD. Dose levels 1 to 3 (100, 130, and 160 mg/m2) evaluated oxaliplatin monotherapy administered every 3 weeks. Dose level 4 evaluated 160 mg/m2 oxaliplatin administered every 3 weeks with oral carbamazepine. Dose level 5 evaluated the safety of 85 mg/m2 oxaliplatin administered every 2 weeks to determine if this dose could be used for Phase 1 combination studies or Phase 2 studies.

Patients could have received up to 6 courses of treatment (or 9 doses of oxaliplatin for the patients enrolled at dose level 5). If a patient was doing well on treatment the Principal Investigator in consultation with NCI could consider extending therapy with additional courses of oxaliplatin.

Objectives
The primary objectives were 1) to determine the MTD of the intravenous (IV) preparation of oxaliplatin, given as a 2-hour IV infusion in an outpatient setting at 3-week intervals, for pediatric patients with metastatic or unresectable solid tumors for which standard treatment does not exist or is no longer effective; and 2) to assess the safety of the intravenous preparation of oxaliplatin, given at a dose of 85 mg/m2 as a 2-hour IV infusion in an outpatient setting at 2-week intervals, for pediatric patients with metastatic or unresectable solid tumors for which standard treatment does not exist or is no longer effective.

The secondary objectives were to 1) determine the DLT of oxaliplatin when administered intravenously, including qualitative and quantitative toxicities, and to define their duration

and reversibility; 2) characterize the pharmacokinetics of oxaliplatin in children with drug resistant malignant solid tumors; 3) evaluate the relationship between pharmacokinetic parameters, toxicity, and/or response; 4) note any anti-tumor effects, as measured by standard response criteria; and 5) determine the value of dynamic contrast enhanced magnetic resonance imaging (DEMRI) in assessing response in patients with bone or soft tissue lesions of the extremities, comparing images obtained before and after two courses of oxaliplatin.

Efficacy, safety, and pharmacokinetic evaluations
Efficacy was not a primary objective of this study. Best overall response to treatment was summarized for all patients enrolled.
Exposure to oxaliplatin was summarized by number of doses administered. Total number of doses, median, minimum, and maximum were shown for each treatment group and for the total population.

Dose limiting toxicities were summarized. A DLT was defined as any Grade 3 nonhematologic or Grade 4 hematologic AE including:
• ≥Grade 2 neuropathy that did not resolve prior to initiation of the next cycle of therapy;
• Grade 4 neutropenia that did not resolve in 7 days;
• Grade 4 thrombocytopenia persisting for ≥7 days (or requiring platelet transfusion for ≥7 days);
• ≥Grade 3 nausea and ≥ Grade 3 vomiting that occurred despite maximal antiemetic therapy;
• ≥Grade 3 diarrhea that occurred despite patient compliance with loperamide therapy;
or, treatment delays of ≥4 weeks.

Adverse events and clinical laboratory parameters were summarized by all grades and Grade 3 or 4. Specific neurological events were summarized separately according to an oxaliplatin-specific scale. SAEs and AEs leading to study medication discontinuation were summarized. All deaths were listed including deaths within 28 days of the last dose of oxaliplatin.
Plasma PK parameters were listed by patient and summarized using descriptive statistics by dose level.

Phase 2 studies

ARD5021

Study Design
This was an open-label, single-agent Phase 2 study of oxaliplatin in pediatric patients with recurrent or refractory embryonal CNS tumors. These patients were stratified according to histology and prior recurrences.

Stratum IA: medulloblastoma patients with measurable disease after failure of initial therapy;

Stratum IB: recurrent or refractory medulloblastoma patients with only positive CSF cytology or with linear leptomeningeal disease;

Stratum 1C: medulloblastoma patients with measurable residual disease at second or later relapse;

Stratum II: patients with recurrent or refractory supratentorial primitive

neuroectodermal tumor (S-PNET) including pineoblastomas, and ependymoblastomas;
Stratum III: patients with recurrent or refractory atypical teratoid rhabdoid tumor (ATRT).

The study was conducted at 10 US centers. Patients had to be ≤21 years of age at the time of registration on the protocol with histologically confirmed medulloblastoma, supratentorial PNET (including pineoblastoma, ependymoblastoma), or ATRT that is recurrent or refractory to therapy. Patients had to have a Karnofsky or Lansky performance status ≥ 50% and had to have adequate bone marrow, renal, hepatic, cardiac, pulmonary, and CNS function.

Simon's two-stage Phase 2 minimax design was to be used to stop accrual to this study in the event 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 each for cohorts IA and IC.

Oxaliplatin, 130 mg/m^2, was to be administered intravenously over 2 hours, every 21 days and could be continued for one year in the absence of disease progression or unacceptable toxicity. Patients < 10 kg received a dose of 4.3 mg/kg.

Objectives

The primary objectives were 1) to estimate the objective response rate (CR plus PR) to oxaliplatin in patients with recurrent or refractory medulloblastoma at first progression; and 2) to estimate the objective response (CR plus PR) rate to oxaliplatin 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 teratoid 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 pharmacokinetics of oxaliplatin in the serum and CSF of the above patient group using a limited sampling strategy.

Efficacy, safety, and pharmacokinetic evaluations
Assuming a binomial distribution for the number of objective responses, a group sequential monitoring rule based on Simon's two-stage Phase 2 minimax design (see table 2) was used to stop accrual to the study in the event the data suggested that the drug did not warrant further investigation. Objective response rate and progression free survival were summarized by stratum for all patients enrolled; 95% confidence limits were calculated. Exposure to oxaliplatin was summarized by number of cycles administered. Total number of cycles, median, minimum, and maximum were shown for each dose group and for the total population.

Adverse events were summarized by all grades and Grade 3 or 4. Specific neurological events were summarized separately according to an oxaliplatin-specific scale. SAEs and

AEs leading to study medication discontinuation were summarized. All deaths were listed including deaths within 28 days of the last dose of oxaliplatin. Clinical laboratory results were summarized.

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/m2 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, the following two stage design was employed. Entry was terminated to any particular diagnostic category if the stopping criteria for the multistage rule were met.

Table 2 Simon's two-stage Phase 2 minimax design

(b) (4)

Objectives
The objectives of the study were to determine the response rate of various disease strata of recurrent or refractory solid malignant tumors of childhood to oxaliplatin.

The target tumors were:

1. Ewing sarcoma or peripheral PNET;
2. Osteosarcoma;
3. Rhabdomyosarcoma;
4. Neuroblastoma;
5. High grade astrocytoma and multiforme glioblastoma;
6. Low grade astrocytoma;
7. Ependymoma;
8. Brain stem glioma;
9. Hepatoblastoma;
10. Malignant germ cell tumors of any site;
11. Other rare tumors of interest. Rare tumors of interest included soft tissue sarcoma, hepatocellular carcinoma and other carcinomas such as childhood/adolescent

colorectal carcinoma, renal cell carcinoma, adrenocortical carcinoma and nasopharyngeal carcinoma.

The results of the first 4 strata (Ewing sarcoma, osteosarcoma, neuroblastoma, and rhabdomyosarcoma) are presented in this submission per the PWR. Patients in the 4 strata were enrolled at 35 centers in the US, Canada, and Australia. Other strata are continuing to enroll patients.

Other objectives were to determine the cumulative toxicity of oxaliplatin administered over multiple courses to children with different recurrent solid tumors; characterize the pharmacokinetic profile of oxaliplatin when administered to pediatric patients with recurrent or refractory solid tumors; assess the relation between the extent of oxaliplatin exposure and response (eg, toxicities and antitumor effects); and determine the time to progression and overall survival of children treated with oxaliplatin for recurrent solid tumors.

Efficacy, safety, and pharmacokinetic evaluations
Objective response rate was summarized by stratum for all patients enrolled; 95% confidence limits were calculated. PFS and overall survival were not evaluated in this interim report.

Exposure to oxaliplatin was summarized by number of cycles administered. Total number of cycles, median, minimum, and maximum were shown for each dose group and for the total population.

Adverse events were summarized by all grades and grade 3 or 4. Dose limiting toxicities were also summarized. Specific neurological events were summarized separately. Each site was asked to complete a specific panel in the database, which listed neurotoxicities associated with oxaliplatin. This panel included events such as paresthesias/dysesthesias, cold related dysesthesias, laryngopharyngeal dysesthesia, and muscle cramping/spasm/jaw pain. At each cycle, the study staff was asked to assess whether or not each of these events was present. Hematology and clinical chemistry values were graded according to NCI-CTC Version 3 at the institutional level and reported as clinical AEs.

SAEs and AEs leading to study medication discontinuation were summarized. All deaths were listed including deaths within 28 days of the last dose of oxaliplatin.
Platinum pharmacokinetic parameters were listed by patient and summarized using descriptive statistics.

Reviewer's comments: The applicant responded successfully to our PWR.

4.3 Review Strategy

The efficacy and safety review is based primarily on analysis of data submitted as SAS transport files for 4 trials in pediatric solid tumors.

4.4 Data Quality and Integrity:

Adequate.

4.5 Compliance with Good Clinical Practices

Adequate

4.6 Financial Disclosures

Three studies, ARD5530, DFI7434 and ARD5021 were sponsored with the National Cancer Institute under their IND (b) (4) in collaboration with two participating cooperative groups and one single site. Study ARD5531 was conducted in conjunction with the Institut Gustave Roussy.

Sanofi-aventis attempted to retrospectively collect financial information from participating investigators and was successful in obtaining information for most investigators.

Reviewer's note: Only 3 investigators in study ARD5330 and 1 investigator in ARD5331 did not provide financial disclosure to the applicant despite efforts by the applicant to obtain this information

5 CLINICAL PHARMACOLOGY

The following are excerpts from Dr. Ramchandani, Clinical Pharmacology reviewer

5.1 Pharmacokinetics:

PK data was collected in all 4 studies included in the current submission, using a combination of rich and sparse samples, in a total of 105 patients.

PK data collected in the phase 1 studies, ARD5531 and DFI7434, were used to obtain non-compartmental and compartmental PK estimates for platinum (Pt) in plasma and plasma ultrafiltrate (PUF). Data from all 4 studies were also combined for a population PK analysis to estimate PK parameters and evaluate the variability and effect of covariates on the PK parameters. Cmax, AUC0-48, AUC, Vss and CL values were determined by non-compartmental analysis. t1/2α, t1/2β, and t1/2γ were determined by compartmental analysis. Results showed that exposure to Pt following oxaliplatin appears to increase linearly with dose. The half-life estimates, obtained from compartmental analysis appeared to be consistent across dose levels.

The sponsor also conducted a population PK analysis for oxaliplatin using Pt concentrations in plasma ultrafiltrate (PUF) from all 4 studies (total number of subjects=105). Data were fit to a 3-compartment model. The effect of several covariates on the PK of oxaliplatin was also evaluated. Based on individual estimates derived from the final model, the mean clearance in the combined study sample was 5.1 L/hr. Covariate analysis indicated significant effects of glomerular filration rate (GFR) and body weight on clearance and of body weight on volume. Inter-patient variability associated with clearance was estimated to be 37% and with V3 was 6%, while that with V2 was more than 300%. The residual variability for the final model was 41%.

Comparison of PK of oxaliplatin in pediatric and adult patients

The PK of oxaliplatin in the pediatric population was compared with the PK parameters for oxaliplatin obtained from studies of oxaliplatin as a single agent in adult cancer patients. The results indicate that the exposures seen in pediatric and adult patients were comparable both in plasma and PUF, following comparable doses. This suggests that the PK parameters for pediatric and adult patients are comparable. The population estimate for oxaliplatin clearance in pediatric patients is 5.1 L/hr or 4.7 L/hr/m^2 (%CV=37%) when normalized for body surface area (BSA). The estimate of oxaliplatin clearance in adults is reported to be 9.3 L/hr at 130 mg/m^2 (previous NDA submission and Graham et al., Clin Pharmacokinet 2000). Using a nominal BSA of 1.73 m^2, these clearances would translate to 5.4 L/hr/m^2. These estimates indicate that the PK in pediatric patients can be predictable from adults.

5.2 Pharmacodynamics

There was only 1 partial response in 159 patients

5.3 Exposure-Response Relationships:

The sponsor conducted an exposure-toxicity analysis to evaluate the incidence of some of the major toxicities as a function of platinum exposure (AUC) following oxaliplatin. The major toxicities evaluated were hematological toxicity, gastrointestinal toxicity, neurological toxicity, and renal and urinary toxicity. The sponsor only used data from the phase 2 studies for this analysis, and could only include patients with PK data, which resulted in a total of 46 patients. The incidence of all grades of toxicities as well as for grades 3 and 4 were evaluated. No significant relationships with exposure were seen for any of the toxicities evaluated.

The Agency combined the data from both phase 1 and phase 2 studies, and evaluated exposure-response relationships for grade 3/4 toxicities, including nausea, vomiting, diarrhea, neuropathy, neutropenia, febrile neutropenia, anemia and thrombocytopenia. No significant relationships were found for incidence of 3/4 toxicity and exposure.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: refractory solid tumors in children

6.1.1 Methods

The efficacy and safety review is based primarily on analysis of data submitted as SAS transport files for the 4 trials in pediatric solid tumors.

6.1.2 General Discussion of Endpoints:

For Phase 1, MTD. For Phase 2 trials, objective response rate.

Reviewer's comment: endpoints for Phase 1 and Phase 2 studies are appropriate

6.1.3 Study Design:

Table 3 Study Design ARD5530

Study Design	An open label, multi-center, single-agent Phase II study of oxaliplatin in pediatric patients with recurrent or refractory solid malignant tumors. Patients with any of the following tumor types are eligible: - Ewing sarcoma or peripheral PNET - Osteosarcoma - Rhabdomyosarcoma - Neuroblastoma - High grade astrocytoma and multiforme glioblastoma - Low grade astrocytoma - Brain stem glioma - Ependymoma - Hepatoblastoma - Malignant germ cell tumors of any site - Other rare tumors of interest Oxaliplatin, 130 mg/m2, will be administered intravenously, over 2 hr, every 21 days (one course) and can be administered up to 17 times or up to 12 months.
Protocol Defined Statistical Analysis	**Endpoint(s):** **Primary** To estimate the objective response rate (CR plus PR) to oxaliplatin in patients treated for 2-17 courses per year. **Statistical Methods:** Descriptive statistics will be provided according to the nature of the variables.

The response evaluation rule (see Table 2) will be applied if sufficient numbers of patients with brain stem glioma, hepatoblastoma, malignant germ cell tumors or other tumors of interest are enrolled. Otherwise study entry onto ARD5530 will be terminated when the first seven categories have been evaluated.

Four disease strata were identified for reporting upon completion of evaluation of the particular disease stratum. These disease strata are: (1) Ewing sarcoma or peripheral PNET; (2) osteosarcoma; (3) rhabdomyosarcoma; and (4) neuroblastoma.

Within each category, the following two stage design (see Table 2) will be employed:

(b) (4)

Patients with hepatoblastoma, malignant germ cell tumors of any site or rare tumors of interest including hepatocellular, childhood/adolescent colorectal, renal cell, adrenocortical and nasopharyngeal carcinomas were entered. The seven primary tumor types will be evaluated according to the multistage rule. Entry will be terminated to any particular diagnostic category if the stopping criteria for the multistage rule are met. Otherwise, all patient entries will be terminated when evaluation of the above mentioned seven categories is completed.

6.1.4 Efficacy Findings:

Patient disposition

A total of 159 patients were treated with at least one dose. Of these, only 5 completed treatment (5/159, See Tables 4 and 5)

Table 4 Patient disposition - All studies

	Phase 1		Phase 2			Total
	DFI7434	ARD5531	ARD5531 RD cohort	ARD5021	ARD5530	
Included	26	29	16	43	48a	162
Evaluable for safety	26	28	15	43	47	159
Completed prescribed dosing	3	0	0	2	NR	5

a Patient numbers 715256 and 746558 represent the same patient. The patient was initially enrolled as 715256 but was required to sign a revised informed consent and was subsequently re-enrolled and treated as patient 746558. This patient is only counted once in all disposition and demographic summary tables. Source: Module 5.3.5.2; DFI7434 Table (10.1) 1; ARD5531 Table (10.1) 1; ARD5021 Table (10.1) 1; ARD5530. Table (10.1) 1. Source: (2.1) 1

In DFI7434, 26 patients were treated and evaluable for safety. Three patients completed the study. Study completion was defined as receiving up to 6 cycles of treatment for dose levels 1 to 4 or 9 doses of oxaliplatin at dose level 5.

In ARD5531, 29 patients were enrolled in the Phase 1 portion of the study, 28 were treated and evaluable for efficacy and safety. One patient was not treated due to organ toxicity (audiometric test Grade III). Another patient received partial treatment with 75 mg/m2 in Cycle 1 and was not included in the evaluation of DLTs.

In the Phase 2 RD cohort of ARD5531, 16 patients were enrolled, 15 were treated and evaluable for efficacy and safety. One patient was removed from the study due to disease progression (bone metastasis) prior to baseline measurements. Therefore, he did not receive treatment and was not evaluable for efficacy or safety.

In ARD5021, 43 patients were enrolled, treated, and evaluable for safety.

In ARD5530, 48 patients were enrolled and 47 patients were treated. One patient was enrolled in the study twice under 2 different patient numbers (715256 and 746558). He was first enrolled as Patient 715256 and was not treated because an incorrect informed consent was signed. He was re-enrolled as Patient 746558 and was subsequently treated. This patient is counted only once in the disposition and demographic summary tables.

The reasons for stopping treatment in the pediatric studies are summarized in Table 5. Disease progression was the most common reason for stopping treatment in all studies.

Table 5 Summary of reasons for stopping treatment in enrolled patients - All studies

	Phase 1		Phase 2		
Reason for Stopping Study Drug	**DFI7434**	**ARD5531**	**ARD5531 RD cohort**	**ARD5021**	**ARD5530**
	N=26	**N=29**	**N=16**	**N=43**	**N=48**
Completed Prescribed Dosing	3 (11.5%)	0 (0.0%)	0 (0.0%)	2 (4.7%)	NR
Death	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (2.3%)	NR
Adverse Event	0 (0.0%)	2 (6.9%)	2 (12.5%)	1 (2.3%)	1 (2.1%)
Disease Progression	22 (84.6%)	23 (79.3%)	11 (68.8%)	32 (74.4%)	32 (66.7%)
Investigator's decision	0 (0.0%)	0 (0.0%)	1 (6.3%)	NR	5 (10.4%)
Refusal/withdrawal[a]	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (14.0%)	4 (8.4%)
Met protocol-defined criteria for removal	NR	NR	NR	NR	6 (12.5%)
Alternative treatment	NR	NR	NR	1 (2.3%)	NR
Other	1 (3.8)	4 (13.8%)	1 (6.3%)	NR	NR
Still on Study	0 (0.0%)	0 (0.0%)	0 (0.0%)	NR	NR

NR = not reported. a Reported as refusal in ARD5531, DFI7434, and ARD5530; reported as withdrawal in ARD5021.
Source: Module 5.3.5.2; DFI7434 Table (10.1) 2; ARD5531 Table (10.1) 3; ARD5021 Table (10.1) 3; ARD5530
Source: sponsor's table (2.1) 2.

Reviewer's note: Based on the lack of antitumor activity for oxaliplatin, these results are expected.

Demography

Demographic data and baseline characteristics in all pediatric studies are summarized in Table 6.
In DFI7434, patients ranged in age from 5 to 20 years with a median age of 10 years; 65% of the patients were males and 89% had an ECOG performance status of 0 or 1.
In the Phase 1 portion of ARD5531, patients ranged in age from 2 to 19 years with a median age of 9 years. Males accounted for 60% of the patients. The majority of patients (86.2%) had an ECOG performance status of 0 or 1.

In the Phase 2 RD cohort of ARD5531, patients ranged in age from 1 to 19 years with a median age of 7 years. There was a 3:2 ratio of females to males. The majority of patients (87.5%) had an ECOG performance status of 0 or 1. In ARD5021, patients ranged from 7 months to 18 years with a median age of 8 years; 70% of patients were males. In ARD5530, patients ranged from 1 to 22 years with a median age of 14 years. Performance scores in both studies were generally 90 or 100%.

Table 6 Summary of demographic data and baseline characteristics in enrolled patients- All studies

	Phase 1		Phase 2		
	DFI7434	**ARD5531**	**ARD5531 RD cohort**	**ARD5021**	**ARD5530**
	N=26	**N=29**	**N=16**	**N=43**	**N=48**
Age (years)					
Median	10.0	9	7	8	14
Range [Min - Max]	5 - 20	2 - 19	1 - 19	7 mo - 18	1-22
Sex					
Female	9 (34.6%)	12 (41.4%)	9 (56.3%)	13 (30.2%)	13 (27.1%)
Male	17 (65.4%)	17 (58.6%)	7 (43.8%)	30 (69.8%)	35 (72.9%)
Race					
Black	8 (30.8%)			2 (4.7%)	6 (12.5%)
Caucasian	16 (61.5%)	not reported	not reported	37 (86.0%)	39 (81.3%)
Other	2 (7.7%)			4 (9.3%)	3 (6.3%)
ECOG PS					
0	19 (73.1%)	23 (79.3%)	10 (62.5%)		
1	4 (15.4%)	2 (6.9%)	4 (25.0%)		
2	3 (11.5%)	3 (10.3%)	1 (6.3%)	not	not
3	-a	1 (3.4%)	0 (0.0%)	used	used
4	-a	0 (0.0%)	0 (0.0%)		
Not done	-a	0 (0.0%)	1 (6.3%)		
Karnofsky Score				**n=23**	**n=30**

50				0	1 (2.1%)
60				1 (2.3%)	2 (4.2%)
70				2 (4.7%)	4 (8.3%)
80				5 (11.6%)	4 (8.3%)
90	not	not	not	4 (9.3%)	11 (22.9%)
100	used	used	used	11 (25.6%)	8 (16.7%)
Lansky Score				**n=20**	**n=18**
50				0	1 (2.1%)
70				3 (7.0%)	2 (4.2%)
80				2 (4.7%)	1 (2.1%)
90				9 (20.9%)	4 (8.3%)
100				6 (14.0%)	10 (20.8%)

Protocol did not include patients with ECOG status >2. . Source: Sponsor's Table (2.2) 1. RD: recommended dose

Reviewer's comments: the demographics data appears adequate for the tumors studied. As requested by the PWR, the sponsor needed to enroll 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. Indeed, the sponsor included patients in this patients range (> 1 month to 21 years old). Also, the sponsor accrued an adequate number of patients to achieve their objectives.

Age, gender, and racial distribution across studies

Table 7 summarizes age, gender, and racial distribution across studies. Across all studies, the majority of patients were >2 – 12 years old (50.3%). Forty-two patients (26.4%) were >16 years old, and 26 patients (16.4%) were >12-16 years old. There were no patients who were 0-1 month and only 11 patients (6.9%) who were >1 month – 2 years old.
The majority of patients were Caucasian (57.2%); 10.1% were Black, and 5.0% were classified as other. Data on race were not required to be collected in ARD5531, which was conducted in the EU. Across all studies, the majority of patients were male (64.8%).

Table 7 Distribution of treated patients by age, gender, and race - All studies

Study	**Age (year)**	**ARD5531 N=43**	**DFI7434 N=26**	**ARD5021 N=43**	**ARD5530 N=47**	**All N=159**
Gender	Male Female	22 (51.2%) 21 (48.8%)	17 (65.4%) 9 (34.6%)	30 (69.8%) 13 (30.2%)	34 (72.3%) 13 (27.7%)	103 (64.8%) 56 (35.2%)
Age	> 1 month - 2 years > 2 years - 12 years > 12 years - 16 years > 16 years	1 (2.3%) 24 (55.8%) 9 (20.9%) 9 (20.9%)	0 (0.0%) 16 (61.5%) 3 (11.5%) 7 (26.9%)	9 (20.9%) 21 (48.8%) 5 (11.6%) 8 (18.6%)	1 (2.1%) 19 (40.4%) 9 (19.1%) 18 (38.3%)	11 (6.9%) 80 (50.3%) 26 (16.4%) 42 (26.4%)
Race	Black Caucasian Other Unknown	0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	8 (30.8%) 16 (61.5%) 2 (7.7%) 0 (0.0%)	2 (4.7%) 37 (86.0%) 4 (9.3%) 0 (0.0%)	6 (12.8%) 38 (80.9%) 2 (4.3%) 1 (2.1%)	16 (10.1%) 91 (57.2%) 8 (5.0%) 1 (0.6%)

Sponsor's table : (2 2 1) 1

Initial diagnosis

In DFI7434, most patients had cancers that were classified as other (34.6%); 26.9% of patients had neuroblastoma and 19.2% had medulloblastoma.

In the Phase 1 portion of ARD5531, the majority of patients had either neuroblastoma (37.9%) or osteosarcoma (20.7%). In the Phase 2 RD cohort of ARD5531, the majority of patients had either neuroblastoma (43.8%), osteosarcoma (12.5%), Ewing's sarcoma (12.5%), or hepatoblastoma (12.5%).

The initial diagnosis of patients enrolled in the Phase 2 studies is summarized in Table 8.

Table 8 Summary of initial diagnosis and treatment strata- Phase 2 studies

ARD5021		**N=43**
	Stratum IA: Medulloblastoma with measurable disease at FIRST relapse	15 (34.9%)
	Stratum IB: Recurrent or refractory medulloblastoma with only CSF (+) or linear leptomeningeal disease	3 (7.0%)
	Stratum IC: Medulloblastoma at SECOND or LATER progression with measurable residual disease	12 (27.9%)
	Stratum II: Recurrent Supratentorial primitive neuroectodermal tumors (PNET)	8 (18.6%)
	Stratum III: Recurrent Atypical Teratoid Rhabdoid Tumors (ATRT)	5 (11.6%)
ARD5530		**N=48**
	Neuroblastoma	13 (27.1%)
	Osteosarcoma	13 (27.1%)
	Rhabdomyosarcoma	10 (20.8%)
	Ewing's sarcoma	12 (25.0%)

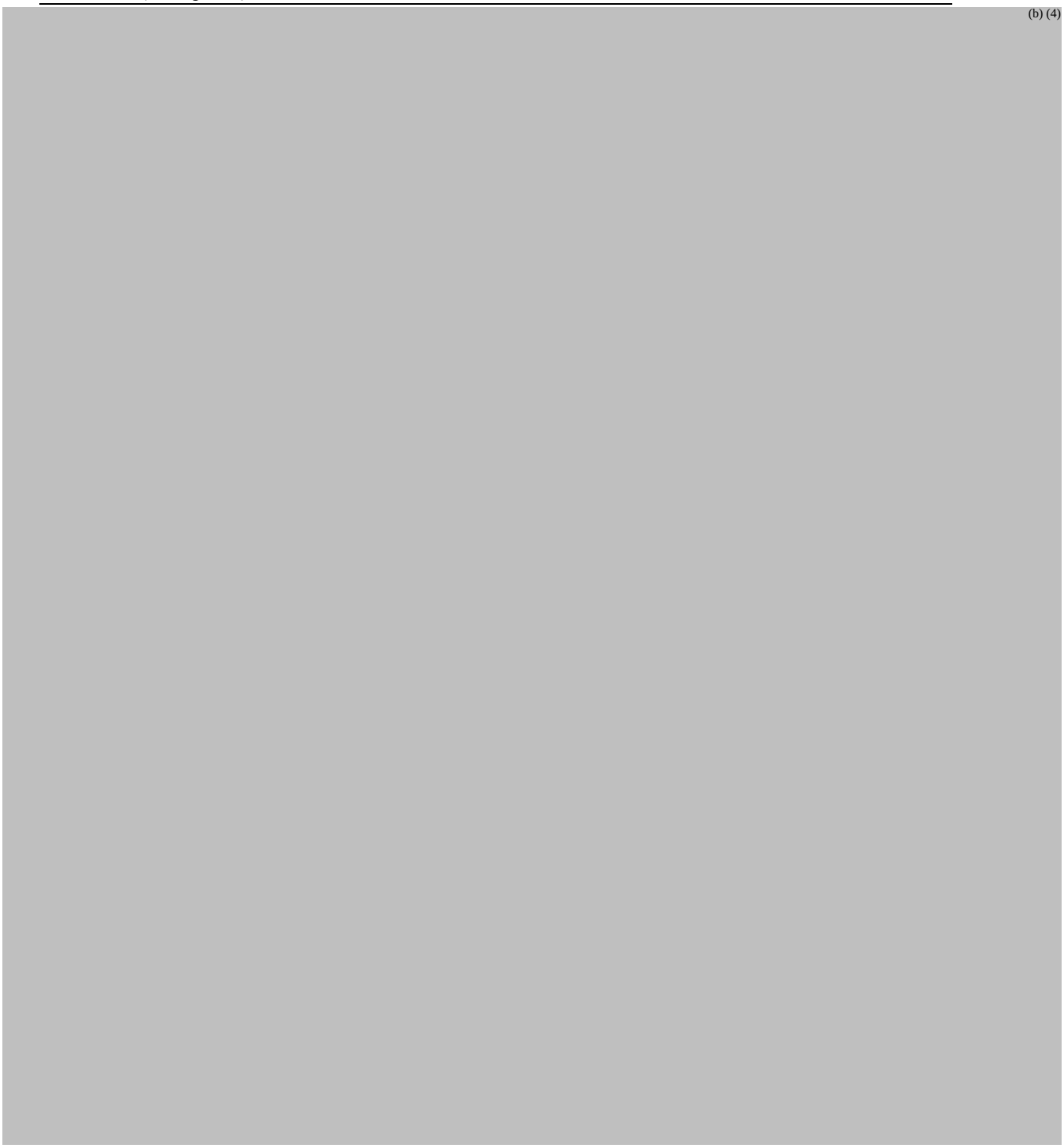
Source: Sponsor's Table

Efficacy

There were no responses in either DFI7434, ARD5530 or ARD5531. Only 1 response (PR (b) (4)) was observed in study ARD5021 (b) (4) .

(b) (4)

(b) (4)



6.1.5 Clinical Microbiology: NA

NA

6.1.6 Efficacy Conclusions:

(b) (4)

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Table 10 Dose limiting toxicities - Phase 1 studies

Dose Level	Treated	Evaluable for Toxicity	Protocol Defined DLT	Number of events
DFI7434				
q 3 weeks				
100 mg/m2	3	3	None	0
130 mg/m2	6	6	Myositis	1
160 mg/m2	2	2	Ataxia Neuropathy-sensory	1 2
160 mg/m2 with carbamazepine	6	6	None	0
q 2 weeks				
85 mg/m2	9	9	None	0
ARD5531				
40 mg/m2	3	3	None	0
50 mg/m2	6	6	Sepsis	1
60 mg/m2	6	6	None	0
75 mg/m2	4	4	None	0
90 mg/m2	6	6	Dysaesthesia	1
110 mg/m2	3	3	Dysaesthesia Paresthesia	1 1

Source: Sponsor's Table (4.1.1) 1 –

Reviewer's comments: DLT's are qualitatively similar to the ones observed in adults

7.1.1 Deaths

In ARD5531, all-cause deaths were reported in 23 patients (82.1%) during Phase 1 and 11 patients (73.3%) in the RD cohort died. All deaths occurred during the follow-up period and were due to progressive disease. Two Phase 1 patients (7.1%) and 3 patients in the Phase 2 RD cohort (20.0%) died within 28 days of last dose.

In DFI7434, all-cause deaths were reported in 22 patients - 7 in the q 2 weeks treatment

group and 15 in the q 3 weeks group. There were no deaths within 28 days of last dose of study medication. All deaths were due to disease progression.

In ARD5021, all-cause deaths were reported in 27 patients - due to progressive disease. Four of these patients died within 28 days; 3 (7.0%) due to progressive disease and 1 (2.3%) for other reasons (after starting alternative treatment). After being removed from the study by his parent's decision, this patient (Patient 10266) started oral etoposide and died from progressive disease 5 days after starting etoposide treatment. Six patients died for reasons classified as other or unknown: 3 of these patients had a status of death at follow-up and the cause of death and date of death were unknown, 1 patient (described above) died after etoposide treatment, 1 patient died with an event of seizures due to progressive disease that was classified as unrated to study drug, 1 patient died with an event of neurological disorder related to progressive disease that was classified as unrelated to study drug; and 1 patient did not have a reason reported.

In ARD5530, all-cause deaths were reported in 26 patients, all due to progressive disease. Seven patients died within 28 days of last dose.

Reviewer's note: number of deaths reflects the population exposed to oxaliplatin (end-stage solid tumors).

7.1.2 Other Serious Adverse Events

In DFI7434, 1 patient in the q 2 weeks group had 4 SAEs (fever without neutropenia, vomiting, anorexia, and weight loss), of which the anorexia was Grade 3 or 4. Five patients (29.4%) in the q 3 weeks group had an SAE and 4 patients had a Grade 3 or 4 SAE. Grade 3 or 4 SAEs included sensory neuropathy, ataxia, myositis, sensory disturbance, vomiting, and musculoskeletal-other.

During the dose escalation phase of ARD5531, 17 patients (60.7%) experienced SAEs (all grades) during the study. Sixteen patients (57.1%) had Grade 3/4 SAEs. The most common SAEs were disease progression, dysesthesia, metastatic pain, pyrexia, urinary retention, and vomiting, all of which occurred in 7.1% of patients. All of these events were Grade 3 or 4 except 1 case of pyrexia and 1 case of vomiting.

In the Phase 2 RD cohort of ARD5531, 8 patients (53.3%) experienced SAEs during the study and all were Grade 3 or 4. The most common SAEs were superior vena cava occlusion, pyrexia, and thrombocytopenia, all of which occurred in 13.3% of patients. SAEs in Phase 2 studies are summarized by preferred term in Table 11. SAEs occurred in 20.0% of patients overall; Grade 3/4 SAEs occurred in 17.8% of patients overall. Headache was the most common SAE overall (4.4% all grades; 2.2% Grade 3 or 4). Serious hypersensitivity reactions occurred in 3.3% of patients overall. All cases were in ARD5530 and all were Grade 3 or 4. There were no other SAE in either study that occurred at a rate >5%.

Table 11 Summary of SAEs by preferred term, all grades and grades 3 or 4 - number (%) of patients - Phase 2 studies.

	ARD5021 N=43				ARD5530 N=47				Overall N=90			
Preferred term	**All Grades**		**Grades 3 or 4**		**All Grades**		**Grades 3 or 4**		**All Grades**		**Grades 3 or 4**	
Any serious adverse event	11	(25.6%)	9	(20.9%)	7	(14.9%)	7	(14.9%)	18	(20.0%)	16	(17.8%)
Headache	4	(9.3%)	2	(4.7%)	0	(0.0%)	0	(0.0%)	4	(4.4%)	2	(2.2%)
Hypersensitivity	0	(0.0%)	0	(0.0%)	3	(6.4%)	3	(6.4%)	3	(3.3%)	3	(3.3%)
Convulsions	2	(4.7%)	2	(4.7%)	0	(0.0%)	0	(0.0%)	2	(2.2%)	2	(2.2%)
Infection	2	(4.7%)	2	(4.7%)	0	(0.0%)	0	(0.0%)	2	(2.2%)	2	(2.2%)
Sensory neuropathy	2	(4.7%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	2	(2.2%)	1	(1.1%)
Ataxia	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Back pain	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Catheter related infection	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Confusional state	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Dehydration	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Depressed level of consciousness	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Dysaesthesia	0	(0.0%)	0	(0.0%)	1	(2.1%)	1	(2.1%)	1	(1.1%)	1	(1.1%)
Dyspnoea	0	(0.0%)	0	(0.0%)	1	(2.1%)	1	(2.1%)	1	(1.1%)	1	(1.1%)
Haemorrhagic stroke	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Hemianopia	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Hydrocephalus	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Hypertension	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Hypokalaemia	0	(0.0%)	0	(0.0%)	1	(2.1%)	1	(2.1%)	1	(1.1%)	1	(1.1%)
Irritability	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Migraine	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Myalgia	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Nausea	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Neuralgia	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Nystagmus	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Pancreatitis	0	(0.0%)	0	(0.0%)	1	(2.1%)	1	(2.1%)	1	(1.1%)	1	(1.1%)
Pyrexia	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Rigors	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)
Speech disorder	1	(2.3%)	1	(2.3%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	1	(1.1%)
Ureteric obstruction	0	(0.0%)	0	(0.0%)	1	(2.1%)	1	(2.1%)	1	(1.1%)	1	(1.1%)
Vomiting	1	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.1%)	0	(0.0%)

If the same patient experienced several AEs with the same term, the patient is counted once for that term. The verbatim term is reported for adverse events that have not been coded. Source: Applicant's Table (4.1.5) 1

7.1.3 Dropouts and Other Significant Adverse Events

Adverse events leading to withdrawal

There were no AEs that lead to study withdrawal in DFI7434.

During Phase 1 of ARD5531, 5 patients (17.9%) withdrew from the study due to adverse events, all of which were Grade 3 or 4 [Table (4.1.6) 1]. In the Phase 2 RD cohort, 6 patients (40.0%) withdrew from the study due to adverse events, 5 of whom had AEs that were Grade 3 or 4 (33.3%). Although only 2 patients were listed as having withdrawn due to disease progression, all AEs leading to withdrawal were associated with tumor progression. Three patients had SAEs that lead to study withdrawal (dehydration,

respiratory distress, thrombocytopenia).

Table 12 Summary of adverse events leading to withdrawal - number (%) of patients- ARD5531

	ARD5531			
	Phase 1 N=28		RD Cohort - 90 mg/m2 N=15	
Body system organ Adverse event	**All Grades**	**Grade 3 or 4**	**All Grades**	**Grade 3 or 4**
Any class[a]	5 (17.9%)	5 (17.9%)	6 (40.0%)	5 (33.3%)
Blood and lymphatic system disorders	1 (3.6%)	1 (3.6%)	1 (6.7%)	1 (6.7%)
Thrombocytopenia	1 (3.6%)	1 (3.6%)	1 (6.7%)	1 (6.7%)
General disorders and administration site conditions	1 (3.6%)	1 (3.6%)	1 (6.7%)	1 (6.7%)
Disease progression	1 (3.6%)	1 (3.6%)	1 (6.7%)	1 (6.7%)
Pain	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Immune system disorders	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)
Drug hypersensitivity	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)
Metabolism and nutrition disorders	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)
Dehydration	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)
Musculoskeletal and connective tissue disorders	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Bone pain	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Metastatic pain	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Nervous system disorders Horner's syndrome b	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Urinary retention	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (3.6%)	1 (3.6%)	1 (6.7%)	1 (6.7%)
Pleural effusion	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
Respiratory distress	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)
Vascular disorders	1 (3.6%)	0 (0.0%)	1 (6.7%)	1 (6.7%)
Haematoma	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Superior vena caval occlusion	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)

If the same patient experienced several AEs with the same term, the patient is counted once for that term. The same rule applies for the results by body system. a Data taken from the AE page of the CRF. b Bone pain and Horner's syndrome were recorded by the Investigator as reason for withdrawal from study. However, Horner's syndrome is considered to be due to progression of the primary diagnosis of neuroblastoma. Source: Applicant's Table (4.1.6) 1

In ARD5021, 1 patient withdrew from the study due to a non-serious AE. This patient withdrew after cycle 3 due to persistent lip swelling that worsened after each cycle. He received his last oxaliplatin dose on 1 May 2003 and went off treatment on 30 May 2003. At cycle 3, Grade 3 hypersensitivity NOS and Grade 2 urticaria NOS were reported.
In ARD5530, 1 patient was withdrawn from the study due to non-serious thrombocytopenia. The patient had a history of thrombocytopenia since 20 February 2003. At the time of study entry (17 December 2004), the patient's platelet count was 128,000. The anticipated start of course 2 was delayed by 14 days due to Grade 2 thrombocytopenia. The patient did not meet the protocol requirements for platelet count recovery in order to start next course and was subsequently withdrawn.

Reviewer's comments: AEs leading to withdrawal were associated with tumor progression, as expected in this end-stage population.

7.1.3.1 Overall profile of dropouts

See Table 12.

7.1.3.2 Adverse events associated with dropouts

See Table 12.

7.1.3.3 Other significant adverse events

Neurotoxicity

Phase 1

In general, patients in Phase 1 studies who received a higher cumulative dose of oxaliplatin experienced neurotoxicity.

Phase 2

In ARD5021, 23 patients (53.5%) experienced neurological events (all grades) and 4 patients (9.3%) experienced Grade 3/4 neurological events. Central system neuropathy events were reported in 9 patients (20.9%), primarily ataxia and depressed level of consciousness. Only 1 patient (2.3%) had a Grade 3/4 central system neuropathy event. Nineteen patients (44.2%) reported a peripheral neuropathy event with 3 patients (7.0%) reporting a Grade 3/4 peripheral neuropathy event. This was primarily peripheral sensory neuropathy (39.5% all grades, 4.7% Grade 3/4).

In ARD5530, each site was asked to complete a specific panel in the database, which listed neurotoxicities associated with oxaliplatin. This panel included events such as paresthesias/dysesthesias, cold related dysesthesias, laryngopharyngeal dysesthesia, and muscle cramping/spasm/jaw pain. These peripheral sensory neuropathy events were referred to as "targeted toxicities". At each cycle, the study staff was asked to assess whether or not each of these events was present.

Due to the age of the patients on this trial, it was difficult to assess some of the details and actual grades of some of the events, especially laryngopharyngeal dysesthesias. The incidence of all grades and Grade 3 and 4 targeted laryngopharyngeal dysesthesia was higher than what has been seen in some of the other pediatric trials and in trials with the adult population (see table 13) . All of the Grade 1 and 2 events were oropharyngeal dysesthesia and not severe laryngopharyngeal dysesthesias as reported in other studies. There were 5 patients (10.6%) who experienced Grade 3 laryngopharyngeal dysesthesias. Upon reviewing the detailed description of these 5 events, it appears that some of them were adverse events that did not meet the true description of laryngopharyngeal dysesthesia. There were no Grade 4 events reported. More details on these patients can be found in the ARD5530 clinical study report located in Module 5.3.5.2.

Table 13 Summary of PSN adverse events in treated patients, all grades and grade 3/4 - ARD5530

Adverse Event	Total N=47			
	All Grades		Grades 3 or 4	
Any event	25	(53.2%)	7	(14.9%)
Paresthesias/dysesthesias	21	(44.7%)	4	(8.5%)
Cold related dysesthesia	19	(40.4%)	2	(4.3%)
Laryngopharyngeal dysesthesia	14	(29.8%)	5	(10.6%)
Muscle cramping/spasm/jaw pain	6	(12.8%)	0	(0.0%)

If the same patient experienced several AEs with the same term, the patient is counted once for that term.
The same rule applies for the results by body system.
The verbatim term is reported for adverse events that have not been coded. Source: Applicant's Table (4.1.2.1) 1

Gastrointestinal toxicity

Overall, gastrointestinal disorders were reported by 65.6% of patients. There was a higher incidence of gastrointestinal disorders in ARD5021 compared with ARD5530 (81.4% vs 51.1%). Vomiting (47.8%), nausea (28.9%), and diarrhea (24.4%) were the most common GI events overall, with vomiting and diarrhea occurring more frequently in ARD5021 compared with ARD5530 (vomiting; 61.5% ARD5021 vs 31.9% ARD5530; diarrhea: 39.5% ARD5021 vs 10.6% ARD5530). The incidence of these events in both studies is lower than that seen in single agent oxaliplatin studies at the same dose in adults. because the children received fewer cycles (median=2) whereas adults received a median of 4 cycles. Only 7.8% of patients overall had Grade 3/4 GI events; 9.3% in ARD5021 and 6.4% in ARD5530. Grade 3/4 nausea, vomiting and diarrhea ranged from 1.1-3.3% overall, and 0-7.0% within each study.

Hematologic toxicity

Decreased hemoglobin (all grades) and decreased platelet count (all grades) were each reported by 52.2% of patients overall. Decreased neutrophil count (all grades) was reported in 38.9% of patients overall. The incidence of each of these events was higher in ARD5021 than in ARD5530.
Grade 3/4 decreased hemoglobin was 10.0% overall and was more frequent in ARD5530 (14.9%) compared with ARD5021 (4.7%). Grade 3/4 decreased neutrophil count was 11.1% overall and was more frequent in ARD5021 (16.3%) compared with ARD5530 (6.4%). Grade 3/4 decreased platelet count was 26% overall and in each study. The incidence of these events (all grades and grade 3/4) is higher than that seen in single agent oxaliplatin studies in the adult population. The patients in the Phase 1 studies also had a higher incidence of hematotoxicity than adults. The hematotoxicty was characterized primarily by thrombocytopenia. This was possibly due to the aggressive pathology and natural history of the baseline malignancies. Specifically, these patients frequently had bone marrow infiltration. Also, these pediatric populations were heavily pretreated with multiple combination chemotherapies and/or extensive radiation making them more susceptible to hematotoxicity.

Reviewer's comments: there appears to be no significant differences between children and adults with respect to the safety profile of oxaliplatin administered as monotherapy.

7.1.4 Other Search Strategies

NA

7.1.5 Common Adverse Events

All adverse events are reported in this summary document, regardless of relationship to oxaliplatin.

In DFI7434 q 2 weeks treatment group, the most common AEs reported were fatigue (77.8% all grades; 0% Grade 3/4), vomiting (66.7% all grades; 0% Grade 3/4), and nausea (66.7% all grades; 11.1% Grade 3/4). Sensory neuropathy (94.1% all grades; 11.8% Grade 3/4), abnormal leukocytes [leukopenia] (88.2% all grades; 29.4% Grade 3/4), abnormal platelets [thrombocytopenia] (76.5% all grades; 35.3% Grade 3/4), and abnormal neutrophils/granulocyctes [neutropenia] (70.6% all grades; 35.3% Grade 3/4) were the most common AEs reported among patients in the q 3 weeks treatment group. During Phase 1 of ARD5531, all patients had at least 1 AE and 23 patients (82.1%) had a Grade 3/4 AE. Paresthesia (50% all grades, 3.6% Grade 3/4), abdominal pain (39.3% all grades, 10.7% Grade 3/4), and pyrexia [fever] (35.7% all grades, 3.6% Grade 3/4) were the most common AEs reported during Phase 1.

In the Phase 2 RD cohort of ARD5531, all patients had at least 1 AE and 11 patients (73.3%) had a Grade 3/4 AE. Paresthesia (60.0% all grades, 6.7% Grade 3/4), pyrexia (40.0% all grades, 6.7% Grade 3/4), and thrombocytopenia (40.0% all grades, 26.7% Grade 3/4) were the most common AEs reported in the RD cohort.
All adverse events are reported in this summary document, regardless of relationship to oxaliplatin.

In DFI7434 q 2 weeks treatment group, the most common AEs reported were fatigue (77.8% all grades; 0% Grade 3/4), vomiting (66.7% all grades; 0% Grade 3/4), and nausea (66.7% all grades; 11.1% Grade 3/4). Sensory neuropathy (94.1% all grades; 11.8% Grade 3/4), abnormal leukocytes [leukopenia] (88.2% all grades; 29.4% Grade 3/4), abnormal platelets [thrombocytopenia] (76.5% all grades; 35.3% Grade 3/4), and abnormal neutrophils/granulocyctes [neutropenia] (70.6% all grades; 35.3% Grade 3/4) were the most common AEs reported among patients in the q 3 weeks treatment group. During Phase 1 of ARD5531, all patients had at least 1 AE and 23 patients (82.1%) had a Grade 3/4 AE. Paresthesia (50% all grades, 3.6% Grade 3/4), abdominal pain (39.3% all grades, 10.7% Grade 3/4), and pyrexia [fever] (35.7% all grades, 3.6% Grade 3/4) were the most common AEs reported during Phase 1.

In the Phase 2 RD cohort of ARD5531, all patients had at least 1 AE and 11 patients

(73.3%) had a Grade 3/4 AE. Paresthesia (60.0% all grades, 6.7% Grade 3/4), pyrexia (40.0% all grades, 6.7% Grade 3/4), and thrombocytopenia (40.0% all grades, 26.7% Grade 3/4) were the most common AEs reported in the RD cohort.

AEs by preferred term (in ε2% of treated patients with Grade 3/4 events overall) in the Phase 2 studies are summarized in Table (4.1.2) 1. ARD5021 was coded using MedDRA Version 6.0 whereas ARD5530 was coded with MedDRA Version 8.1. The difference in coding required that AE terms be combined in this summary document. The following terms were combined:

Cardiac disorders
Sinus tachycardia and tachycardia
Gastrointestinal disorders
Vomiting NOS and vomiting
Diarrhoea NOS and diarrhoea
Abdominal pain NOS and abdominal pain
General disorders
Pain and pain NOS
Immune system disorder
Hypersensitivity and hypersensitivity NOS
Infections and infestations
Otitis media and otitis media serous NOS
Metabolism and nutrition
Hyperglycaemia and hyperglycaemia NOS
Hypoglycaemia NOS and hypoglycaemia
Skin and subcutaneous tissue disorder
Urticaria and urticaria NOS
Vascular disorder
Hypertension NOS and hypertension
Hypotension NOS and hypotension
Investigations
Hemoglobin and hemoglobin decreased
Neutrophils and neutrophil count decreased

In the Phase 2 studies overall, 94.4% of patients reported an AE and 66.7% of patients reported a Grade 3/4 AE. The most common AEs reported overall were hemoglobin decreased [anemia] (52.2%), platelet count decreased [thrombocytopenia] (52.2%), vomiting (47.8%), neutrophil count decreased [neutropenia] (38.9%), and leukopenia (32.2%). The most common Grade 3/4 AEs were platelet count decreased [thrombocytopenia] (25.6%), neutrophil count decreased [neutropenia] (11.1%), hemoglobin decreased [anemia] (10.0%), and lymphopenia (8.9%).

AEs in the Phase 2 studies by preferred term and body system are presented in Table 14

Table 14 Summary of AEs by preferred term in ≥2% of treated patients with Grade 3 or4 events overall, all grades and grades 3 or 4 - number (%) of treated patients - Phase 2 studies

	ARD5021 N=43				ARD5530 N=47				Overall N=90			
Adverse event	**All Grades**		**Grades 3 or 4**		**All Grades**		**Grades 3 or 4**		**All Grades**		**Grades 3 or 4**	
Any event	43	(100.0%)	30	(69.8%)	42	(89.4%)	30	(63.8%)	85	(94.4%)	60	(66.7%)
Platelet count decreased	28	(65.1%)	11	(25.6%)	19	(40.4%)	12	(25.5%)	47	(52 2%)	23	(25.6%)
Neutrophil count decreased	25	(58.1%)	7	(16 3%)	10	(21.3%)	3	(6.4%)	35	(38 9%)	10	(11.1%)
Haemoglobin decreased	28	(65.1%)	2	(4.7%)	19	(40.4%)	7	(14.9%)	47	(52 2%)	9	(10.0%)
Lymphopenia	11	(25.6%)	3	(7.0%)	9	(19.1%)	5	(10.6%)	20	(22 2%)	8	(8.9%)
Hypersensitivity	4	(9.3%)	3	(7.0%)	7	(14.9%)	4	(8.5%)	11	(12 2%)	7	(7.8%)
ALT increased	12	(27.9%)	3	(7.0%)	10	(21.3%)	3	(6.4%)	22	(24.4%)	6	(6.7%)
Dyspnoea	3	(7.0%)	1	(2.3%)	6	(12.8%)	4	(8.5%)	9	(10.0%)	5	(5.6%)
Laryngopharyngeal dysesthesia	0	(0.0%)	0	(0.0%)	14	(29.8%)	5	(10.6%)	14	(15.6%)	5	(5.6%)
Leukopenia	29	(67.4%)	5	(11.6%)	0	(0.0%)	0	(0.0%)	29	(32.2%)	5	(5.6%)
Headache	16	(37.2%)	4	(9.3%)	1	(2.1%)	0	(0.0%)	17	(18 9%)	4	(4.4%)
Hypokalaemia	10	(23.3%)	2	(4.7%)	4	(8.5%)	2	(4.3%)	14	(15.6%)	4	(4.4%)
Hypoxia	1	(2.3%)	1	(2.3%)	4	(8.5%)	3	(6.4%)	5	(5.6%)	4	(4.4%)
Infection	6	(14.0%)	4	(9.3%)	1	(2.1%)	0	(0.0%)	7	(7.8%)	4	(4.4%)
Paresthesias/dysesthesias	0	(0.0%)	0	(0.0%)	21	(44.7%)	4	(8.5%)	21	(23 3%)	4	(4.4%)
AST increased	11	(25.6%)	1	(2.3%)	12	(25.5%)	2	(4.3%)	23	(25.6%)	3	(3.3%)
Convulsions	5	(11.6%)	3	(7.0%)	0	(0.0%)	0	(0.0%)	5	(5.6%)	3	(3.3%)
Hyponatraemia	6	(14.0%)	2	(4.7%)	5	(10.6%)	1	(2.1%)	11	(12 2%)	3	(3.3%)
Packed red blood cell transfusion	3	(7.0%)	3	(7.0%)	0	(0.0%)	0	(0.0%)	3	(3.3%)	3	(3.3%)
Platelet transfusion	3	(7.0%)	3	(7.0%)	0	(0.0%)	0	(0.0%)	3	(3.3%)	3	(3.3%)
Vomiting	28	(65.1%)	3	(7.0%)	15	(31.9%)	0	(0.0%)	43	(47.8%)	3	(3.3%)
Anorexia	11	(25.6%)	1	(2.3%)	5	(10.6%)	1	(2.1%)	16	(17.8%)	2	(2.2%)
Cancer pain	0	(0.0%)	0	(0.0%)	3	(6.4%)	2	(4.3%)	3	(3.3%)	2	(2.2%)
Catheter related infection	1	(2.3%)	1	(2.3%)	1	(2.1%)	1	(2.1%)	2	(2.2%)	2	(2.2%)
Cold related dysesthesia	0	(0.0%)	0	(0.0%)	19	(40.4%)	2	(4.3%)	19	(21 1%)	2	(2.2%)
Diarrhoea	17	(39.5%)	2	(4.7%)	5	(10.6%)	0	(0.0%)	22	(24.4%)	2	(2.2%)
Neutropenic infection	2	(4.7%)	2	(4.7%)	0	(0.0%)	0	(0.0%)	2	(2.2%)	2	(2.2%)
Pain in extremity	0	(0.0%)	0	(0.0%)	6	(12.8%)	2	(4.3%)	6	(6.7%)	2	(2.2%)
Peripheral sensory neuropathy	17	(39.5%)	2	(4.7%)	1	(2.1%)	0	(0.0%)	18	(20.0%)	2	(2.2%)

If the same patient experienced several AEs with the same term, the patient is counted once for that term.
The verbatim term is reported for adverse events that have not been coded
The 2% cut-off based on Grades 3, 4 group in Overall category. Table (4.1.2) 1 -

Adverse events by age category

The greatest number of patients were >2 to 12 years of age. In this age category, the most common AEs were platelet count decreased [thrombocytopenia] (60.0%), hemoglobin decreased [anemia] (55.0%), vomiting (55.0%), neutrophil count decreased [neutropenia] (45.0%), and leukopenia (32.5%). AEs in the Phase 2 studies by age category, body system, and preferred term are presented in Table 15.

Table 15 presents Grade 3/4 AEs in the Phase 2 studies by age category in ≥2% of treated patients overall and sorted by preferred term and decreasing frequency of Grade 3/4 events in patients >2 to 12 years of age.
The most common Grade 3/4 AEs in this age category were platelet count decreased [thrombocytopenia] (30.0%), neutrophil count decreased [neutropenia] (15.0%), hypersensitivity (12.5%), and hemoglobin decreased [anemia] (10.0%).

Table 15 Summary of AEs by preferred term in ≥2% of treated patients with Grade 3/4 events overall by age category, sorted by decreasing frequency of Grade 3/4 events in patients >2 - 12 years, - Phase 2 studies

	ARD5021				ARD5530				Overall			
Adverse event	> 1 month - 2 years N=9	> 2 years - 12 years N=21	> 12 years - 16 years N=5	> 16 years N=8	> 1 month - 2 years N=1	> 2 years - 12 years N=19	> 12 years - 16 years N=9	> 16 years N=18	> 1 month - 2 years N=10	> 2 years - 12 years N=40	> 12 years - 16 years N=14	> 16 years N=26
Any event	6 (66.7)	15 (71.4)	5 (100)	4 (50.0)	1 (100)	13 (68.4)	6 (66.7)	10 (55.6)	7 (70.0)	28 (70.0)	11 (78.6)	14 (53.8)
Platelet count decreased	1 (11.1)	6 (28.6)	1 (20.0)	3 (37.5)	1 (100)	6 (31.6)	3 (33.3)	2 (11.1)	2 (20.0)	12 (30.0)	4 (28.6)	5 (19.2)
Neutrophil count decreased	2 (22.2)	4 (19.0)	1 (20.0)	0 (0)	0 (0)	2 (10.5)	0 (0)	1 (5.6)	2 (20.0)	6 (15.0)	1 (7.1)	1 (3.8)
Hypersensitivity	0 (0)	2 (9.5)	0 (0)	1 (12.5)	0 (0)	3 (15.8)	1 (11.1)	0 (0)	0 (0)	5 (12.5)	1 (7.1)	1 (3.8)
Haemoglobin decreased	1 (11.1)	1 (4.8)	0 (0)	0 (0)	1 (100)	3 (15.8)	1 (11.1)	2 (11.1)	2 (20.0)	4 (10.0)	1 (7.1)	2 (7.7)
Alanine aminotransferase increased	1 (11.1)	1 (4.8)	0 (0)	1 (12.5)	0 (0)	2 (10.5)	0 (0)	1 (5.6)	1 (10.0)	3 (7.5)	0 (0)	2 (7.7)
Headache	0 (0)	3 (14.3)	1 (20.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (7.5)	1 (7.1)	0 (0)
Laryngopharyngeal dysesthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (15.8)	0 (0)	2 (11.1)	0 (0)	3 (7.5)	0 (0)	2 (7.7)
Leukopenia	0 (0)	3 (14.3)	1 (20.0)	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (7.5)	1 (7.1)	1 (3.8)
Hypokalaemia	0 (0)	2 (9.5)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (5.6)	1 (10.0)	2 (5.0)	0 (0)	1 (3.8)
Hypoxia	0 (0)	1 (4.8)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	2 (11.1)	0 (0)	2 (5.0)	0 (0)	2 (7.7)
Packed red blood cell transfusion	1 (11.1)	2 (9.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10.0)	2 (5.0)	0 (0)	0 (0)
Paresthesias/dysesthesias	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (10.5)	0 (0)	2 (11.1)	0 (0)	2 (5.0)	0 (0)	2 (7.7)
Vomiting	0 (0)	2 (9.5)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.0)	0 (0)	1 (3.8)
Anorexia	1 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	1 (10.0)	1 (2.5)	0 (0)	0 (0)
Aspartate aminotransferase increased	1 (11.1)	0 (0)	0 (0)	0 (0)	1 (100)	1 (5.3)	0 (0)	0 (0)	2 (20.0)	1 (2.5)	0 (0)	0 (0)
Blood amylase increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Blood lactate dehydrogenase increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Convulsions	1 (11.1)	1 (4.8)	1 (20.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10.0)	1 (2.5)	1 (7.1)	0 (0)
Cystitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Diarrhoea	0 (0)	1 (4.8)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	1 (3.8)
Dysaesthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Dyspnoea	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (5.3)	0 (0)	3 (16.7)	0 (0)	1 (2.5)	0 (0)	4 (15.4)
Haemorrhagic stroke	0 (0)	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Hemianopia	0 (0)	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Lipase increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Lymphopenia	1 (11.1)	1 (4.8)	0 (0)	1 (12.5)	0 (0)	0 (0)	2 (22.2)	3 (16.7)	1 (10.0)	1 (2.5)	2 (14.3)	4 (15.4)
Myalgia	0 (0)	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Neck pain	0 (0)	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Neuralgia	0 (0)	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Neutropenic infection	1 (11.1)	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10.0)	1 (2.5)	0 (0)	0 (0)
Pain in extremity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	1 (5.6)	0 (0)	1 (2.5)	0 (0)	1 (3.8)
Pancreatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Platelet transfusion	0 (0)	1 (4.8)	0 (0)	2 (25.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	2 (7.7)
Serum ferritin increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)
Ureteric obstruction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)

If the same patient experienced several AEs with the same term, the patient is counted once for that term.
The verbatim term is reported for adverse events that have not been coded
The 2% cut-off based on >2 years - 12 years age group in Overall category. Source: Sponsor's table (4.1.3) 1

Reviewer's note: Based on the small number of patients in these trials, it is very difficult to determine whether any particular age group is more susceptible to any AEs.

Adverse events by gender

AEs in the Phase 2 studies by gender, body system and preferred term are presented in Table 16. AEs occurred in 92.2% of males and 100% of females. In males, the most common AEs were hemoglobin decreased [anemia] (57.8%), platelet count decreased [thrombocytopenia] (54.7%), vomiting (46.9%), neutrophil count decreased [neutropenia] (42.2%), and leukopenia (35.9%).

In females, the most common AEs were vomiting (50.0%), platelet count decreased [thrombocytopenia] (46.2%), hemoglobin decreased [anemia] (38.5%), paresthesia/dysesthesia (34.6%), nausea (30.8%), lymphopenia (30.8%), and neutrophil count decreased [neutropenia] (30.8%).

Table 16 1 presents Grade 3/4 AEs in the Phase 2 studies by gender in ≥2% of

patients overall and sorted by preferred term and decreasing frequency in male patients. Grade 3/4 AEs occurred in 68.8% of males. The most common Grade 3/4 AEs in males were platelet count decreased [thrombocytopenia] (28.1%), hemoglobin decreased [anemia] (12.5%), hypersensitivity (9.4%), neutrophil count decreased [neutropenia] (9.4%), and ALT increased (7.8%), dyspnea (7.8%), and leukopenia (7.8%).
Grade 3/4 AEs occurred in 61.5% of females. In females, the most common Grade 3/4 AEs were platelet count decreased [thrombocytopenia] (19.2%), neutrophil count decreased [neutropenia] (15.4%), lymphopenia (15.4%), headache (7.7%), and paresthesia/dysesthesia (7.7%).

Table 16 Summary of AEs by preferred term in ≥2% of treated patients with Grade 3/4 events overall by gender, sorted by decreasing frequency of Grade 3/4 events in male patients - Phase 2 studies

	ARD5021				ARD5530				Overall			
Adverse event	Male N=30		Female N=13		Male N=34		Female N=13		Male N=64		Female N=26	
Any event	24	(80.0%)	6	(46.2%)	20	(58.8%)	10	(76.9%)	44	(68.8%)	16	(61.5%)
Platelet count decreased	9	(30.0%)	2	(15.4%)	9	(26.5%)	3	(23.1%)	18	(28.1%)	5	(19.2%)
Haemoglobin decreased	2	(6.7%)	0	(0.0%)	6	(17.6%)	1	(7.7%)	8	(12.5%)	1	(3.8%)
Hypersensitivity	3	(10.0%)	0	(0.0%)	3	(8.8%)	1	(7.7%)	6	(9.4%)	1	(3.8%)
Neutrophil count decreased	6	(20.0%)	1	(7.7%)	0	(0.0%)	3	(23.1%)	6	(9.4%)	4	(15.4%)
ALT increased	3	(10.0%)	0	(0.0%)	2	(5.9%)	1	(7.7%)	5	(7.8%)	1	(3.8%)
Dyspnoea	1	(3.3%)	0	(0.0%)	4	(11.8%)	0	(0.0%)	5	(7.8%)	0	(0.0%)
Leukopenia	5	(16.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	5	(7.8%)	0	(0.0%)
Hypokalaemia	2	(6.7%)	0	(0.0%)	2	(5.9%)	0	(0.0%)	4	(6.3%)	0	(0.0%)
Laryngopharyngeal dysesthesia	0	(0.0%)	0	(0.0%)	4	(11.8%)	1	(7.7%)	4	(6.3%)	1	(3.8%)
Lymphopenia	2	(6.7%)	1	(7.7%)	2	(5.9%)	3	(23.1%)	4	(6.3%)	4	(15.4%)
AST increased	1	(3.3%)	0	(0.0%)	2	(5.9%)	0	(0.0%)	3	(4.7%)	0	(0.0%)
Convulsions	3	(10.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(4.7%)	0	(0.0%)
Hyponatraemia	2	(6.7%)	0	(0.0%)	1	(2.9%)	0	(0.0%)	3	(4.7%)	0	(0.0%)
Hypoxia	1	(3.3%)	0	(0.0%)	2	(5.9%)	1	(7.7%)	3	(4.7%)	1	(3.8%)
Infection	3	(10.0%)	1	(7.7%)	0	(0.0%)	0	(0.0%)	3	(4.7%)	1	(3.8%)
Packed red blood cell transfusion	3	(10.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(4.7%)	0	(0.0%)
Platelet transfusion	3	(10.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(4.7%)	0	(0.0%)
Anorexia	1	(3.3%)	0	(0.0%)	1	(2.9%)	0	(0.0%)	2	(3.1%)	0	(0.0%)
Catheter related infection	1	(3.3%)	0	(0.0%)	1	(2.9%)	0	(0.0%)	2	(3.1%)	0	(0.0%)
Headache	2	(6.7%)	2	(15.4%)	0	(0.0%)	0	(0.0%)	2	(3.1%)	2	(7.7%)
Neutropenic infection	2	(6.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(3.1%)	0	(0.0%)
Pain in extremity	0	(0.0%)	0	(0.0%)	2	(5.9%)	0	(0.0%)	2	(3.1%)	0	(0.0%)
Paresthesias/dysesthesias	0	(0.0%)	0	(0.0%)	2	(5.9%)	2	(15.4%)	2	(3.1%)	2	(7.7%)
Peripheral sensory neuropathy	2	(6.7%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(3.1%)	0	(0.0%)
Vomiting	2	(6.7%)	1	(7.7%)	0	(0.0%)	0	(0.0%)	2	(3.1%)	1	(3.8%)

If the same patient experienced several AEs with the same term, the patient is counted once for that term.
The verbatim term is reported for adverse events that have not been coded
The 2% cut-off based on Male group in Overall category. Source: Sponsor's Table: (4.1.1)1

Reviewer's note: It appears that males have higher incidence for some AEs, in comparison to females. However, it is difficult to determine this with certainty as there are small number of patients in these trials.

7.1.5.1 Eliciting adverse events data in the development program

NA

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adequate

7.1.5.3 Incidence of common adverse events

See 7.5.1

7.1.5.4 Common adverse event tables

See 7.5.1

7.1.5.5 Identifying common and drug-related adverse events

See 7.5.1

7.1.5.6 Additional analyses and explorations

None

7.1.6 Less Common Adverse Events

See 7.5.1

Reviewer's comments: there appears to be no significant differences between children and adults with respect to the safety profile of oxaliplatin administered as monotherapy.

7.1.7 Laboratory Findings

Clinical laboratory evaluations

On-study hematological aberrations in the Phase 1 studies are presented in Table 17
In the q 3 week group of DFI7434, all grade and Grade 3/4 laboratory abnormalities for leukocytes, neutrophils, and platelets were higher than those seen in the q 2 week group; however, the patient numbers are too small to make any conclusions.

During Phase 1 of ARD5531, the incidence of Grade 3/4 anemia was 14.3%. Grade 3/4

thrombocytopenia was seen in 28.6% of patients. The incidence of Grade 3/4 neutropenia was 7.1% (see Table 17).

Table 17 Summary of on-study hematologic laboratory tests by NCI grade - (%) of patients - Phase 1 studies

	ARD5531		DFI7434			
	Phase 1 N=28		85 mg/m2 q 2 weeks N= 9		q 3 weeks N= 17	
Hematology Test	All Grades	Grades 3 or 4	All Grades	Grades 3 or 4	All Grades	Grades 3 or 4
Hemoglobin [anemia]	24 (85.7%)	4 (14.3%)	9 (100.0%)	3 (33.3%)	16 (94.1%)	4 (23.5%)
Leukocytes [leukopenia]	13 (46.4%)	1 (3.6%)	4 (44.4%)	0 (0.0%)	15 (88.2%)	5 (29.4%)
Neutrophils [neutropenia	11 (39.3%)	2 (7.1%)	2 (22.2%)	1 (11.1%)	11 (64.7%)	6 (35.3%)
Platelets [thrombocytopenia]	22 (78.6%)	8 (28.6%)	5 (55.6%)	0 (0.0%)	13 (76.5%)	5 (29.4%)

Source: Sponsor's Table (4.1.8) 1

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

7.2.1.2 Demographics

7.2.1.3 Extent of exposure (dose/duration)

Extent of exposure
Table 18 summarizes treatment administration in ARD5531. The doses were administered once weekly every 28 days. A total of 59 cycles were administered in ARD5531 during Phase 1. Patients received a median of 2 cycles with a range of 1 to 6 cycles. The mean cumulative dose was 388.9 mg/m2 in the Phase 1 cohort.

Table 18- Treatment administration - ARD5531

Treated Population	Phase 1
Number of cycles administered	
40 mg/m2	7
50 mg/m2	13
60 mg/m2	16
75 mg/m2	6
90 mg/m2	10
110 mg/m2	7
Total	**59**
Median number of cycles (range)	2 (1 – 6)

Source: Sponsor's table Table (4.1) 1

In DFI7434, a total of 87 doses were administered Table 19. A single dose of 130 mg/m2 was administered every 3 weeks. Patients received a median of 2 doses with a range of 1 to 9 doses. The median cumulative dose was 373 mg.

Table 19 Treatment administration - DFI7434

Treated Population	Phase 1
Number of doses administered	
100 mg/m2 single dose every 3 weeks	11
130 mg/m2 single dose every 3 weeks	13
160 mg/m2 single dose every 3 weeks	10
160 mg/m2 single dose + carbamazepine every 3 weeks	12
85 mg/m2 single dose every 2 weeks	41
Total	**87**
Median number of cycles (range)	2 (1 – 9)

Source: Sponsor's table Table (4.1) 2

The extent of exposure in the Phase 2 RD cohort of ARD5531 is presented in Table 20. One cycle consisted of 3 weekly doses every 28 days. In the Phase 2 RD cohort, a total of 28 cycles were administered with a median of 2 cycles per patient. The mean cumulative dose was 425.3 mg/m2 in the Phase 2 RD cohort.

Table 20- Extent of exposure for oxaliplatin - ARD5531 - Phase 2 RD cohort

	90 mg/m2 oxaliplatin N=15
Number of cycles[a]	
N	28
Mean (SD)	1.9 (1.0)
Median	2
Range [Min - Max]	1 - 4
Total cumulative dose (mg/m2)	
N	15
Mean (SD)	425.33 (245.93)
Median	363.6
Range [Min - Max]	90.6 - 1070.2
Duration of Dosing (number of weeks)	
N	15
Mean (SD)	7.63 (4.34)
Median	8.0
Range [Min - Max]	4.0 - 18.3
Dose intensity(mg/m2/week)	
N	15
Mean (SD)	56.20 (13.27)
Median	58.5
Range [Min - Max]	22.7 - 68.8
Relative dose intensity (%)	
N	15
Mean (SD)	83.26 (19.66)
Median	86.7
Range [Min - Max]	33.6 - 101.9

a One cycle consisted of 3 weekly doses every 28 days. Source: Sponsor's table Table (4.1) 3

Table 21 summarizes extent of exposure in the Phase 2 studies. Exposure parameters were similar in both studies. In both studies, patients received a median of 2 cycles. One cycle consisted of a single dose every 28 days. The median duration of dosing was 6 weeks in both studies. The median cumulative dose was 260 mg/m2 in ARD5021 and 253 mg/m2 in ARD5530.

Table 21Extent of exposure for oxaliplatin - Phase 2 studies

	ARD5021 N=43	ARD5530 N=47
Number of cycles[a]		
N	147	102
Median	2	2
Range [Min - Max]	1 - 17	1 - 12
Cumulative dose of oxaliplatin(mg/m2)		
N	43	47

	ARD5021 N=43	ARD5530 N=47
Median	260.1	253.2
Range [Min - Max]	79.5 - 1962.7	125.8 – 1559.5
Duration of Dosing (number of weeks)		
N	43	47
Median	6.0	6.0
Range [Min - Max]	3.0 - 53.9	3.0 – 42.0
Dose intensity(mg/m2/week)		
N	43	47
Median	42.5	43.1
Range [Min - Max]	26.5 - 45.5	29.4 – 49.2
Relative dose intensity (%)b		
N	43	47
Median	98.8	99.5
Range [Min - Max]	68.1 - 108.8	67.8 – 113.5

a One cycle consisted of a single dose every 28 days.
b Five patients who weighed <10 kg were dosed at 4.3 mg/kg and are included in the calculation of RDI. Source: Sponsor's table Table (4.1) 4

7.2.3 Adequacy of Overall Clinical Experience

Clinical experience is adequate

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

none

7.2.5 Adequacy of Routine Clinical Testing

Adequate

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Eloxatin 130 mg/m^2 IV every 21 days

8.2 Drug-Drug Interactions

None

9 OVERALL ASSESSMENT

9.1 Conclusions

(b) (4)

Safety profile is similar to the safety profile observed in adults. PK analysis demonstrated similar profile, comparing with adults

9.2 Recommendation on Regulatory Action

This reviewer recommends approval of this sNDA supplement N21492\S008 for Eloxatin® (oxaliplatin for injection) to add information from the pediatric cancer trials to the label.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No new recommendations. Continue post-marketing surveillance

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

No new requests

9.4 Labeling Review

See labeling revised by review team

9.5 Comments to Applicant

See labeling revised by review team

10 APPENDICES

10.1 Review of Individual Study Reports

See above

10.2 Line-by-Line Labeling Review

See labeling revised by review team

10.3 Other relevant tables

Written Request Items	Information Submitted/ Sponsor's response
Types of studies/ Study Design: Phase 1 studies: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered must be sufficient to achieve Phase 1 objectives; this would require 18-25 patients. Two Phase 1 studies are to be submitted. Phase 2 or pilot studies: Each of these studies must enroll at least 14 pediatric patients with refractory or relapsed tumors per trial and must obtain pharmacokinetic data. Studies must be performed at facilities that have the experience, support.	**Types of studies:** The Sponsor is including in this sNDA two Phase 1 studies ARD5531 and DFI7434conducted in pediatric patients. ARD5531 enrolled 45 patients with solid tumors. DFI 7434 enrolled 26 patients with solid tumors. Pharmacokinetic data were obtained from patients in both studies. The Sponsor is including in this sNDA two Phase 2 studies ARD5021 and ARD5530 conducted in pediatric patients. ARD5021 enrolled 43 patients with recurrent or refractory embryonal CNS tumors. ARD5530 enrolled 48 patients with solid tumors Pharmacokinetic data were obtained from patients in both studies.
Indication(s) to be studied: Refractory or relapsed pediatric solid tumors.	**Indication(s) studied:** Each of the four studies mentioned above

Written Request Items	Information Submitted/ Sponsor's response
	enrolled patients with relapsed or refractory solid tumors.
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	**ARD5331:** ranged in age from 1 to 19 years (N=41) Distribution by age ➢ >1 mo-2 yr: 2.3 % ➢ > 2 years-12 yr: 55.8% ➢ > 12 yrs-16 yr: 20.9% ➢ > 16 yr: 20.9% Distribution by gender ➢ Male: 51.2% ➢ Female: 48.8% Distribution by race: NA **DFI7434**: ranged in age from 5 to 20 years. Distribution by age ➢ >1 mo-2 yr: 0 % ➢ > 2 years-12 yr:61.5% ➢ > 12 yrs-16 yr: 11.5% ➢ > 16 yr: 26.9% Distribution by gender ➢ Male: 65.4% ➢ Female: 34.6% Distribution by race: ➢ Black: 30.8 % ➢ Caucasian: 61.5%

Written Request Items	Information Submitted/ Sponsor's response
	➢ Other: 7.7% ➢ Unknown: 0% **ARD 5021**: ranged in age from 7 months to 18 years. Distribution by age ➢ >1 mo-2 yr: 20.9% ➢ > 2 years-12 yr:48.8% ➢ > 12 yrs-16 yr: 11.6% ➢ > 16 yr: 18.6% Distribution by gender ➢ Male: 69.8% ➢ Female: 30.2% Distribution by race: ➢ Black: 4.7 % ➢ Caucasian: 86% ➢ Other: 9.3% ➢ Unknown: 0% ARD5530: ranged in age from 1 to 22 years. Distribution by age ➢ >1 mo-2 yr: 2.1 % ➢ > 2 years-12 yr: 40.4% ➢ > 12 yrs-16 yr: 19.1% ➢ > 16 yr: 38.3% Distribution by gender

Written Request Items	Information Submitted/ Sponsor's response
	➢ Male: 72.3% ➢ Female: 27.7% Distribution by race: ➢ Black: 12.8 % ➢ Caucasian: 80.9% ➢ Other: 4.3% ➢ Unknown: 2.1%
Number of patients to be studied or power of study to be achieved: 2 phase 1 trials of approx 18-25 patients in each trial. 2 Phase 2 trials of least 14 pediatric patients in each trial.	**Number of patients studied or power achieved:** The Sponsor is including in this sNDA two Phase 1 studies ARD5531 and DFI7434: ARD5531 enrolled 45 patients. DFI 7434 enrolled 26 patients. The Sponsor is including in this sNDA two Phase 2 studies ARD5021 and ARD5530. ARD5021 enrolled 43 patients. ARD5530 enrolled 48 patients.
Written Request Items	Information Submitted/ Sponsor's response
Entry criteria: Refractory or relapsed pediatric solid tumors	Entry criteria used: Refractory or relapsed pediatric solid tumors
Clinical endpoints: The Phase 1 studies should seek the maximum tolerated dose (MTD) (or biologically effective dose = BED) as a primary endpoint with measurements of blood (and CSF if appropriate) concentrations, and pharmacokinetic (PK) parameters including clearance, volume of	**Clinical endpoints used:** Phase 1 studies: MTD Platinum concentrations in plasma and plasma ultrafiltrate were measured. Traditional (rich) sampling was used and pharmacokinetic parameters were estimated using non-compartmental and compartmental methods.

Written Request Items	Information Submitted/ Sponsor's response
distribution and half-life as secondary endpoints. A traditional or sparse sampling technique should be used to estimate the pharmacokinetic parameters. The Phase 2 or pilot studies must have a disease-specific surrogate endpoint or a clinically relevant endpoint. A traditional or sparse sampling technique should be used to estimate the pharmacokinetic parameters. Data from the Phase 1 and Phase 2 studies should be combined to develop population pharmacokinetic and pharmacodynamic (PK-PD) models and to explore PK-PD relationships for measures of safety and effectiveness.	The applicant had planned to collect CSF samples in study ARD5021 in patients with Ommaya reservoirs as a secondary Objective. However, no patients with Ommaya reservoirs were enrolled and thus no CSF samples were collected. Phase 2 studies: antitumor response rate Plasma concentrations in plasma ultrafiltrate were measured. Sparse sampling was used and pharmacokinetic parameters were estimated using population PK analysis. Data from the phase 1 and phase 2 studies were combined to develop a population PK model (POH0048). PK-PD analysis was conducted for measures of toxicity (POH0049). PK-PD analysis for measures of effectiveness was not done due to low number of responses.
Timing of assessments: if appropriate NA	**Timing of assessments:** NA
Written Request Items	Information Submitted/ Sponsor's response
Drug specific safety concerns: Peripheral neuropathy, neutropenia, thrombocytopenia, bleeding, infections, anemia, hepatotoxicity and death	**Drug specific safety concerns evaluated:** Peripheral neuropathy, neutropenia, thrombocytopenia, bleeding, infections, anemia, hepatotoxicity and death Tests: routine labs and clinical visits.
Drug information: Route of administration: Intravenous Regimen: As determined by Phase 1 study. If you are using doses in Phase 2 studies that have not been justified by the Phase 1 studies, you must provide adequate justification for using such doses.	**Drug information:** Route of administration: Intravenous Phase II: based on the Phase 1 trials performed by the sponsor, the regimen used in the Phase 2 studies was oxaliplatin 130 mg/m^2 as a 2-hour infusion on day 1 q3w .

Written Request Items	Information Submitted/ Sponsor's response
Statistical information (statistical analyses of the data to be performed): Statistical analysis appropriate to the phase of the study, including descriptive statistics for the Phase 2 studies must be submitted. Descriptive statistics of the PK parameters, clearance, half-life, volume of distribution and area under the curve must be included.	**Statistical information (statistical analyses of the data to be performed):** Descriptive statistics of the PK parameters are provided within each study report. Population PK parameters for oxaliplatin across all studies are provided in the Population PK report (POH0048). Descriptive statistics for the Phase 2 studies are submitted.
Written Request Items	Information Submitted/ Sponsor's response
Labeling that may result from the studies: Appropriate sections of the label may be changed to incorporate the findings of the studies.	**Labeling that may result from the studies:** Sponsor did submit proposed labeling. The following revisions to the current labeling are being proposed with this supplement. CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations The following has been added to the CLINICAL PHARMACOLOGY section: PK data Pediatric use sub-section (b) (4) has added the following:. Doses studied, PK, safety and tumor response data . Effectiveness in children has not been established. The labeling documents provided in this submission are being provided in the old format. The Sponsor believes the new labeling rule: Draft Guidance for Industry, Labeling for Human Prescription Drug and Biological Products –Implementing the New Content and Format Requirements, January 2006, is not applicable for this submission since a new indication, dosage, efficacy claim or new patient population is not being sought. However the Sponsor is prepared to provide the labeling in the new format at the FDA's

Written Request Items	Information Submitted/ Sponsor's response
	request.
Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. Include other information as appropriate. All pediatric patients enrolled in the studies 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 must be used: Hispanic/Latino or Not Hispanic/Latino. Reference is made to the 30 March 2006 FDA meeting minutes in which the Division agreed to the following: Data would be provided in CDISC Version 2 format such as demography, treatment exposure, lab data and adverse event data. A Clinical Overview would be submitted in lieu of an Overall Summary, Summary of Efficacy, Summary of Safety and Summary of Pharmacokinetics. Case report forms would be provided on the following patients (Attachment 1): o Deaths that were due to causes other than progressive disease o All patients who withdrew due to an SAE o Any AEISAE that is determined to need explanation to fully understand the content of	**Format of reports submitted:** Submission is provided entirely in electronic format, consistent with the January 1999 "Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs." The archival copy is a fully electronic dossier, with the exception of administrative NDA 2 1-492; Oxaliplatin (SR96669) Sanofi-aventis U.S. Inc. – CONFIDENTIAL 10 July 2006 Supplemental NDA Submission documents requiring an original signature that are provided in paper. Full navigation to all provided documents is available from the submission Table of Contents (suppltoc.pdf). Full reports for all studies including full analysis for all studies and racial information for 1 Phase 1 and 2 phase 2 studies are included. Reference is made to the 30 March 2006 FDA meeting minutes in which the Division agreed to the following: Data were provided in CDISC Version 2 format such as demography, treatment exposure, lab data and adverse event data. A Clinical Overview was submitted in lieu of an Overall Summary, Summary of Efficacy, Summary of Safety and Summary of Pharmacokinetics. Case report forms were provided on the following patients : o Deaths that were due to causes other than

Written Request Items	Information Submitted/ Sponsor's response
the event Each electronic dataset would include the pharmacokinetic data. Datasets used for the population PK and PKPD would be provided. .	progressive disease o All patients who withdrew due to an SAE o Any AEISAE that is determined to need explanation to fully understand the content of the event Case reports forms were submitted for study ARD5531 and patient profiles or electronic CRF screen shots are being submitted for the remaining studies (ARD5530, DFI7434 and ARD5021). Each electronic dataset included the pharmacokinetic data. Datasets used for the population PK and PK/PD were provided.
Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before 8/8/07.	Timeframe for submitting reports of the studies: The studies were submitted to the Agency on 7/10/06

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/s/

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