**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

# NDA 21-492 SE8- s008

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| **Drug name:** | ELOXATIN® |
| **Generic name:** | Oxaliplatin |
| **Formulation:** | 50 mg or 100 mg vial of sterile, preservative-free lyophilized powder for reconstitution |
| **Adult Indication:** | Metastatic carcinoma of the colon or rectum |
| **Pediatric Indication:** | None |
| **Current Submission:** | Pediatric Supplement |
| **Applicant:** | Sanofi-Aventis US Inc.<br>300 Somerset Corporate Boulevard<br>Bridgewater, NJ 08807 |
| **OCP Division:** | Division of Clinical Pharmacology 5 (HFD-860) |
| **OODP Division:** | Division of Drug Oncology Products (HFD-150) |
| **Submission Dates:** | 10-July-2006 |
| **Primary Reviewer:** | Roshni Ramchandani, Ph.D. |
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| **Type of Submission:** | NDA-Supplement |

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# I. EXECUTIVE SUMMARY

Oxaliplatin is a platinum-based neoplastic agent approved, in combination with 5-fluorouracil for the treatment of colorectal cancer. The current submission includes studies conducted by the applicant in response to a pediatric written request for studies of oxaliplatin in pediatric malignancies. Two phase 1 studies were conducted to evaluate the safety and pharmacokinetics (PK) of oxaliplatin in children with advanced solid tumors. Two phase 2 studies were conducted to evaluate response rates in children with CNS tumors. A population PK model was developed for oxaliplatin in the pediatric population across the 4 studies. The clearance of oxaliplatin in pediatric patients was consistent with estimates obtained in adults. Exposure-response analysis did not indicate any significant relationships between AUC and incidence of severe (grade 3/4) toxicity including neutropenia, thrombocytopenia, anemia, neuropathy, nausea, vomiting and diarrhea. The applicant is not currently seeking an indication for use of oxaliplatin in pediatric malignancies. The applicant has proposed to include information on the safety and pharmacokinetics of oxaliplatin in pediatric patients in the label.

## *A. RECOMMENDATIONS*

The clinical pharmacology information submitted by the applicant in the current submission is acceptable, from the Office of Clinical Pharmacology perspective.

The following are some modifications to the sponsor's proposed labeling regarding the pharmacokinetics of oxaliplatin in pediatric patients.

**Applicant's Labeling:**

**Agency's Proposed Labeling:**

> The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in (b) (4) 105 pediatric patients during the first cycle. The (b) (4) clearance in pediatric patients estimated by the population pharmacokinetic analysis was (b) (4) 4.7 L/h/m$^2$. The inter-patient variability of platinum clearance in pediatric cancer patients was (b) (4) 41%. Mean platinum pharmacokinetic parameters in ultrafiltrate were $C_{max}$ of (b) (4) 0.75 + 0.24 (b) (4)/mL, $AUC_{0-48}$ of (b) (4) 7.52 ± 5.07 (b) (4).h/mL and $AUC_{inf}$ of (b) (4) 8.83 + 1.57 (b) (4).h/mL at 85 mg/m² of oxaliplatin and $C_{max}$ of (b) (4) 1.10 ± (b) (4) /mL, $AUC_{0-48}$ of (b) (4) 9.74 ± 2.52 (b) (4).h/mL and $AUC_{inf}$ of (b) (4) 17.30 ± 5.34 (b) (4).h/mL at 130 mg/m² of oxaliplatin. (b) (4)

## *B. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS*

The applicant has conducted two phase 1 studies to characterize the safety and pharmacokinetics (PK) of oxaliplatin in children with advanced solid tumors. Oxaliplatin was given as a single agent in a weekly regimen in one study and an every-3-week regimen in the other study. The applicant has also conducted two phase 2 studies to characterize the safety, PK and activity of oxaliplatin in patients with advanced CNS tumors. Oxaliplatin was given at a dose of 130 mg/m$^2$ every 3 weeks in both studies.

The PK data from the four studies were combined and a population PK model was developed to describe the PK of oxaliplatin. A three-compartment model, with inter-individual variability on CL, V2 and V3 and with a proportional residual error model, described platinum concentrations in plasma ultrafiltrate (PUF) collected in pediatric cancer patients. Inter-individual variability of PUF platinum clearance was significantly related to body weight and glomerular filtration rate, and that of V3 was significantly related to body weight. The residual variability for the final model was 41%.

Oxaliplatin exposures seen in pediatric and adult patients were comparable both in plasma and PUF, following comparable doses of 130 mg/m$^2$. This suggests that the PK parameters for pediatric and adult patients are comparable. The population mean oxaliplatin clearance in pediatric patients is 5.1 L/hr (%CV=41%) or 4.7 L/hr/m$^2$ 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$^2$. 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 predicted from adults.

The sponsor also conducted an exposure-response analysis to examine the relationship between exposure and incidence of various toxicities associated with oxaliplatin, including neutropenia, thrombocytopenia, GI toxicities (nausea, vomiting, diarrhea) and CNS toxicities (peripheral neuropathy). An analysis conducted in patients with exposure (AUC) data did not reveal any significant association between incidence of severe (grade 3/4) toxicity and exposure across studies.

# II. Question Based Review

## *A. General Attributes of the Drug*

**A1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?**

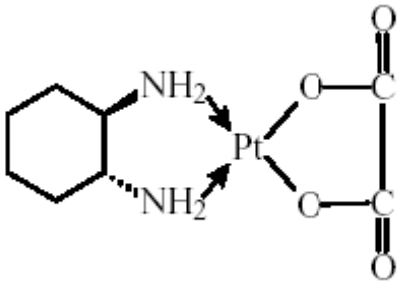
Oxaliplatin is an anti-neoplastic agent belonging to the class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane ("DACH") and an oxalate group.

Oxaliplatin, in combination with infusional 5-fluorouracil (5-FU) and leucovorin (LV), was originally approved in 1999 for the treatment of patients with advanced colorectal cancer. In 2002, the applicant received approval for oxaliplatin, in combination with 5-FU and LV, for the treatment of patients with metastatic colorectal cancer that has recurred or progressed following initial irinotecan plus 5-FU/LV therapy.

In 2004, the Agency issued a pediatric written request (PWR) to the applicant to evaluate oxaliplatin in pediatric cancer patients. The current submission includes 4 studies conducted by the applicant in fulfillment of the PWR.

**A2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology review?**

Oxaliplatin is an organoplatinum complex in which the platinum (Pt) atom is complexed with 1,2-diaminocyclohexane (DACH) and an oxalate group. The molecular weight is 397.3.




The drug is formulated as a sterile, preservative-free lyophilized powder for reconstitution, in vials containing 50 and 100 mg.

**A3. What are the proposed mechanism(s) of action and therapeutic indication(s)?**

The cytotoxic activity of oxaliplatin is the result of the formation of adducts with strands of DNA. The aqua-derivatives resulting from the biotransformation of oxaliplatin, interact with

DNA to form both inter and intra strand cross-links, resulting in the disruption of DNA synthesis, and leading to cell death.

ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for the treatment of advanced carcinoma of the colon or rectum.

**A4. What are the proposed dosage(s) and route(s) of administration?**

In adults the following is the approved dosage regimen:

Oxaliplatin is administered in combination with 5-FU/LV every 2 weeks for first line treatment of colorectal cancer according to the following regimen. In the adjuvant setting, treatment is recommended for a total of 6 months (12 cycles).

FOLFOX regimen:
- Day 1: ELOXATIN 85 mg/m$^2$ intravenous (IV) infusion in 250-500 mL 5% Dextrose Injection, USP (D5W) and LV 200 mg/m$^2$ IV infusion in D5W, both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m$^2$ IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m$^2$ IV infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.
- Day 2: LV 200 mg/m$^2$ IV infusion over 120 minutes, followed by 5-FU (same administration as for Day 1).

A dose reduction of ELOXATIN to 75 mg/m² (adjuvant setting) or 65 mg/m² (advanced colorectal cancer) is recommended in the following situations:
- if persistent grade 2 neurosensory events that do not resolve
- after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until neutrophils ≥ 1.5 x $10^9$/L and platelets ≥ 75 x $10^9$/L.

Treatment should be discontinued if grade 3 neurosensory events persist.

Currently as there is no indication in pediatrics, there is no proposed dosage regimen. For dosage regimens studied in the pediatric studies, see section C1.

## *B. Pediatric Study Decision Tree*

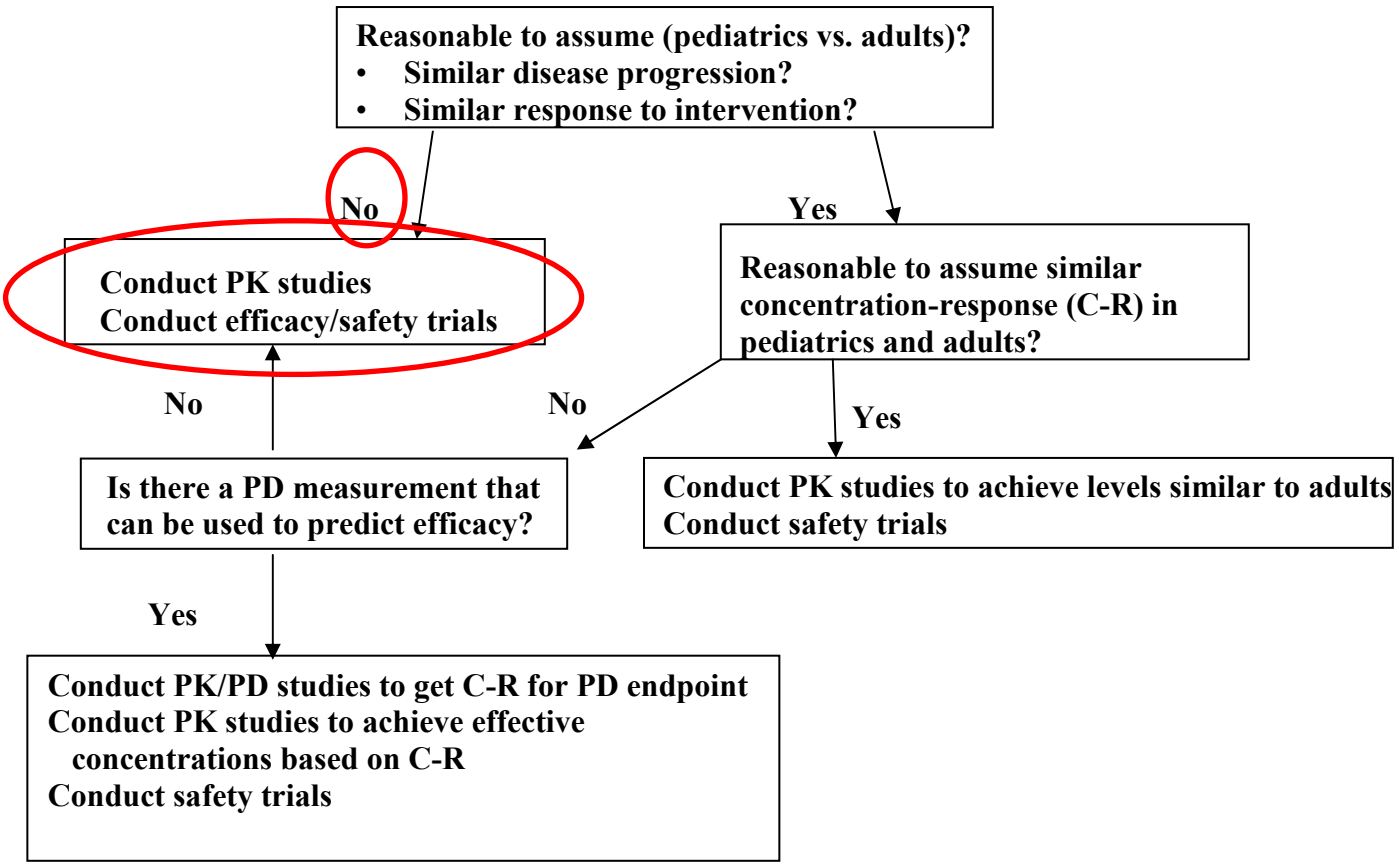
Oxaliplatin was evaluated in pediatric cancer patients for the treatment of solid tumors, including embryonal CNS tumors in this submission. The drug has been approved for use in adults in combination with 5-fluorouracil (and leucovorin) for the first-line treatment of colorectal cancer.

**B1. Is it reasonable to assume similar disease progression in pediatrics vs. adults?**

Due to differences in cancer type, and differences between adults and children with regard to disease progression, it would not be reasonable to assume similar disease progression.

**B2. Is it reasonable to assume a similar response to intervention in pediatrics vs. adults?**

The overall pharmacological effect of the drug, i.e., complexation with DNA leading to cytotoxic effects on tumor cells would be expected to be similar in pediatrics vs. adults. However, there are some important differences in the disease between adults and pediatrics. Oxaliplatin is approved for the treatment of colorectal cancer in adults, this type of cancer is extremely rare in children. In the pediatric studies conducted, the patients had CNS tumors and other soft tissue sarcomas, which is different from colorectal cancer in etiology, clinical manifestation, prognosis and treatment. Also, in terms of the effect of the drug, the sensitivity and dose-response characteristics of pediatric tumors to intervention could be different from that in adults. Thus it would not be reasonable to assume that pediatric and adult patients would have similar disease progression and similar response to intervention.



Therefore, according to the decision tree, the applicant would need to conduct PK studies of oxaliplatin in pediatrics, as well as studies to establish effectiveness and safety of oxaliplatin. In fact, the studies submitted by the applicant include two phase 1 PK and safety studies and two phase 2 studies examining response rates (effectiveness) and safety of the drug.

## *C. Clinical Pharmacology*

**General attributes**

### C1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The oxaliplatin pediatric program consists of 4 studies – two Phase 1 studies (ARD5531 and DFI7434) and 2 Phase 2 studies (ARD5021 and ARD5530). These studies are described in Table I.

*Table I: Description of studies included in current submission.*

| Study | Phase | Description of treatments | N[a] | 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<br>• 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<br>• 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<br>• 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<br>• 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<br>• 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<br>• Cycle repeated every 3 weeks<br>• Four strata completed; 7 strata ongoing | 48[b] | Ongoing |

a Number of patients entered
b Number of patients enrolled in 4 completed strata of interest per the PWR.

**C2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?**

The response endpoint evaluated in the phase 2 studies was the objective response rate (complete response + partial response) following treatment with oxaliplatin. Complete response was defined by the complete resolution of all tumors identified initially, without the appearance of any new areas of disease. Partial response was defined by a greater than 50% decrease in the product of the maximum perpendicular diameters of the tumor relative to baseline without the appearance of any new areas of disease. These definitions were based on WHO criteria for measurement of disease.

**C3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Yes. The pharmacokinetics of platinum were evaluated in all 4 studies. A rich sampling scheme was used in the phase 1 studies and a sparse sampling scheme was used in the phase 2 studies. PK data was collected in 105 of the 159 patients enrolled in the 4 studies.

Platinum levels in plasma and plasma ultrafiltrate (PUF) were measured using a validated inductively coupled plasma mass spectrometry (ICP-MS) method with a limit of quantification (LOQ) of 3 ng/mL in plasma and 1 ng/mL in PUF. Please see the Analytical Section for details.

**Exposure-response**

**C4. Is there a relationship between platinum exposure following oxaliplatin and effectiveness (response rates) in pediatric patients?**

No. Across the four studies, the best response seen was a partial response, seen in two patients in study ARD5531 and 1 patient in ARD5021. In both phase 2 studies, a 2-stage design was used where a minimum (pre-set) response rate was required in the first stage of patients enrolled, before additional patients were included in the study. In both phase 2 studies, the minimum response rate was not achieved, and enrollment was terminated.

No exposure-response relationships for measures of effectiveness could be determined.

**C5. Is there a relationship between oxaliplatin exposure and incidence of adverse events in pediatric patients?**

The major toxicities following oxaliplatin are:

- hematological toxicity including anemia, neutropenia and thrombocytopenia
- gastrointestinal toxicity including nausea, vomiting and diarrhea, and
- neurological toxicity including sensory neuropathy.

The sponsor conducted an exposure-toxicity analysis to evaluate the incidence of some of the major toxicities as a function of platinum exposure following oxaliplatin. The analysis was conducted using logistic regression analysis.

The sponsor evaluated the toxicities listed in the following table as a function of AUC, estimated from the individual CL estimates for each patient. 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. The following table shows the results of the sponsor's analysis. No significant relationships with exposure were seen for any of the toxicities evaluated.

*Table 2: Summary of the effect of AUC (mg*h/L) on the incidence of selected toxicities (Category = Grades 3/4) – Sponsor's Analysis.*

| **Body System or Selected Toxicity** | **Parameter Estimate** | **Wald Chi-Square** | **p-value** |
|---|---|---|---|
| GI Body System | -0.0318 | 0.1416 | 0.7067 |
| Nervous System Body System | -0.1136 | 1.2777 | 0.2583 |
| Renal and Urinary Disorders Body System | -0.00225 | 0.0005 | 0.9829 |
| Neutropenia | -0.1325 | 1.2144 | 0.2705 |
| Febrile Neutropenia | -0.2582 | 0.7672 | 0.3811 |
| Thrombocytopenia | 0.00251 | 0.0052 | 0.9425 |

The exposure-response analysis was repeated by the Agency with the following changes:
The dataset was expanded to include all 4 studies. This resulted in a total of 105 of 159 patients in the sample, as only 105 of had PK data.
The following individual toxicities were examined: nausea, vomiting, diarrhea, neuropathy, neutropenia, febrile neutropenia, anemia and thrombocytopenia. For all these toxicities, the incidence of grade 3/4 toxicity was evaluated as a function of AUC using logistic regression.

The results of the Agency's analysis are shown in the following table. No significant relationships were found for incidence of 3/4 toxicity and exposure. This could be due to the small number of toxicity events seen in the sample.

*Table 3: Summary of the effect of AUC (µg*h/ml) on the incidence of selected toxicities (Category = Grades 3/4 or as indicated) – Agency Analysis*

| **Selected Toxicity** | **Frequency*** | **Effect of AUC (Logistic Regression) p-value** |
|---|---|---|
| Neutropenia | 6/105 | 0.5261 |
| Anemia | 12/105 | 0.8502 |
| Thrombocytopenia | 20/105 | 0.8016 |
| Neuropathy<br>Grade 3/4<br>Grade 2/3/4 | <br>4/105<br>15/105 | <br>0.3093<br>0.2189 |
| Nausea | 3/105 | 0.6631 |
| Vomiting | 7/105 | 0.7565 |

| | | |
|---|---|---|
| Diarrhea | 2/105 | 0.5688 |

*: frequency estimated within group of patients with estimated AUC.

**C6. Does this drug prolong the QT or QTc interval?**

Prolongation of QT or QTc interval was not evaluated in the pediatric patients in any of the submitted studies. It is not known if oxaliplatin prolongs QT or QTc interval in adult patients.

**Pharmacokinetics**

**C7. What are the PK characteristics of the drug?**

The clinical pharmacology of oxaliplatin was extensively reviewed in the original NDA (NDA 21-063). The following is a summary of the PK of oxaliplatin, based on previous reviews and information included in the label.

Following IV administration, oxaliplatin undergoes hydrolysis to yield a number of Pt – containing metabolites. The pharmacokinetics of oxaliplatin are described by a three-compartment model with t1/2's of 0.43, 16.8 and 391 hours. Interpatient and intrapatient variability in ultrafilterable platinum exposure ($AUC_{0\text{-}48hr}$) assessed over 3 cycles was moderate to low (23% and 6%, respectively). The pharmacokinetics of oxaliplatin appears to be linear between 40 and 130 mg/m$^2$.

Oxaliplatin does not undergo cytochrome P-450 metabolism, nor does it inhibit any cytochrome P-450 isozymes. Therefore, no cytochrome P-450 based drug-drug interactions are anticipated. The extent of oxaliplatin plasma protein binding is approximately 90 to 95 % in vivo, and Pt accumulates in erythrocytes with repeated administration of oxaliplatin, although there is no apparent adverse reaction associated with accumulation.
The major route of platinum elimination is renal excretion. At five days after a single 2-hour infusion of oxaliplatin, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Platinum was cleared from plasma at a rate (10 – 17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of ultrafilterable platinum. The renal clearance of ultrafilterable platinum was significantly correlated with GFR

**C8. What are the PK characteristics of the drug in pediatric patients?**

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 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.

The following figure shows the mean plasma Pt concentration vs. time profiles and Pt in plasma ultrafiltrate (PUF) vs. time profiles for study ARD5531. Tables 4 and 5 show the PK parameters for Pt in plasma and PUF following oxaliplatin from study ARD5531.

*Figure 1: Mean (SD) Pt concentration vs. time profiles in plasma (upper panel) and in plasma ultrafiltrate (lower panel) for study ARD5531.*

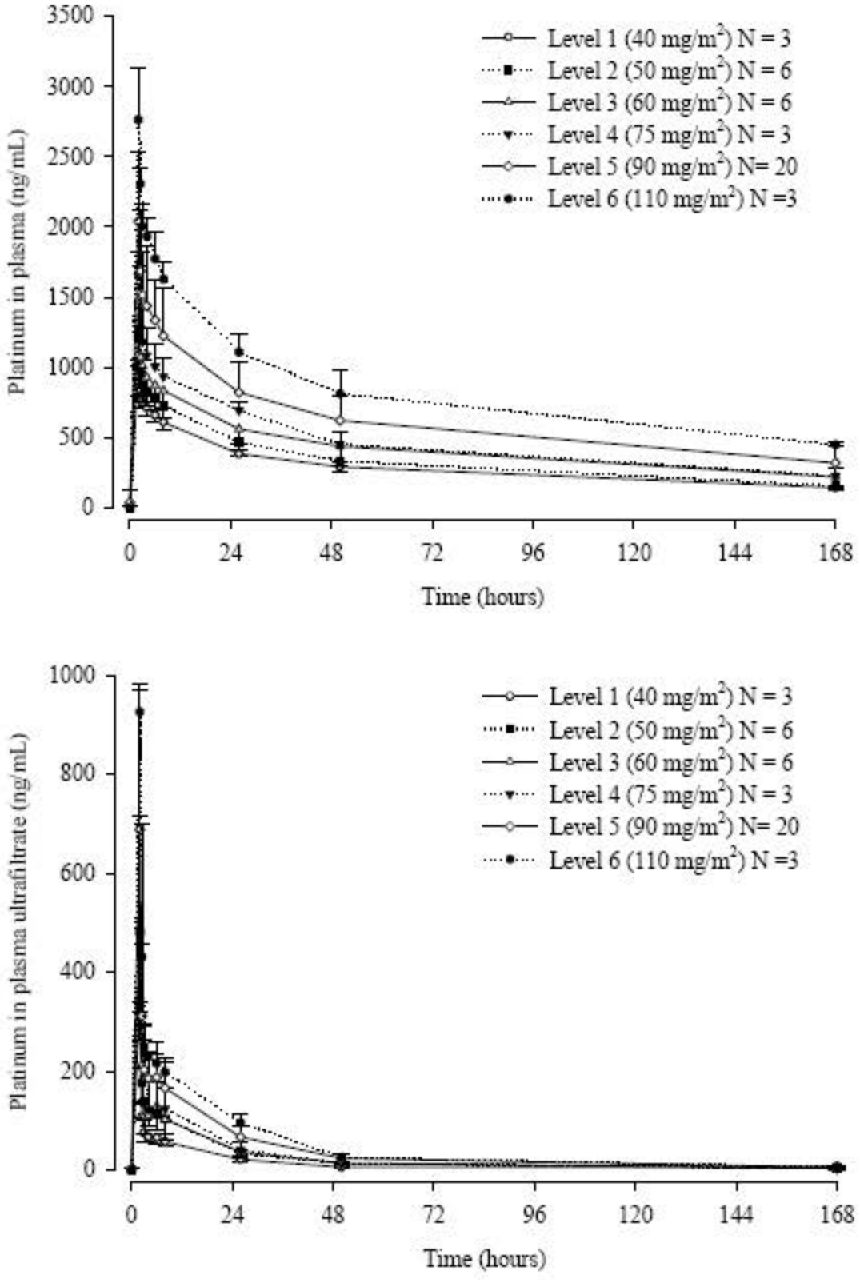


*Table 4A: Summary of PK parameters for **Pt in plasma** following oxaliplatin in study ARD5531 (dosing on days 1, 8 and 15)*

| **Level** | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| **Dose** | **40 mg/m2** | **50 mg/m2** | **60 mg/m2** | **75 mg/m2** | **90 mg/m2** | **110 mg/m2** |
| **Parameter** | **(N=3)** | **(N=6)** | **(N=6)** | **(N=3)** | **(N=20)** | **(N=3)** |
| **Cmax (ng/mL)** | 1020 (204) | 1210 (209) | 1480 (433) | 1650 (171) | 2070 (495) | 2770 (362) |
| **AUC0-48 (ng.h/mL)** | 22000 (1580) | 25800 (2910) | 30800 (5530) | 34800 (4830) | 44500 (11100) | 60100 (5380) |
| **AUC (ng.h/mL)** | 69400 [a] | 76500 [b] (6980) | 92900 [c] (10400) | 94000 [a] | 121000 [d] (29900) | 207000 [e] |
| **t1/2α (h)** | 0.279 (0.111) | 0.259 [f] (0.118) | 0.281 (0.164) | 0.393 (0.223) | 0.386 [g] (0.376) | 0.259 [a] |
| **t1/2β (h)** | 8.07 (2.03) | 11.8 [f] (1.28) | 12.0 (5.30) | 15.1 (4.59) | 12.1 [g] (7.55) | 8.10 [a] |
| **t1/2γ (h)** | 121 (12.2) | 124 [f] (19.8) | 223 (227) | 166 (47.4) | 152 [g] (66.4) | 129 [a] |

a N=2, b N=4, c N=3, d N=8, e N=1, f N=5, g N=18.
Cmax, AUC0-48, AUC were determined by non-compartmental analysis. AUC values excluded if extrapolated portion of AUC > 30%. t1/2α, t1/2β, and t1/2γ were determined by compartmental analysis.

*Table 4B: Summary of PK parameters for **Pt in plasma ultrafiltrate** following oxaliplatin in study ARD5531.*

| **Level** | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| **Dose** | **40 mg/m2** | **50 mg/m2** | **60 mg/m2** | **75 mg/m2** | **90 mg/m2** | **110 mg/m2** |
| **Parameter** | **(N=3)** | **(N=6)** | **(N=4)** | **(N=3)** | **(N=17)** | **(N=3)** |
| **Cmax (ng/mL)** | 344 (82.2) | 481 (143) | 489 (171) | 669 (400) | 696 (287) | 926 (45.8) |
| **AUC0-48 (ng.h/mL)** | 1830 (262) | 3020 (764) | 2990 (624) | 3120 (1340) | 4880 (1240) | 6370 (1090) |
| **AUC (ng.h/mL)** | 2240 [a] | 4350 [b] (947) | 4100 (910) | 4790 [a] | 6670 [c] (1790) | 7910 [a] |
| **t1/2α (h)** | 0.161 (0.038) | 0.168 [d] (0.101) | 0.193 [e] (0.080) | 0.378 [a] | 0.248 [f] (0.226) | 0.133 [a] |
| **t1/2β (h)** | 10.6 (2.10) | 9.61 d (2.63) | 13.4 [e] (2.66) | 10.3 [a] | 10.8 [f] (4.89) | 13.4 [a] |
| **t1/2γ (h)** | 337 (318) | 281 [a] (319) | 224 [e] (98.7) | 390 [a] | 282 [f] (281) | 390 [a] |
| **Vss (L)** | 321 [a] | 280 [b] (82.9) | 303 (92.4) | 349 [a] | 362 [c] (206) | 273 [a] |
| **Cl (L/h)** | 8.14 [a] | 7.02 [b] (1.58) | 7.09 (1.38) | 8.04 [a] | 8.65 [c] (5.06) | 6.66 [a] |

a N=2, b N=5, c N=16, d N=5, e N=3, f N=13.
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.

*Table 5A: Summary of PK parameters after first infusion for **Pt in plasma** following oxaliplatin in study DFI 7434.*

| Level | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Dose | 100 mg/m$^2$ | 130 mg/m$^2$ | 160 mg/m$^2$ | 160 mg/m$^2$ + CBZ | 85 mg/m$^2$ |
| Schedule | q 3 weeks | | | | q 2 weeks |
| Parameter | (N=3) | (N=6) | (N=2) | (N=6) | (N=9) |
| $C_{max}$ (ng/mL) | 2800 (824) | 3390 (823) | 4500 | 5080 (994) | 1710 (432) |
| $AUC_{0-48}$ (ng.h/mL) | 59700 (17800) | 74400 (10100) | 102000 | 101000 (7690) | 32400 (7050) |
| AUC (ng.h/mL) | 254000 (60288) | 296000 (55700) | 469000 | 430000 (102000) | 128000 [a] (8010) |
| $t_{1/2\alpha}$ (h) | 0.274 (0.187) | 0.295 (0.122) | 0.173 | 0.359 (0.447) | 0.361 [b] (0.191) |
| $t_{1/2\beta}$ (h) | 17.9 (6.49) | 22.4 (18.7) | 13.9 | 21.4 (15.6) | 17.7 [b] (7.68) |
| $t_{1/2\gamma}$ (h) | 242 (52.3) | 218.3 (64.2) | 197 | 331 (272) | 377 [b] (253) |

[a]: N=4, [b]: N=7.

$C_{max}$, $AUC_{0-48}$, AUC were determined by non-compartmental analysis. $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined by compartmental analysis.

*Table 5B: Summary of PK parameters for **Pt in plasma ultrafiltrate** following oxaliplatin in study DFI7434.*

| Level | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Dose | 100 mg/m$^2$ | 130 mg/m$^2$ | 160 mg/m$^2$ | 160 mg/m$^2$ + CBZ | 85 mg/m$^2$ |
| Schedule | q 3 weeks | | | | q 2 weeks |
| Parameter | (N=3) | (N=6) | (N=2) | (N=6) | (N=9) |
| $C_{max}$ (ng/mL) | 980 (486) | 1100 (428) | 1520 (1040) | 2120 (667) | 754 (244) |
| $AUC_{0-48}$ (ng.h/mL) | 7520 (5070) | 9740[b] (2520) | 12700 (1570) | 11400 (2130) | 7520[c] (5070) |
| AUC (ng.h/mL) | 21800[a] | 17300[c] (5340) | N/A | 15700[e] | 8830[c] (1570) |
| $t_{1/2\alpha}$ (h) | 0.208 (0.0620) | 0.152 (0.0120) | 0.157 | 0.166 (0.028) | 0.180[f] (0.0210) |
| $t_{1/2\beta}$ (h) | 15.3 (4.07) | 18.9 (9.72) | 16.0 | 13.4 (2.04) | 16.3 [f] (5.41) |
| $t_{1/2\gamma}$ (h) | 402 (322) | 372 (344) | 641 | 371 (285) | 451[f] (323) |
| $V_{ss}$ (L) | 221[a] | 505[c] (209) | N/A | 719[e] | 414[c] (123) |
| Cl (L/h) | 1.85[a] | 5.35 (1.89) | N/A | 8.53[e] | 5.71[c] (1.68) |

[a]: N=1, [b]: N=4, [c]: N=3, [d]: N=7, [e]: N=2, [f]: N=6.

N/A: Not available. $C_{max}$, $AUC_{0-48}$, AUC, $V_{ss}$ and CL values were determined by non-compartmental analysis. $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined by compartmental analysis.

As the above tables show, the exposure to Pt following oxaliplatin appears to increase linearly with dose. The half-life estimates, obtained from compartmental analysis appear to be consistent across dose levels.

Population PK Analysis

The PK data for oxaliplatin was modeled using non-linear mixed-effects modeling (NONMEM version V). The Pt concentrations in plasma ultrafiltrate (PUF) from all 4 studies (total number of subjects=105) were fit to a 3-compartment model. The effect of several covariates on the PK of oxaliplatin was also evaluated.

The dose of platinum administered and used in the pharmacokinetic analysis was based on the atomic weight of platinum and the molecular weight of oxaliplatin. Therefore, the total oxaliplatin dose each patient received during the sample collection period was multiplied by the conversion factor of 0.491 (=195/397) to derive the dose of platinum.

The population PK analysis proceeded as follows:
1) Characterize structural models for platinum in PUF in pediatric patients. Inter-individual variability in parameter models was modeled using an exponential error term. Residual variability in concentrations was modeled using both exponential and additive terms.
2) After this, the relationships between covariates and individual pharmacokinetic parameters were explored. Models were built in a stepwise manner, increasing in complexity. Covariates were screened using univariate analysis to obtain a subset of covariates for each parameter (CL, V1, V2 and V3). Model selection was based on decrease in objective function, visual inspection of residual plots and observed vs. predicted plots.

Results: A 3-compartment model with exponential inter-individual error terms on CL, V2 and V3, and a proportional residual error model, was identified as the final model.
Covariate analysis indicated significant effects for GFR and WT on CL, and WT on V3.
Table 6 provides gives the history of the model development. Examination of the ETA for clearance following the inclusion of GFR into the CL parameter model (model 3 in table 6) showed a trend when plotted as a function of WT (figure 2A). After WT was included in the model (model 4 in table 6), the trend disappeared and the data seemed more uniformly distributed (figure 2B).

Table 7 gives the final parameter estimates and Figure 3 shows the goodness-of-fit plots.

*Figure 2A: Scatter plot of ETA (residual error) for clearance vs. body weight for model 3 in table 6. Clearance was modeled as a function of GFR and the residual error of clearance shows a trend with body weight.*
*Figure 2B: Scatter plot of ETA (residual error) for clearance vs. body weight for model 4 in table 6. Clearance was modeled as a function of GFR and body weight, and the trend for residual error of clearance with body weight disappears.*

Figure 2A

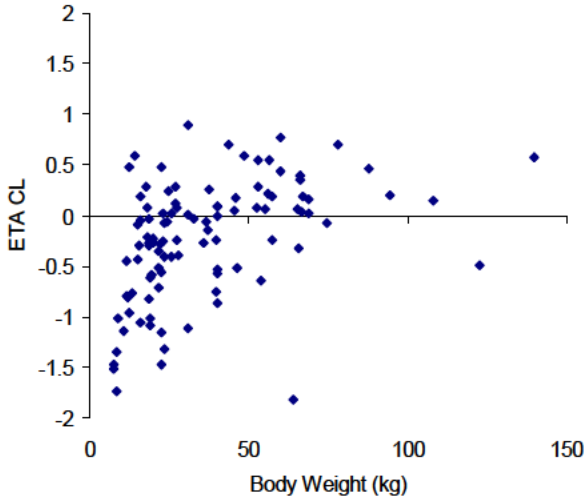



Figure 2B

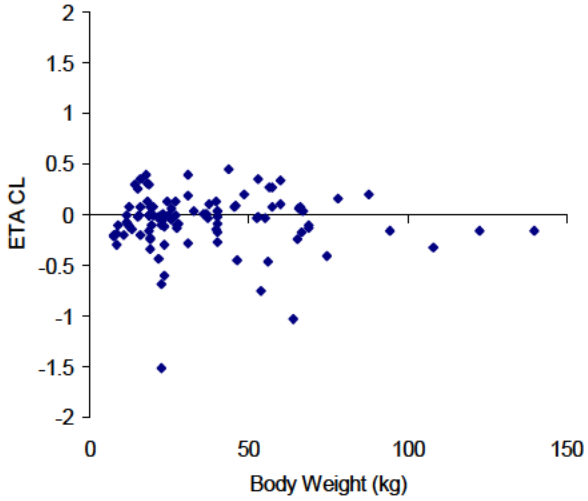


*Table 6: Population PK model for oxaliplatin – Model building history.*

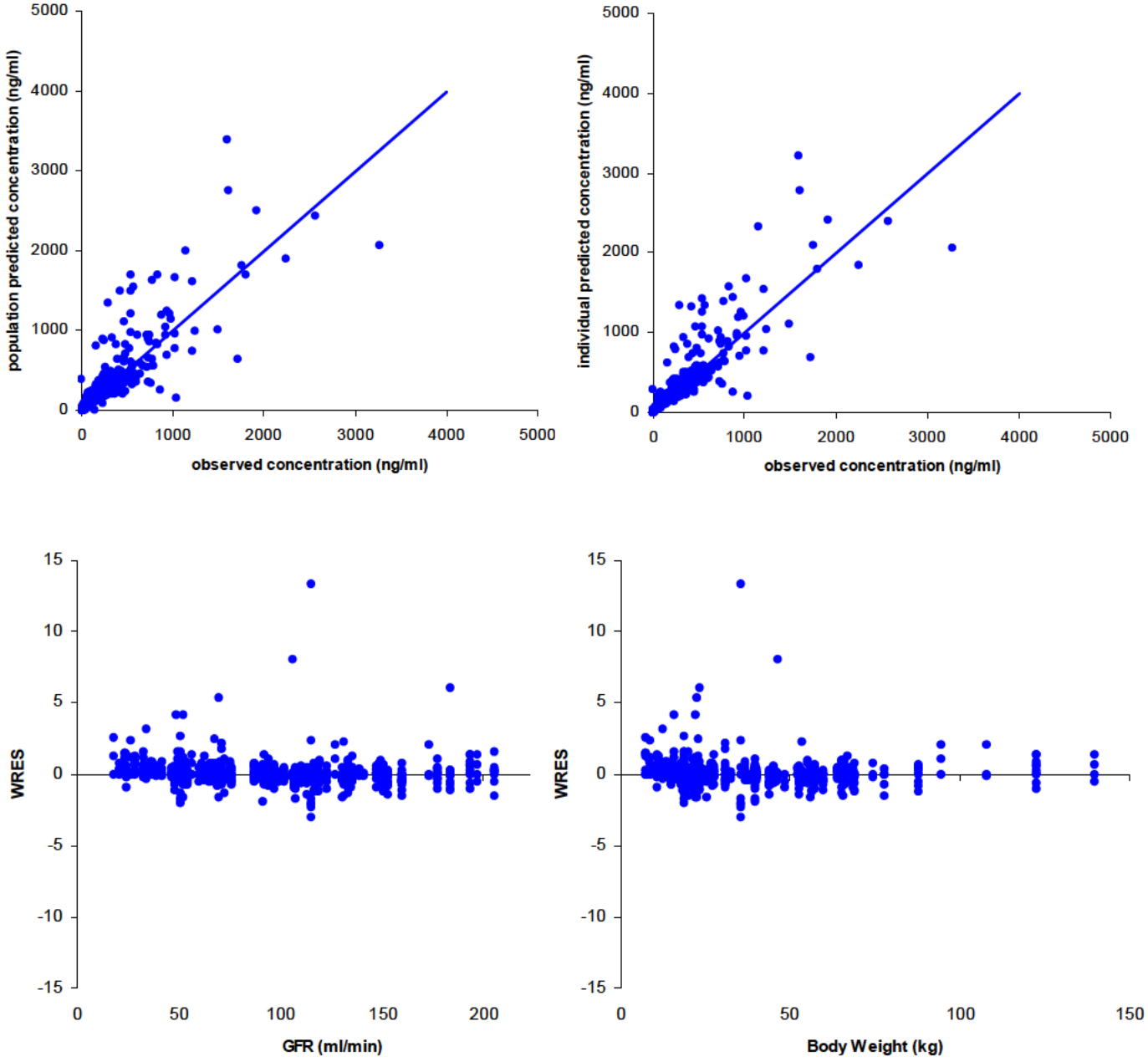
| Model Number | Model Name | Description | OBJ | Between-Subject Variability |
|---|---|---|---|---|
| 1 | base_model2 | proportional residual error | 5895.676 | BSV-CL=87%<br>BSV-V3=25% |
| 2 | base_model2_adderr | additive residual error | 6438.065 | BSV-CL=22%<br>BSV-V3=88% |
| 3 | base_model2_GFRCL | Model 1 + GFR on CL | 5880.115 | BSV-CL=85% |
| 4 | base_model2_WTCL | Model 1 + WT on CL (linear) | 5825.039 | BSV-CL=33% |
| 5 | base_model2_WTCL_exp | Model 1 + WT on CL (exp) | 5822.501 | BSV-CL=30% |
| 6 | base_model2_WTGFRCL_exp | Model 5 + GFR on CL<br>ETA on V2 and V3 | 5810.260 | BSV-CL=33% |
| **7 (final)** | **base_model2_WTGFRCL_WTV3_exp** | **Model 6 + WT on V3<br>ETA on V2 and V3** | **5714.471** | **BSV-CL=37%<br>BSV-V2=361%<br>BSV-V3=6.2%** |
| 8 | base_model2_WTGFRCL_WTV3_noeta v3_exp | Model 6 + WT on V3<br>ETA on V2 | 5714.664 | BSV-CL=37%<br>BSV-V2=363% |
| 9 | final_model_sponsor_2 (sponsor's "final model") | Model 5 + WT on V3<br>ETA on V2 | 5721.694 | BSV-CL=39%<br>BSV-V2=426% |

*Table 7: Estimates from final model for oxaliplatin.*

| **Estimated parameter** | **Estimate** | **(SE%)** |
|---|---|---|
| **Structural model parameters** | | |
| CL (L/h) = THETA(1) | 4.41 | 9% |
| * (WT / 27.1) ^THETA(7) | 0.435 | 54% |
| + THETA(8) * (GFR / 92.3) | 0.873 | 31% |
| V1 (L) = THETA(2) | 4.53 | 21% |
| Q2 (L/H) = THETA(3) | 1.70 | 20% |
| V2 (L) = THETA (4) | 505 | 24% |
| Q3 (L/H) = THETA (5) | 17.3 | 22% |
| V3 (L/H) = THETA (6) | 41.2 | 18% |
| + THETA (9) * (WT / 27.1) | 45.6 | 26% |
| **Inter-individual variability parameters** | | |
| %CV for CL | 37% | 28% |
| %CV for V2 | 361% | 82% |
| %CV for V3 | 6% | 338% |
| **Residual error parameters** | | |
| % CV (Proportional) | 41% | 48% |

%CV=% coefficient of variation. RSE = relative standard error of the estimate = SE/Parameter Estimate

*Figure 3: Goodness-of-fit plots for final PK model for oxaliplatin. Upper left panel: observed concentrations vs. population predicted concentrations. Upper right panel: observed concentrations vs. individual predicted concentrations. Lower left panel: weighted residuals vs. GFR. Lower right panel: weighted residuals vs. body weight.*



Based on the above estimates, the typical value of clearance for oxaliplatin (for a child weighing 27.1 kg with a GFR of 92.3 ml/min) is estimated to be 5.3 L/hr.

Summary statistics were also computed for the individual POSTHOC estimates of the PK parameters across the 105 subjects included in the analysis (see table 8).

*Table 8: Summary of PK parameters obtained from POSTHOC PK estimates across the 105 patients included in the analysis.*

| Parameter | Mean | %CV | Median | Range |
|---|---|---|---|---|
| CL (L/hr) | 5.1 | 41% | 4.9 | 1.3 – 11.2 |
| V1 (L) | 4.53 | - | - | - |
| Q2 (L/hr) | 1.7 | - | - | - |
| V2 (L) | 459 | 82% | 385 | 5 – 2647 |
| Q3 (L/hr) | 17.1 | - | - | - |
| V3 | 102 | 41% | 86 | 53 – 273 |

In summary, a three-compartment model, with inter-individual variability on CL, V2 and V3 and with proportional residual error, adequately described platinum concentrations in PUF collected in pediatric cancer patients. Inter-individual variability of PUF platinum clearance was significantly related to body weight and glomerular filtration rate, and that of V3 was significantly related to body weight. 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%.

## *D. Intrinsic Factors*

### D1. What covariates have significant effects on the PK of oxaliplatin in pediatric patients?

The effect of various covariates on the PK of oxaliplatin were evaluated as part of the population PK analysis conducted on data across all 4 studies. The details of the analysis are described in the previous section. Briefly, significant effects were found for GFR and body weight on clearance and for body weight on volume (V3).

Scatter plots of clearance vs. GFR and vs. body weight are shown below. The scatter plot of clearance vs. age showed a high correlation (see figure 5a), however this was due to age-related differences in body size. The correlation between body size and age was very high (r=0.77), and after accounting for body size, age did not have a significant effect on clearance (figure 5b).

*Figure 4: Scatter plots of oxaliplatin clearance vs. covariates (GFR and body weight).*

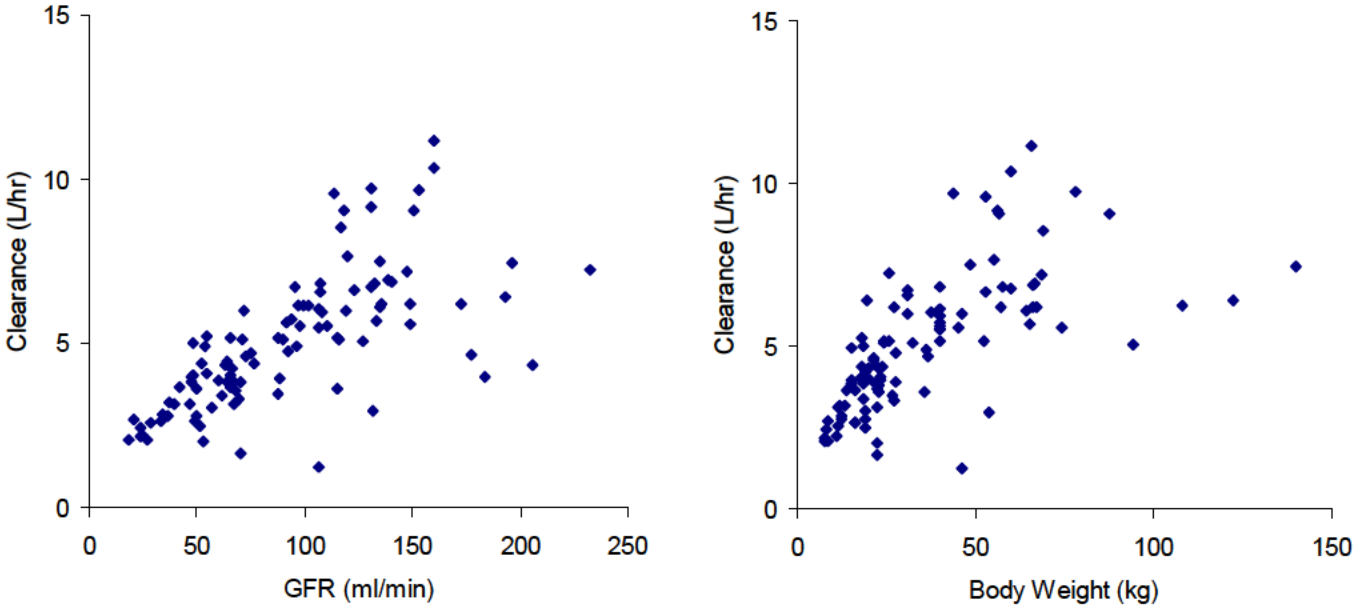



*Figure 5a: Scatter plot of oxaliplatin clearance vs. age.*

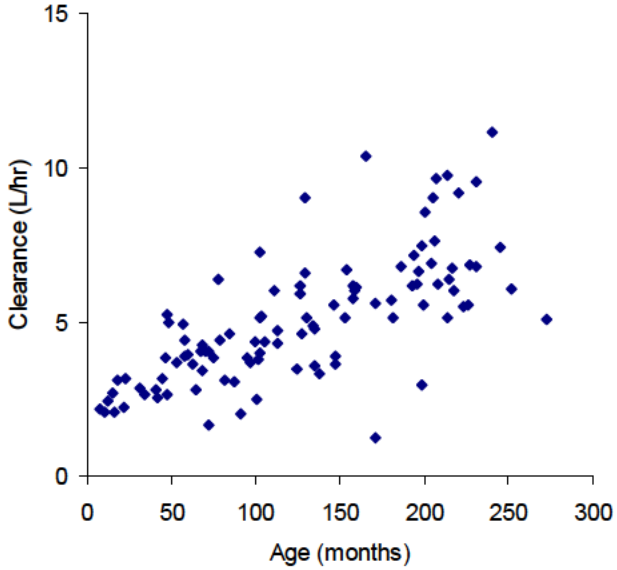
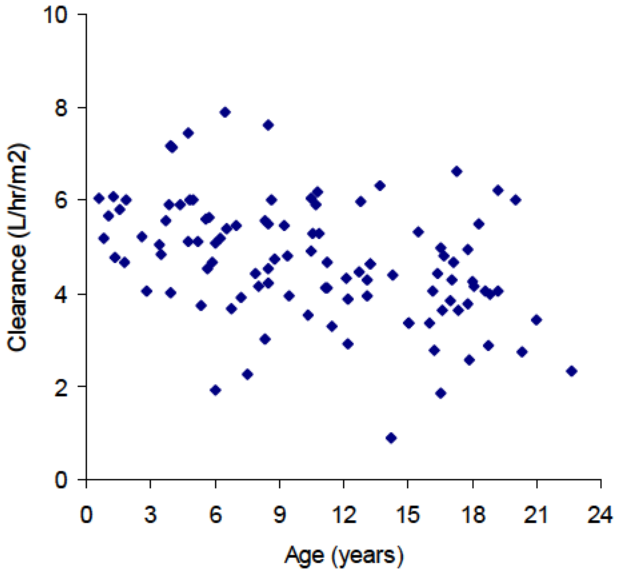


*Figure 5b: Scatter plot of oxaliplatin BSA-normalized clearance vs. age.*




**D2. Is there a difference between PK of oxaliplatin in pediatrics and adults?**

The applicant has compared the PK of oxaliplatin in the pediatric population with the PK parameters for oxaliplatin obtained from studies of oxaliplatin as a single agent in adult cancer patients. A summary table of PK parameters for oxaliplatin in adults and children is shown below.

*Table 9: Comparison of exposures (Cmax, AUC0-48 and AUCinf) obtained in pediatric and adult patients.*

| Matrix | Dose (mg/m2) | Pediatric | Adult |
|---|---|---|---|
| **Cmax(µg/mL)** | | | |
| Plasma | 40 | 1.02 ± 0.204 | 1.41 ± 0.930 |
| Plasma | 85 | 1.71 ± 0.432 | 2.12 ± 0.319 |
| Plasma | 130 | 3.39 ± 0.823 | 2.96 ± 0.570 |
| PUF | 130 | 1.10 ± 0.428 | 0.83 ± 0.36 |
| | | | |
| **AUC0-48(µg.h/mL)** | | | |
| Plasma | 85 | 32.4 ± 7.05 | 47.2 ± 5.10 |
| Plasma | 130 | 74.4 ± 10.1 | 71.5 ± 13.3 |
| PUF | 130 | 9.74 ± 2.52 | 8.12 ± 2.80 |
| | | | |
| **AUCinf (µg.h/mL)** | | | |
| Plasma | 85 | 128 ± 8.01 | 123 ± 49.0 |
| Plasma | 130 | 296 ± 55.7 | 278 ± 81.0 |
| PUF | 130 | 17.3 ± 5.34 | 12.9 ± 4.50 |

As the above table indicates, the exposures seen in pediatric and adult patients are comparable both in plasma and PUF, following comparable doses. This suggests that the PK parameters for

pediatric and adult patients are comparable. The population mean oxaliplatin clearance in pediatric patients is 5.1 L/hr or 4.7 L/hr/$m^2$ (%CV=41%) 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 predicted from adults.

## *E. Extrinsic Factors*

**E1. Is there a significant pharmacokinetic interaction with anticonvulsants administered concomitantly in these patients?**

Oxaliplatin is excreted renally, therefore it would not be expected to interact with anticonvulsants which may induce CYP3A4 enzymes. As part of study DFI7434, the sponsor did include a cohort of patients who received oxaliplatin while on oral carbamezapine. The following table shows the PK parameters obtained in that study. Comparison of data for dose level 3 (oxaliplatin 160 mg/m2) and Dose level 4 (oxaliplatin 160 mg/m2 + carbamezapine) indicates that the PK of oxaliplatin in the two groups are similar. This suggests that carbamezapine does not affect the PK of oxaliplatin.

*Table 10: Pharmacokinetics of oxaliplatin in study DFI7434. Patients in dose level 4 received oxaliplatin in combination with carbamezapine.*

| **Level** | **1** | **2** | **3** | **4** | **5** |
|---|---|---|---|---|---|
| **Dose** | **100 mg/$m^2$** | **130 mg/$m^2$** | **160 mg/$m^2$** | **160 mg/$m^2$ + CBZ** | **85 mg/$m^2$** |
| **Schedule** | **q 3 weeks** | | | | **q 2 weeks** |
| **Parameter** | **(N=3)** | **(N=6)** | **(N=2)** | **(N=6)** | **(N=9)** |
| **Cmax (ng/mL)** | 980 (486) | 1100 (428) | 1520 (1040) | 2120 (667) | 754 (244) |
| **AUC0-48 (ng.h/mL)** | 7520 (5070) | 9740 [b] (2520) | 12700 (1570) | 11400 (2130) | 7520 [c] (5070) |
| **AUC (ng.h/mL)** | 21800 [a] | 17300 [c] (5340) | N/A | 15700 [e] | 8830 [c] (1570) |
| **t1/2α (h)** | 0.208 (0.0620) | 0.152 (0.0120) | 0.157 | 0.166 (0.028) | 0.180 [f] (0.0210) |
| **t1/2β (h)** | 15.3 (4.07) | 18.9 (9.72) | 16.0 | 13.4 (2.04) | 16.3 [f] (5.41) |
| **t1/2γ (h)** | 402 (322) | 372 (344) | 641 | 371 (285) | 451 [f] (323) |
| **Vss (L)** | 221 [a] | 505 [c] (209) | N/A | 719 [e] | 414 [c] (123) |
| **Cl (L/h)** | 1.85 [a] | 5.35 (1.89) | N/A | 8.53 [e] | 5.71 [c] (1.68) |

a: N=1, b: N=4, c: N=3, d: N=7, e: N=2, f: N=6. N/A: Not available. Cmax, AUC0-48, AUC, Vss and CL values determined by non-compartmental analysis. t1/2α, t1/2β, and t1/2γ were determined by compartmental analysis.

**E2. Based on the above (intrinsic and extrinsic factors), are there any recommendations for dosing adjustments for this population?**

As there is no indication for the use of oxaliplatin in the pediatric solid tumor population, there are no recommendations for dosing adjustments.

## *F. Analytical Section*

**F1. How are the active moieties identified and measured in the plasma in the clinical pharmacology studies?**

Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient Pt-containing reactive species are formed, including monoaquo and diaquo DACH platinum. The analytical method measures total platinum in plasma and in plasma ultrafiltrate (PUF) in the samples collected in all four studies.

**F2. Which metabolites have been selected for analysis and why?**

No metabolites were measured. Only total platinum in plasma and PUF was measured.

**F3. For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?**

Total platinum levels as well as levels in PUF (free platinum levels) were measured in the studies. It is appropriate to measure levels of platinum in PUF since it is this fraction that distributes into tissues and is excreted.

**F4. What is the bioanalytical method that is used to assess concentrations of oxaliplatin and its metabolites?**

The method used to measure platinum levels in plasma and in PUF was Inductively Coupled Plasma Mass Spectrometry (ICPMS).

**F5. What are the figures of merit and performance characteristics for the methods used to assess concentrations of oxaliplatin?**

The analytical method is the same one that was used in studies submitted as part of a previous supplement (in 2002). Please see earlier review by Dr. Booth (NDA 21492 dated Aug 2002) for details of the analytical method validation. The assay was found to be adequately validated. The

assay had a linear range from 1 to 1000 ng/ml. The LLOQ was 1 ng/ml. QC samples included during sample runs were within acceptable limits – all runs with control values outside the acceptable range were repeated.

# III. DETAILED LABELING RECOMMENDATIONS

The applicant has included information regarding the pediatric studies with oxaliplatin under the Precautions section of the label.

Recommended changes to applicant's proposed label are indicated below.

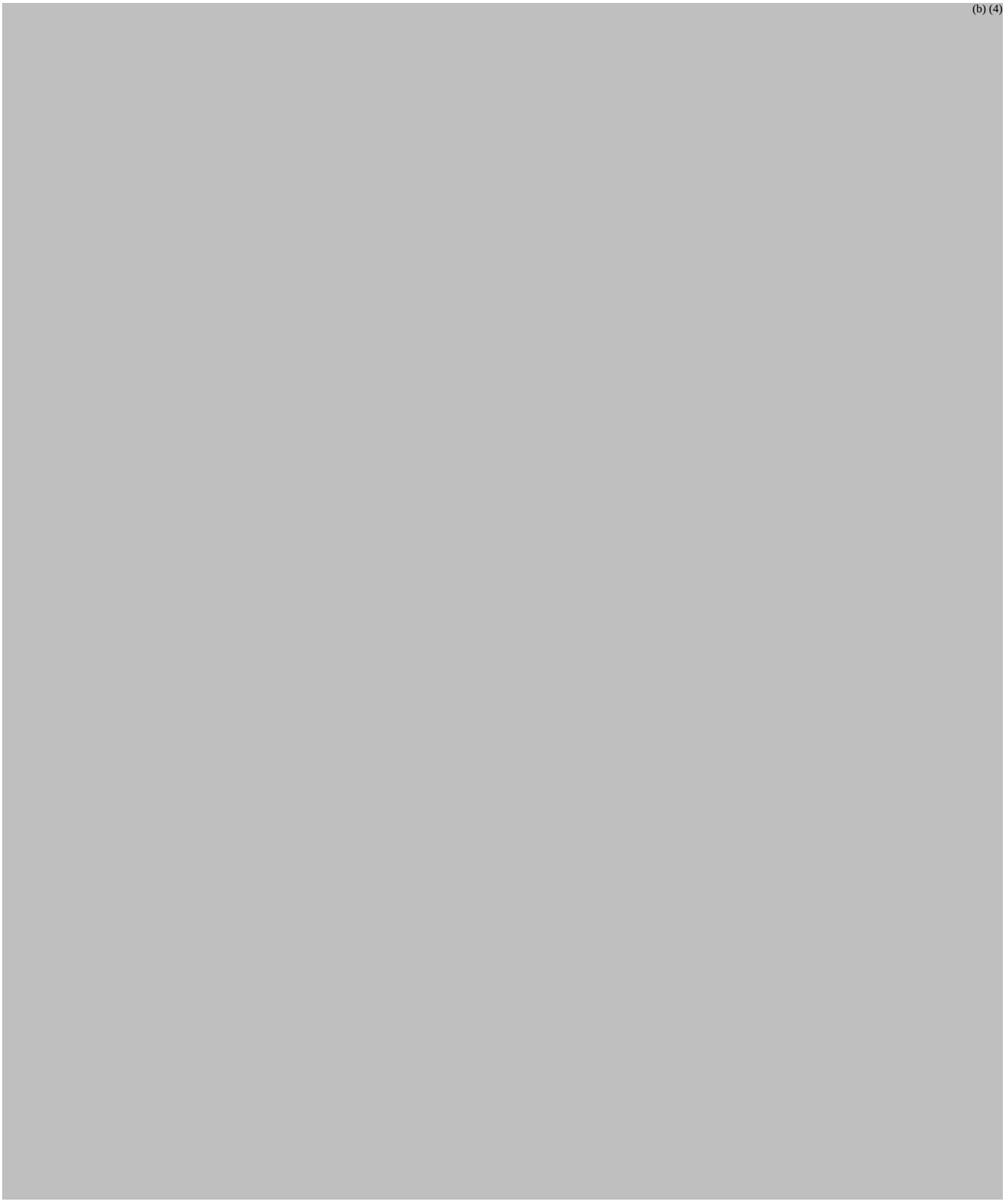
**Applicant's Labeling:**

**Agency's Proposed Labeling:**

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in [redacted] 105 pediatric patients during the first cycle. The [redacted] clearance in pediatric patients estimated by the population pharmacokinetic analysis was [redacted] 4.7 L/h/m$^2$. The inter-patient variability of platinum clearance in pediatric cancer patients was [redacted] 41%. Mean platinum pharmacokinetic parameters in ultrafiltrate were $C_{max}$ of [redacted] 0.75 ± 0.24 [redacted] mL, $AUC_{0-48}$ of [redacted] 7.52 ± 5.07 [redacted] .h/mL and $AUC_{inf}$ of [redacted] 8.83 + 1.57 [redacted] .h/mL at 85 mg/m² of oxaliplatin and $C_{max}$ of [redacted] 1.10 ± [redacted] /mL, $AUC_{0-48}$ of [redacted] 9.74 ± 2.52 [redacted] .h/mL and $AUC_{inf}$ of [redacted] 17.30 + 5.34 [redacted] .h/mL at 130 mg/m² of oxaliplatin. [redacted]

# IV. APPLICANT'S PROPOSED LABEL

(b) (4)



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# V. APPENDICES

## *A. INDIVIDUAL STUDY SYNOPSES*

**Study Number: ARD5531**

**Title:** Phase 1-2 study of weekly oxaliplatin in childhood refractory or relapsed malignant solid tumors

**Objectives:**
Primary
- To establish the maximum tolerated dose (MTD) of single agent weekly oxaliplatin, and thus, a recommended dose (RD) for Phase 2 study.

Secondary:
- To define dose limiting toxicities (DLTs);
- To define the safety profile;
- To examine pharmacokinetic parameters;
- To evaluate efficacy.

**Methodology:**
Multi-center, Phase 1/2 study, open-label, non-comparative, non-randomized study with direct individual benefit.

**Diagnosis and criteria for inclusion:**
• patients must have had histologically or cytologically confirmed malignant solid tumors. Histologically documented diagnosis of solid tumor was not required for brain stem tumors;
• tumors refractory to first line or relapsing after conventional chemotherapy, ie, patients who had been treated previously by at least 2 lines of chemotherapy and/or for whom no effective treatment was available;
• age: 6 months to 21 years;
• life expectancy: more than 6 weeks;
• no concomitant anti-cancer or investigational drug;
• Eastern Cooperative Oncology Group (ECOG) Performance status ≤2 (or Lansky scale if patient less than 12 years of age (per Protocol Amendment 1);
• at least 4 weeks must have elapsed since the last anti-cancer therapy (6 weeks since nitrosourea therapy);
• patients must have had no clinical evidence of peripheral neuropathy sensory or motor (< Grade 2 National Cancer Institute – Common Toxicity Criteria [NCI-CTC]);
• adequate bone marrow reserve:
  − platelets ≥75 x 109/L or ≥50 x 109/L in case of bone marrow involvement;
  − hemoglobin ≥8g/dL;
  − absolute neutrophil count >1.0 x 109/L.

• liver function:
  − aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN);
  − bilirubin ≤1.5 x ULN.
• renal function:
  − creatinine <3 x ULN for age (0-1 year old: <40 µmol/L; 1-15 years old <65 µmol/L; 15-21 years old <110 µmol/L).
• no other serious concomitant illness;
• no organ toxicity including ototoxicity ≥ Grade 2 NCI-CTC version 2;
• written informed consent (if patient was <18 years old, of parent/guardian and if possible child).

**Investigational product:** Oxaliplatin
Phase 1 dose: Oxaliplatin was administered over 2 hours on Days (D) 1, 8, and 15 of each cycle, with a dose escalation of 20% per level (6 levels). Each cycle was repeated every 4 weeks. Patients could only be registered at a new dose level if toxicity during the first cycle had been evaluated in all patients treated at the dose level below.
• Level 1: 40 mg/m²;
• Level 2: 50 mg/m²;
• Level 3: 60 mg/m²;
• Level 4: 75 mg/m²;
• Level 5: 90 mg/m²;
• Level 6: 110 mg/m².

Children younger than 1 year old were treated at the dose level currently investigated when they were registered. The dose was calculated in mg/kg.
• Level 1: 1.3 mg/kg;
• Level 2: 1.7 mg/kg;
• Level 3: 2 mg/kg;
• Level 4: 2.5 mg/kg;
• Level 5: 3 mg/kg;
• Level 6: 3.7 mg/kg.

RD: 90 mg/m2

**Duration of treatment:** Patient continued study treatment until disease progression, unacceptable toxicity, patient refusal, or treatment delay >3 weeks. In the absence of documented disease progression and in the absence of unacceptable toxicity after the first cycle, the treatment was continued as 1 cycle every 28 days for a maximum of 6 cycles. Treatment continuation beyond 6 cycles was discussed with the trial coordinator and the Sponsor.

**Criteria for evaluation:**
Safety:
• DLT at the first cycle;
The following toxicities were considered as a DLT if it was likely they were related to oxaliplatin (per Protocol Amendment 1):

− 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.

• tolerance profiles;
• adverse events (AEs) by NCI-Common Toxicity Criteria (Version 2.0);
• hematology and clinical chemistry.

**Efficacy:** Objective response rate, progression-free survival (PFS), response duration.
**Pharmacokinetics:**
Platinum: *Plasma and plasma ultrafiltrate (PUF)*: The following pharmacokinetic parameters were calculated for the first cycle only with non-compartmental analysis: maximum plasma concentration observed (Cmax), area under the plasma concentration versus time curve from time 0 to the real time 48h (AUC0-48), area under the plasma concentration versus time curve extrapolated to infinity (AUC), distribution volume at the steady-state (Vss) and plasma clearance (Cl). In addition, the following parameters were calculated using compartmental analysis: alpha half-life (t1/2α), beta half-life (t1/2β), and gamma half-life (t1/2γ).

**Pharmacokinetic sampling times and bioanalytical methods:**
Sampling:
Week 1 (first cycle D1 to 3): pre-infusion, end-infusion, 30 min, 1, 2, 4, 6, 24, 48 h post-infusion
Week 2 (first cycle D8): pre-infusion and end-infusion.
Week 3 (first cycle D15): pre-infusion and end-infusion.
Week 4 (first cycle no drug, D22): 1 week post last infusion.
Week 5 (start second cycle, D29/D1): pre-infusion.

Assays: Platinum concentrations in plasma and in PUF were determined using a validated Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method with a limit of quantification (LOQ) of 3 and 1 ng/mL, respectively.

**Statistical methods:**
Safety: Exposure to oxaliplatin was summarized by number of cycles administered. Total numbers 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 3,4. Specific neurological events were summarized separately. Dose limiting toxicities were also summarized. 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. Clinical laboratory results were summarized.

Efficacy: Efficacy was not a primary objective of this study. Best overall response to treatment was summarized for all patients enrolled. Ninety-five% confidence limits were calculated.

Pharmacokinetics: Plasma PK parameters were listed by patient and summarized using descriptive statistics by level.

**Summary of Results:**

Patient characteristics:

| | | RD cohort |
|---|---|---|
| | **Phase 1** | **90 mg/m2** |
| No. included | 29 | 16 |
| No. treated | 28 | 15 |
| No. in safety population | 28 | 15 |

Subject Demographics:

| **ITT Population** | **Phase 1** | **RD cohort 90 mg/m2** |
|---|---|---|
| Sex: Male | 17 (58.6) | 7 (43.8) |
| Female | 12 (41.4) | 9 (56.3) |
| Median age (years) | 9 | 7 |
| **ECOG** | | |
| 0 | 23 (79.3) | 10 (62.5) |
| 1 | 2 (6.9) | 4 (25.0) |
| 2 | 3 (10.3) | 1 (6.3) |
| 3 | 1 (3.4) | 0 (0.0) |
| **Type of cancer** | | |
| Neuroblastoma | 11 (37.9) | 7 (43.8) |
| Osteosarcoma | 6 (20.7) | 2 (12.5) |
| Ewing Sarcoma | 2 (6.9) | 2 (12.5) |
| Nephroblastoma | 2 (6.9) | 1 (6.3) |
| Rhabdomyosarcoma | 2 (6.9) | 0 (0.0) |
| Medulloblastoma | 1 (3.4) | 1 (6.3) |
| Hepatoblastoma | 0 (0.0) | 2 (12.5) |
| Germ cells cancer | 2 (6.9) | 1 (6.3) |
| Other Brain tumor | 2 (6.9) | 0 (0.0) |
| Other malignant tumor | 1 (3.4) | 0 (0.0) |
| **Current disease status** | | |
| Refractory | 3 (10.3) | 3 (18.8) |
| Relapse | 26 (89.7) | 13 (81.3) |

Treatment Administration

| **Treated Population** | **Phase 1** | **RD cohort 90 mg/m2** |
|---|---|---|
| **Number of cycles administered** | | |
| 40 mg/m2 | 7 | NA |
| 50 mg/m2 | 13 | NA |
| 60 mg/m2 | 16 | NA |
| 75 mg/m2 | 6 | NA |
| 90 mg/m2 | 10 | 28 |
| 110 mg/m2 | 7 | NA |
| **Total** | **59** | **28** |
| Median (range) | 2 (1 – 6) | 2 (1 – 4) |

Safety Results:
Dose limiting toxicities seen at at the highest dose tested, 110 mg/m2, were dysaesthesia and paresthesia. The maximum tolerated dose was determined to be 90 mg/m2.

(b) (4)

Pharmacokinetic Results:

Summary of platinum in plasma pharmacokinetic parameters after the first infusion (first cycle):

| Level | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **Dose** | **40 mg/m2** | **50 mg/m2** | **60 mg/m2** | **75 mg/m2** | **90 mg/m2** | **110 mg/m2** |
| **Parameter** | **(N=3)** | **(N=6)** | **(N=6)** | **(N=3)** | **(N=20)** | **(N=3)** |
| **Cmax (ng/mL)** | 1020 (204) | 1210 (209) | 1480 (433) | 1650 (171) | 2070 (495) | 2770 (362) |
| **AUC0-48 (ng.h/mL)** | 22000 (1580) | 25800 (2910) | 30800 (5530) | 34800 (4830) | 44500 (11100) | 60100 (5380) |
| **AUC (ng.h/mL)** | 69400 [a] | 76500 [b] (6980) | 92900 [c] (10400) | 94000 [a] | 121000 [d] (29900) | 207000 [e] |
| **t1/2α (h)** | 0.279 (0.111) | 0.259 [f] (0.118) | 0.281 (0.164) | 0.393 (0.223) | 0.386 [g] (0.376) | 0.259 [a] |
| **t1/2β (h)** | 8.07 (2.03) | 11.8 [f] (1.28) | 12.0 (5.30) | 15.1 (4.59) | 12.1 [g] (7.55) | 8.10 [a] |
| **t1/2γ (h)** | 121 (12.2) | 124 [f] (19.8) | 223 (227) | 166 (47.4) | 152 [g] (66.4) | 129 [a] |

a: N=2, b: N=4, c: N=3, d: N=8, e: N=1, f: N=5, g: N=18
Cmax, AUC0-48, AUC were determined by non-compartmental analysis. AUC values excluded if extrapolated portion of AUC > 30%. t1/2α, t1/2β, and t1/2γ were determined by compartmental analysis.

Summary of platinum in PUF pharmacokinetic parameters after the first infusion (first cycle):

| Level | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **Dose** | **40 mg/m2** | **50 mg/m2** | **60 mg/m2** | **75 mg/m2** | **90 mg/m2** | **110 mg/m2** |
| **Parameter** | **(N=3)** | **(N=6)** | **(N=4)** | **(N=3)** | **(N=17)** | **(N=3)** |
| **Cmax (ng/mL)** | 344 (82.2) | 481 (143) | 489 (171) | 669 (400) | 696 (287) | 926 (45.8) |
| **AUC0-48 (ng.h/mL)** | 1830 (262) | 3020 (764) | 2990 (624) | 3120 (1340) | 4880 (1240) | 6370 (1090) |
| **AUC (ng.h/mL)** | 2240 [a] | 4350 [b] (947) | 4100 (910) | 4790 [a] | 6670 [c] (1790) | 7910 [a] |
| **t1/2α (h)** | 0.161 (0.038) | 0.168 [d] (0.101) | 0.193 e (0.080) | 0.378 [a] | 0.248 [f] (0.226) | 0.133 [a] |
| **t1/2β (h)** | 10.6 (2.10) | 9.61 [d] (2.63) | 13.4 e (2.66) | 10.3 [a] | 10.8 [f] (4.89) | 13.4 [a] |
| **t1/2γ (h)** | 337 (318) | 281 [a] (319) | 224 e (98.7) | 390 [a] | 282 [f] (281) | 390 [a] |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Vss (L)** | 321 [a] | 280 [b] (82.9) | 303 (92.4) | 349 [a] | 362 [c] (206) | 273 [a] |
| **Cl (L/h)** | 8.14 [a] | 7.02 [b] (1.58) | 7.09 (1.38) | 8.04 [a] | 8.65 [c] (5.06) | 6.66 [a] |

a: N=2, b: N=5, c: N=16, d: N=5, e: N=3, f: N=13
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.

**Conclusions:**

- The DLTs were sepsis at 50 mg/m2, dysesthesia at 90 mg/m2 and dysesthesia and paresthesia at 110 mg/m2. The MTD in the Phase 1 portion of this study was 90 mg/m2, which was the RD.
- A total of 25 patients (17 Phase 1 and 8 RD cohort) experienced SAEs; 11 patients (5 Phase 1 and 6 RD cohort) withdrew from the study due to AEs.
- There were 23 deaths during Phase 1 and 11 deaths in the RD cohort. Five deaths (2 Phase 1 and 3 RD cohort) were within 28 days of last dose. All deaths were due to disease progression.
- All doses were tolerable; there was mild hematologic toxicity and neurological toxicity.
- For a 2.75-fold increase in oxaliplatin dose, mean Cmax, AUC0-48 and AUC of platinum in plasma increased by approximately 2.71-, 2.73- and 2.98-fold, respectively, while the values for platinum in PUF increased by approximately 2.69-, 3.48- and 3.53-fold, respectively.
- In conclusion, this Phase 1/2 study of single agent oxaliplatin at escalating dose levels administered on Day 1, Day 8, and Day 15 every 4 weeks in childhood refractory or relapsed solid tumors determined that the RD of oxaliplatin was 90 mg/m2.

**Study Number: DFI7434**

**Title of the study:** A Phase 1 study of oxaliplatin in children with solid tumors.

**Objectives:**
Primary

- to determine the maximum tolerated dosage (MTD) of the intravenous 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;
- 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.

Secondary:

- to determine the dose-limiting toxicities (DLT) of oxaliplatin when administered intravenously, including qualitative and quantitative toxicities, and to define their duration and reversibility;
- to characterize the pharmacokinetics (PK) of oxaliplatin in children with drug resistant malignant solid tumors;
- to evaluate the relationship between pharmacokinetic parameters, toxicity, and/or response;
- to note any anti-tumor effects, as measured by standard response criteria;
- to 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.

**Methodology:** Open label dose ranging study

**Diagnosis and criteria for inclusion:**
• patients 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. Histologically documented diagnosis of solid tumor was not required for brain stem tumors;
• patients must have been under 21 years of age at the time treatment began. Patients under the age of two years are rarely available for admission to primary disease treatment protocols and, therefore, may be rarely available for Phase I studies;
• at least 3 weeks must have elapsed since the last chemotherapy (6 weeks since nitrosourea therapy). No hematopoietic growth factors could have been administered for at least one week before protocol entry:
− information on prior platinum administration was recorded (agent, dosage, schedule, total cumulative dosage);
− the initial cohorts of patients may include patients with prior extensive radiation therapy (XRT) who met the criteria given below. If hematopoietic dose-limiting toxicity was observed in the

initial cohorts of patients, then escalation could have been attempted from this dose level in less heavily pre-treated patients (excluding patients with extensive prior XRT);
− six weeks must have elapsed since XRT to any significant marrow containing compartment;
− six months must have elapsed since craniospinal radiation (>24 Gray [Gy]), total abdominal, pelvic, lung XRT, mantle, Y ports, or total body irradiation (TBI);
− the initial cohorts of patients could have included patients with prior stem cell transplant who otherwise met the eligibility criteria. If hematopoietic dose-limiting toxicity was observed in the initial cohorts of patients, then escalation could have been attempted from this dose level in less heavily-pretreated patients (excluding patients with prior stem cell transplant);
− patients with prior stem cell transplant must have had recovery of all organ systems, with a minimum of 3 months since transplant. A minimum of 6 months was required after TBI preparative regimens. There must have been no active graft-versus-host disease (GVHD), and patients should not have been receiving therapy for GVHD.
• Eastern Cooperative Oncology Group (ECOG) performance status =2 (Lansky Play-Performance Scale 50%);
• normal electrolytes, calcium, phosphorus, and blood sugar;
• patients must have had adequate organ and marrow function;
• patients must have had no evidence of neuropathy;
• patients with pre-existing Grade 1 or 2 neuropathy for whom this therapeutic option appeared appropriate despite possible increased risk could have been treated but were to be evaluated in a separate stratum, and their results should not have been used for dose or response determination in this study. Results in these patients were to be reported separately;
• the effects of oxaliplatin on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because DNA alkylating agents are known to be teratogenic, women of child-bearing potential and men must have agreed to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she was pregnant while participating in this study, she should have informed her treating physician immediately;
• because the risk of toxicity in nursing infants secondary to oxaliplatin treatment of the mother was unknown but may be harmful, breastfeeding should have been discontinued if the mother was treated with oxaliplatin;
• for patients receiving DEMRI, patient must have had a bone tumor, soft tissue tumor of an extremity, or other tumor accessible to biopsy;
• signed informed consent must have been obtained according to institutional guidelines.

**Investigational product:** Oxaliplatin 50 mg and 100 mg for injection

| Dose Level | Oxaliplatin (mg/m2)a | Schedule | Carbamazepine Use |
|---|---|---|---|
| Level 1 | 100 | q 3 weeks | None |
| Level 2 | 130 | q 3 weeks | None |
| Level 3 | 160 | q 3 weeks | None |
| Level 4 | 160 | q 3weeks | Carbamazepine |
| Level 5 | 85 | q 2weeks | None |

**Duration of treatment:** Patients were treated until disease progression, intercurrent illness, unacceptable toxicity, patient refusal, or Investigator judgment. Treatment was administered for a maximum of 6 cycles. Additional courses could be considered if the patient was doing well.

**Duration of observation:** Radiologic measurements were performed every 4 to 6 weeks. Tumor measurements were repeated every 6 weeks. Radiologic documentation had to be provided for patients to be removed from the study due to progressive disease.

**Criteria for evaluation:**
Safety: Adverse events (AE) by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (version 2.0), clinical chemistry, hematology

Efficacy: Objective response rate

Pharmacokinetics: Platinum: *Plasma and plasma ultrafiltrate (PUF)*: the following pharmacokinetic parameters were calculated with non-compartmental analysis: maximum plasma concentration (Cmax,), area under the plasma concentration versus time curve from time 0 to the real time 48h (AUC0-48), area under the plasma concentration versus time curve extrapolated to infinity (AUC), distribution volume at the steady-state (Vss) and plasma clearance (Cl). In addition, the following parameters were calculated using compartmental analysis: alpha half life (t1/2α), beta half-life (t1/2β) and gamma half-life (t1/2γ).
*Carbamazepine (level 4 only)*: plasma trough concentrations.

Pharmacokinetic sampling times and bioanalytical methods:
Sampling: *Plasma and plasma ultrafiltrate (PUF)*: Prior to the first infusion, end of 2 hour-infusion and 30 min, 1, 2, 4, 6, 24, 48, 336 and 504 hours post-infusion. The 504-hour sample was taken prior the start of the second infusion.
*Carbamazepine (level 4 only):* prior to the last dose of carbamazepine during each course.
Assays: Platinum concentrations in plasma and in PUF were determined using a validated Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method with a limit of quantification (LOQ) of 100 and 1 ng/mL, respectively. Plasma concentrations of carbamazepine were determined using a fluorescence polarization imunoassay (FPIA).

**Statistical methods:**
Safety: 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. Adverse events were summarized by all grades and Grade 3,4. Specific neurological events were summarized separately according to an oxaliplatin-specific scale. Dose limiting toxicities were also summarized. 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. Clinical laboratory results were summarized.
Efficacy: Efficacy was not a primary objective of this study. Best overall response to treatment was summarized for all patients enrolled.
Pharmacokinetics: *Plasma and PUF*: Plasma PK parameters were listed by patient and summarized using descriptive statistics by level.

**Summary of Results:**

Patient characteristics:

| | Total |
|---|---|
| No. included | 26 |
| No. treated | 26 |
| No. in safety population | 26 |

Demographics and Baseline characteristics:

| Treated Population [n (%)] | Total N=26 |
|---|---|
| Sex: Male | 17 (65.4) |
| Female | 9 (34.6) |
| Median age (years) | 10 |
| **ECOG** | |
| 0 | 19 (73.1) |
| 1 | 4 (15.4) |
| 2 | 3 (11.5) |
| **Type of cancer** | |
| Neuroblastoma/ganlioneuroblastoma | 7 (26.9) |
| Medulloblastoma | 5 (19.2) |
| Hepatocellular carcinoma | 3 (11.5) |
| Mucinous adenocarcinoma of colon | 2 (7.7) |
| Other tumor types | 9 (34.6) |
| **Previous radiation** | |
| Yes | 15 (57.7) |
| No | 11 (42.3) |

Treatment Administration:

| Treated Population | Total |
|---|---|
| **Number of doses administered** | |
| 100 mg/m$^2$ every 3 weeks | 11 |
| 130 mg/m$^2$ every 3 weeks | 13 |
| 160 mg/m$^2$ every 3 weeks | 10 |
| 160 mg/m$^2$ + carbamazepine | 12 |
| 85 mg/m$^2$ every 2 weeks | 41 |
| **Total** | **87** |
| Median (range) | 2 (1 – 9) |

Safety Results:
The DLT was sensory neuropathy at 160 mg/m2 of single agent oxaliplatin. The MTD and recommended dose (RD) were 130 mg/m2 every 3 weeks.

Efficacy results: There were no responders in this study. (b) (4)

Pharmacokinetic results:

Mean (SD) platinum in plasma pharmacokinetic parameters after the first infusion:

| Level | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Dose | 100 mg/m$^2$ | 130 mg/m$^2$ | 160 mg/m$^2$ | 160 mg/m$^2$ + CBZ | 85 mg/m$^2$ |
| Schedule | q 3 weeks | | | | q 2 weeks |
| Parameter | (N=3) | (N=6) | (N=2) | (N=6) | (N=9) |
| $C_{max}$ (ng/mL) | 2800 (824) | 3390 (823) | 4500 | 5080 (994) | 1710 (432) |
| $AUC_{0-48}$ (ng.h/mL) | 59700 (17800) | 74400 (10100) | 102000 | 101000 (7690) | 32400 (7050) |
| AUC (ng.h/mL) | 254000 (60288) | 296000 (55700) | 469000 | 430000 (102000) | 128000 [a] (8010) |
| $t_{1/2\alpha}$ (h) | 0.274 (0.187) | 0.295 (0.122) | 0.173 | 0.359 (0.447) | 0.361 [b] (0.191) |
| $t_{1/2\beta}$ (h) | 17.9 (6.49) | 22.4 (18.7) | 13.9 | 21.4 (15.6) | 17.7 [b] (7.68) |
| $t_{1/2\gamma}$ (h) | 242 (52.3) | 218.3 (64.2) | 197 | 331 (272) | 377 [b] (253) |

[a]: N=4, [b]: N=7.

$C_{max}$, $AUC_{0-48}$, AUC were determined by non-compartmental analysis. $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined by compartmental analysis.

Mean (SD) platinum in plasma ultrafiltrate (PUF) pharmacokinetic parameters after the first infusion:

| Level | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Dose | 100 mg/m$^2$ | 130 mg/m$^2$ | 160 mg/m$^2$ | 160 mg/m$^2$ + CBZ | 85 mg/m$^2$ |
| Schedule | q 3 weeks | | | | q 2 weeks |
| Parameter | (N=3) | (N=6) | (N=2) | (N=6) | (N=9) |
| $C_{max}$ (ng/mL) | 980 (486) | 1100 (428) | 1520 (1040) | 2120 (667) | 754 (244) |
| $AUC_{0-48}$ (ng.h/mL) | 7520 (5070) | 9740[b] (2520) | 12700 (1570) | 11400 (2130) | 7520[c] (5070) |
| AUC (ng.h/mL) | 21800[a] | 17300[c] (5340) | N/A | 15700[e] | 8830[c] (1570) |
| $t_{1/2\alpha}$ (h) | 0.208 (0.0620) | 0.152 (0.0120) | 0.157 | 0.166 (0.028) | 0.180[f] (0.0210) |
| $t_{1/2\beta}$ (h) | 15.3 (4.07) | 18.9 (9.72) | 16.0 | 13.4 (2.04) | 16.3 [f] (5.41) |
| $t_{1/2\gamma}$ (h) | 402 (322) | 372 (344) | 641 | 371 (285) | 451[f] (323) |
| $V_{ss}$ (L) | 221[a] | 505[c] (209) | N/A | 719[e] | 414[c] (123) |
| Cl (L/h) | 1.85[a] | 5.35 (1.89) | N/A | 8.53[e] | 5.71[c] (1.68) |

[a]: N=1, [b]: N=4, [c]: N=3, [d]: N=7, [e]: N=2, [f]: N=6.

N/A: Not available. $C_{max}$, $AUC_{0-48}$, AUC, $V_{ss}$ and CL values were determined by non-compartmental analysis. $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined by compartmental analysis.

**Conclusions:**

• The DLT was sensory neuropathy at 160 mg/m2 of single agent oxaliplatin. The MTD and RD were 130 mg/m2 every 3 weeks; a dose of 85 mg/m2 every 2 weeks was also found to be tolerable.

• Six patients (23.1%) experienced SAEs; 1 patient in the q 2 week group and 5 in the q 3 weeks group. No patients withdrew from the study due to AEs. There were 22 deaths during the study but none within 28 days of last dose.

• All doses were tolerable; there was mild hematologic toxicity.

• For a 1.60-fold increase in oxaliplatin dose, mean Cmax, AUC0-48 and AUC of platinum in plasma increased by approximately 1.61-, 1.71- and 1.85-fold, respectively, while the values for platinum in PUF mean Cmax and AUC0-48 increased by approximately 1.55- and 1.69-fold, respectively.

• The pharmacokinetics of oxaliplatin following administration with carbamazepine appeared to be similar to that following oxaliplatin administration alone.

• In conclusion, this study confirmed a good safety profile of oxaliplatin monotherapy given on a weekly schedule to pediatric patients, which seems to be similar to that which was reported in pretreated adult patients with the same characteristics in terms of prior anticancer therapies, with some of them heavily pretreated with platinum compounds and/or autologous bone marrow transplant.

Study Number: ARD5021

**Title of the study:**
A Phase II Study of Oxaliplatin in Children with Recurrent or Refractory Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumors and Atypical Teratoid Rhabdoid Tumors

**Objectives:**
Primary**:**
The objectives of the study were as follows:
• To estimate the objective response rate (complete response [CR] plus partial response [PR]) to oxaliplatin in patients with recurrent or refractory medulloblastoma at first progression.
• To estimate the objective response (CR plus PR) rate to oxaliplatin in patients with recurrent or refractory medulloblastoma at second or later relapse.
Secondary**:**
• To estimate the objective response rate to oxaliplatin in patients with recurrent or refractory supratentorial primative neuroectodermal tumors (PNET) or atypical teratoid rhabdoid tumors (ATRT).
• To test for functional mismatch repair (MMR) system in tumor samples and patients' peripheral white blood cells.
• To evaluate the pharmacokinetics of oxaliplatin in the serum and cerebrospinal fluid (CSF) using a limited sampling strategy.

**Methodology:**
This was an open-label, single-agent Phase 2 study of oxaliplatin in pediatric patients with recurrent or refractory embryonal central nervous system (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 ATRT.

**Diagnosis and criteria for inclusion:**
• Patients ≤21 years of age at the time of registration on the protocol. If there was a competing adult study within an institution, the age requirement could have been lowered to 18 years of age;
• Patients with histologically confirmed medulloblastoma, supratentorial PNET (including pineoblastoma, ependymoblastoma), or ATRT that was recurrent or refractory to therapy;
• Patients with measurable recurrent or refractory disease documented by radiographic or cytologic criteria. Patients with linear leptomeningeal disease or positive CSF cytology were also eligible;
• Karnofsky or Lansky performance status ≥50% assessed within 7 days prior to study entry;
• Patients with adequate bone marrow, renal, hepatic, cardiac, pulmonary, and CNS function.

**Investigational product:** Oxaliplatin 50 mg or 100 mg for injection.
Dose: 130 mg/m2 over 2 hours every 21 days; patients <10 kg received oxaliplatin 4.3 mg/kg.

**Duration of treatment:** One year in the absence of disease progression or unacceptable toxicity.

**Duration of observation:**
All included patients were followed for toxicity until 30 days after the last dose of oxaliplatin or until one of the off study criteria were met: patient determined ineligible, consent withdrawn, death, or confirmed objective response at completion of treatment.

**Reference therapy:** None

**Criteria for evaluation:**
Safety: Adverse events (AEs) by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (Version 2.0), clinical chemistry, hematology.

Efficacy: Response rate, progression free survival.

Pharmacokinetics: Platinum concentrations in plasma ultrafiltrate (PUF) during Course 1 were assessed. No CSF samples were obtained in this study.

Pharmacokinetic sampling times and Sampling:
Prior to the first infusion and at 30 min, 4 hours and 168 hours after the end of infusion during course 1.

Bioanalytical methods: Platinum concentrations in PUF were determined using a validated Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method with a limit of quantification (LOQ) of 1 ng/mL.

**Statistical methods:**
Safety: 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 3,4. Specific neurological events were summarized separately. Dose limiting toxicities were also summarized. 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.
Clinical laboratory results were summarized.

Efficacy: 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 was used to stop accrual to the study as soon as the data suggested that the drug did not warrant further investigation.
Objective response rate and progression free survival were summarized for all patients enrolled; 95% confidence limits were calculated.

Pharmacokinetics: Platinum pharmacokinetic parameters in PUF were listed by patient and summarized using descriptive statistics.

**Summary of Results:**

Patient Characteristics:

| | **Oxaliplatin 130 mg/m$^2$ N=43** |
|---|---|
| Included | 43 |
| Treated | 43 |
| Evaluable for safety | 43 |

Patient Demographics:

| **ITT Population (N=43)** | **Oxaliplatin 130 mg/m$^2$** |
|---|---|
| Sex: Male | 30 (69.8) |
| Female | 13 (30.2) |
| Median age (years) | 8 |
| Karnofsky PS **(n=23)** | |
| 60 | 1 (2.3) |
| 70 | 2 (4.7) |
| 80 | 5 (11.6) |
| 90 | 4 (9.3) |
| 100 | 11 (25.6) |
| Lansky PS **(n=20)** | |
| 70 | 3 (7.0) |
| 80 | 2 (4.7) |
| 90 | 9 (20.9) |
| 100 | 6 (14.0) |
| Type of cancer | |
| Medulloblastoma NOS | 24 (55.8) |
| Primitive neuroectodermal tumor | 10 (23.3) |
| Rhabdoid sarcoma | 5 (11.6) |
| Pineoblastoma | 2 (4.7) |
| Desmoplastic medulloblastoma | 1 (2.3) |
| Ependymoblastoma | 1 (2.3) |
| Current diagnosis | |
| Stratum IA | 15 (34.9) |
| Stratum IB | 3 (7.0) |
| Stratum IC | 12 (27.9) |
| Stratum II | 8 (18.6) |
| Stratum III | 5 (11.6) |

ITT = intent to treat; PS = performance status; NOS=not otherwise specified

Treatment Administration:

| Treated Population | Oxaliplatin 130 mg/m$^2$ |
|---|---|
| Number of cycles administered | 147 |
| Median (range) | 2 (1 – 17) |
| Median RDI (%) | 98.8 |

RDI=relative dose intensity

Safety Results:

NCI toxicities (all grades and grade 3 + 4) by patient (%)

| Adverse event | Oxaliplatin 130 mg/m$^2$ All Grades / Gr 3+4 N = 43 |
|---|---|
| Any adverse event | 100 / 70 |
| Leukopenia | 67 / 12 |
| Hemoglobin | 65 / 5 |
| Platelet count decreased | 65 / 26 |
| Vomiting NOS | 65 / 7 |
| Neutrophil count | 58 / 16 |
| Diarrhoea NOS | 40 / 5 |
| Peripheral sensory neuropathy [a] | 40 / 5 |
| Headache | 37 / 9 |
| Fatigue | 30 / 2 |
| Nausea | 28 / 0 |
| Anorexia | 26 / 2 |
| Anxiety | 21 / 0 |

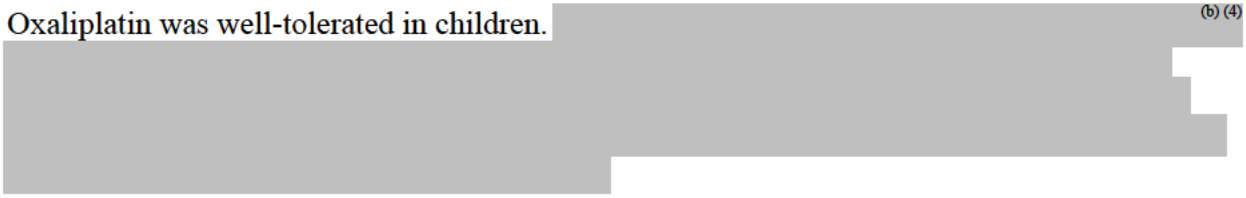
[a] oxaliplatin specific scale

On-study hematology results by patient (%)

| Laboratory Test | Oxaliplatin 130 mg/m$^2$ All Grades / Gr 3+4 N = 43 |
|---|---|
| Anemia | 93 / 7 |
| Granulocytopenia | 65 / 21 |
| Thrombocytopenia | 67 / 28 |


**Pharmacokinetic results:**
Following the first IV infusion of 130 mg/m2 of oxaliplatin over 2 hours, mean ± SD PUF platinum concentration observed at 2.5 hours post infusion was 327 ± 81.0 ng/mL. Mean ± SD of pharmacokinetic parameter estimates systemic clearance (CL), volume of distribution (V), and the elimination rate constant (K10) were 13.6 ± 6.8 L/hr, 348 ± 189 L and 0.040 ± 0.002 hr-1, respectively.

**Conclusions:**
Oxaliplatin was well-tolerated in children.



**Study Number: ARD5530**

**Title of the study:** A Phase 2 Study of Oxaliplatin in Children with Recurrent Solid Tumors

**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:
- − Ewing's sarcoma or peripheral primitive neuroectodermal tumors (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: Soft tissue sarcoma, hepatocellular carcinoma, childhood/adolescent colorectal carcinoma, renal cell carcinoma, adrenocortical carcinoma and nasopharyngeal carcinoma;

• 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);
• determine the time to progression and overall survival of children treated with oxaliplatin for recurrent solid tumors.

**Methodology:**
This was an NCI-sponsored open-label, single agent, Phase 2 study conducted by the COG 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.

Per the pediatric written request agreement with the FDA, this interim report presents the results on the following 4 strata: 1) Ewing's sarcoma or peripheral PNET, 2) Osteosarcoma, 3) Rhabdomyosarcoma, and 4) Neuroblastoma.

**Diagnosis and criteria for inclusion:**
• Patients must have been no greater than 21 years of age inclusive when originally diagnosed with the malignancy to be treated on this protocol;
• Patients with any of the following tumors:
- − Ewing's sarcoma or peripheral PNET;

- Osteosarcoma;
- Rhabdomyosarcoma;
- Neuroblastoma;
- High grade astrocytoma and multiforme glioblastoma;
- Low grade astrocytoma;
- Brain stem glioma (per Protocol Amendment 2);
- Ependymoma;
- Hepatoblastoma;
- Malignant germ cell tumors of any site;
- Other rare tumors of interest: Soft tissue sarcoma, hepatocellular carcinoma, childhood/adolescent colorectal carcinoma, renal cell carcinoma, adrenocortical carcinoma and nasopharyngeal carcinoma.

• Patients must have had histologic verification of the malignancy at original diagnosis (excluding brain stem tumors and visual pathway gliomas);
• Patients must have had measurable disease, documented by clinical, or radiographic (computed tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET]) means, and have relapsed or become refractory to conventional therapy;
• Karnofsky ≥50% for patients >10 years of age and Lansky ≥50 for patients ≤10 years of age. Patients who were unable to walk because of paralysis, but who were up in a wheelchair, were considered ambulatory for the purpose of assessing the performance score;
• Patients must have had a life expectancy of ≥8 weeks;
• Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study;
• Patients with adequate bone marrow, renal, hepatic, and central nervous system (CNS) function.

**Investigational product:** Oxaliplatin 50 mg and 100 mg
Dose: 130 mg/m2 over 2 hours every 21 days; patients ≤12 months of age received oxaliplatin 4.3 mg/kg
**Duration of treatment:** Up to 17 doses or up to 12 months

**Duration of observation:**
All included patients were followed for toxicity until 30 days after the last dose of oxaliplatin or until one of the off study criteria were met. Off study criteria included: death; lost to follow-up, entry into another COG therapeutic study, and withdrawal of consent.

**Reference therapy:** None

**Criteria for evaluation:**
Efficacy: Objective response rate

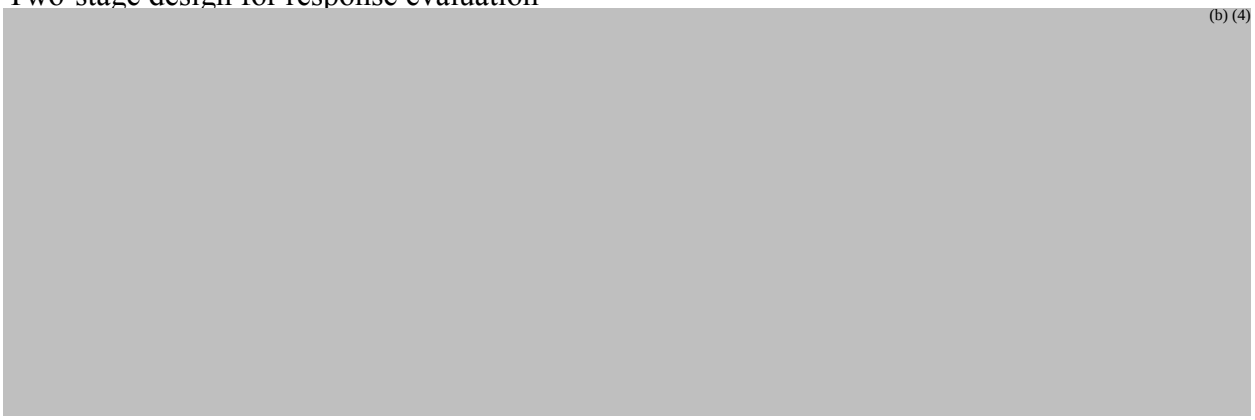
Safety: Adverse events (AE) by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (Version 3.0), clinical chemistry, hematology

Pharmacokinetics: Platinum concentrations in plasma ultrafiltrate (PUF) during Course 1

Pharmacokinetic sampling times and bioanalytical methods: Prior to the first infusion and at 2.5, 6 and ~ 170 hours (day 7) after the start of infusion during Course 1.
Platinum concentrations in PUF were determined using a validated Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method with a lower limit of quantification (LOQ) of 1 ng/mL.

**Statistical methods:**
Efficacy:
Within each stratum, 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.
Response rate was summarized for all patients enrolled; 95% confidence limits were calculated.

Two-stage design for response evaluation




Safety:
Exposure to oxaliplatin was summarized by number of cycles administered. Total numbers of cycles, median, minimum, and maximum were shown for each dose group and for the total population. Adverse events and serious adverse events (SAEs) were summarized by all grades and Grade 3/4. Specific neurological events were summarized separately. Dose limiting toxicities were also summarized. All deaths were listed and deaths within 28 days of the last dose of oxaliplatin were summarized. AEs leading to study medication discontinuation were summarized.

Pharmacokinetics:
Platinum pharmacokinetic parameters in PUF were listed by patient and summarized using descriptive statistics.

**Summary of Results:**

Patient disposition:

| | Total |
|---|---|
| No. included | 48 |
| No. treated | 47 |
| No. in safety population | 47 |

Patient Demographics:

| Enrolled Population [n (%)] | Total N=48 |
|---|---|
| Sex: Male | 35 (72.9) |
| Female | 13 (27.1) |
| Median age (years) | 14 |
| Karnofsky score (n=30) | |
| 50 | 1 (2.1) |
| 60 | 2 (4.2) |
| 70 | 4 (8.3) |
| 80 | 4 (8.3) |
| 90 | 11 (22.9) |
| 100 | 8 (16.7) |
| Lansky score (n=18) | |
| 50 | 1 (2.1) |
| 70 | 2 (4.2) |
| 80 | 1 (2.1) |
| 90 | 4 (8.3) |
| 100 | 10 (20.8) |
| Type of cancer | |
| Neuroblastoma | 13 (27.1) |
| Osteosarcoma | 13 (27.1) |
| Ewing's sarcoma or peripheral PNET | 12 (25.0) |
| Rhabdomyosarcoma | 10 (20.8) |

| Enrolled Population [n (%)] | Total N=48 |
|---|---|
| Previous treatment | |
| Chemotherapy | 47 (100) |
| Radiation | 19 (40.4) |
| Bone marrow transplant | 9 (19.1) |
| Surgery | 17 (36.2) |

PNET = peripheral primitive neuroectodermal tumors

Treatment Administration:

| Treated Population | Oxaliplatin 130 mg/m$^2$ |
|---|---|
| Number of cycles administered | 102 |
| Median (range) | 2 (1-12) |
| Median RDI (%) | 99.5 |

RDI=relative dose intensity


Pharmacokinetic Results:

Twenty patients participated in the PK assessment, however, PK data could be analyzed in 17 patients. The following table lists the PK parameters estimated for platinum in PUF:

| | $K_e$ $(h)^{-1}$ | V ($L/m^2$) | CL ($L/h/m^2$) |
|---|---|---|---|
| N | 17 | 17 | 17 |
| Mean | 0.041 | 210 | 5.02 |
| Median | 0.021 | 206 | 4.34 |
| Std Deviation | 0.083 | 92.7 | 2.65 |
| Range | 0.348 | 377 | 11.2 |
| Minimum | 0.016 | 35.6 | 1.80 |
| Maximum | 0.364 | 412 | 13.0 |

Safety Results:

Selected NCI toxicities (all grades and grade 3 + 4) - % of treated patients

| Adverse event | Oxaliplatin 130 mg/m$^2$ N = 47 | |
|---|---|---|
| | All Grades | Grade 3+4 |
| Any adverse event | 85 | 62 |
| Paresthesia/dysesthesia | 45 | 9 |
| Cold related dysesthesia | 40 | 4 |
| Hemoglobin decreased | 40 | 15 |
| Platelet count decreased | 40 | 26 |
| Vomiting | 32 | 0 |
| Laryngealpharyngeal dysesthesia | 30 | 11 |
| Nausea | 30 | 2 |
| Neutrophil count decreased | 21 | 6 |
| White blood cell count decreased | 21 | 2 |
| Hypersensitivity | 15 | 9 |
| Diarrhea | 11 | 0 |
| Peripheral sensory neuropathy[a] | 2 | 0 |

[a] oxaliplatin specific scale

**Conclusions:**

Oxaliplatin was well-tolerated in children. (b) (4) [redacted]

## *B. POPULATION PK ANALYSIS OUTPUT*

**NONMEM Code for Final model**

(b) (4)

[redacted]

12 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

## *C. PEDIATRIC WRITTEN REQUEST LETTER*

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-492

Sanofi-Synthelabo, Inc.
9 Great Valley Parkway
Malvern, PA 19355

Attention: Mark Moyer
Vice President, Drug Regulatory Affairs

Dear Mr. Moyer:

Reference is made to your Proposed Pediatric Study Request submitted on July 29, 2004, for ELOXATIN™ (oxaliplatin) Injection to IND (b) (4).

To obtain needed pediatric information on oxaliplatin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below. These studies investigate the potential use of oxaliplatin in the treatment of children with cancer.

**Background:**

The development of pediatric oncology drugs presents certain difficulties but is also facilitated by current practices. Compared to most adult malignancies, pediatric cancers afflict small numbers of patients, making formal outcome studies difficult. On the other hand, because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in Phase 3 oncology trials has become the *standard of care* in pediatric oncology. Children with cancer are usually treated at specialized centers by pediatric oncologists who are members of a national pediatric cooperative study group. One of the highest priorities of these groups is to develop improved therapies and effective treatment for patients refractory to current therapy. Early access to new drugs is one mechanism to achieve this goal.

Although in some cases pediatric claims for treatment of a malignancy can be based on results in adults, with appropriate PK and safety information in the pediatric population, the many known and potential differences in the biology of pediatric and adult tumors usually will not permit the extrapolation of clinical activity from adults to children. It is usually necessary to evaluate the effectiveness and safety of new drugs in pediatric populations. In the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA would ordinarily expect to rely on demonstration of tumor response as the basis of approval; other endpoints would probably be used in disease stages where there is existing therapy. In refractory settings, and with rare disease, it may be appropriate to rely on relatively small amounts of safety data.

- *Type of studies needed*:

  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: 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, and expertise to care for children with cancer. Two Phase 2 studies are to be submitted.

- *Indication(s) to be studied (i.e., objective of each study):*

  Refractory or relapsed pediatric solid tumors

- *Age group in which study(ies) will be performed*:

  Infants > 1 month of age to adolescents up to 21 years of age with a distribution of patients that reflects the demographics of the diseases under study

- *Study 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 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.

- *Drug information submitted:*
  - *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 specific safety concerns*:

  Peripheral neuropathy, neutropenia, thrombocytopenia, bleeding, infections, anemia, hepatotoxicity and death

- *Statistical information, including power of study and statistical assessments:*

  Statistical analysis appropriate to the phase of the study, including descriptive statistics for the Phase 2 studies must be submitted. Descriptive statistics for the PK parameters, clearance, half-life, volume of distribution and area under the curve must be included.

- *Labeling that may result from the studies*:
  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *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.

- *Timeframe for submitting reports of the studies:*
  Reports of the above studies must be submitted to the Agency on or before August 8, 2006. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

- *Response to Written Request:*

  As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

## *D. OCP FILING AND REVIEW FORM*

| Office of Clinical Pharmacology<br>New Drug Application Filing and Review Form | | | |
|---|---|---|---|
| **General Information About the Submission** | | | |
| | **Information** | | **Information** |
| **NDA Number** | 21-492 | **Brand Name** | Eloxatin |
| **OCP Division (I, II, III, IV, V)** | DCB-V | **Generic Name** | Oxaliplatin |
| **Medical Division** | HFD-150 | **Drug Class** | Platinum-based anti-cancer drug |
| **OCP Reviewer** | Roshni Ramchandani | **Indication(s)** | Advanced carcinoma of colon or rectum (in combination with infusional 5-FU/LV) |
| **OCP Team Leader** | Brian Booth | **Dosage Form** | IV Injection |
| | | **Dosing Regimen** | - |
| **Date of Submission** | 7/10/06 | **Route of Administration** | Intravenous |
| **Estimated Due Date of OCPB Review** | 12/15/06 | **Sponsor** | Sanofi-aventis US Inc. |
| **PDUFA Due Date** | 1/10/07 | **Priority Classification** | S |
| **Division Due Date** | 12/31/06 | | |

| **Clinical Pharmacology Information** | | | | |
|---|---|---|---|---|
| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | | | | |
| **HPK Summary** | | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| **single dose:** | | | | |
| **multiple dose:** | | | | |
| **Patients-** | | | | |
| **single dose:** | | | | |
| **multiple dose:** | | | | |
| **Dose proportionality -** | | | | |
| **fasting / non-fasting single dose:** | | | | |
| **fasting / non-fasting multiple dose:** | | | | |
| **Drug-drug interaction studies -** | | | | |
| **In-vivo effects on primary drug:** | | | | |
| **In-vivo effects of primary drug:** | | | | |
| **In-vitro:** | | | | |
| **Subpopulation studies -** | | | | |
| **ethnicity:** | | | | |
| **gender:** | | | | |
| **pediatrics:** | X | 4 | 4 | Two phase 1 (safety and PK) studies. Two phase 2 (safety and response) studies. |
| **geriatrics:** | | | | |
| **renal impairment:** | | | | |

| | | | | |
|---|---|---|---|---|
| **hepatic impairment:** | | | | |
| **PD:** | | | | |
| **Phase 2:** | | | | |
| **Phase 3:** | | | | |
| **PK/PD:** | | | | |
| **Phase 1 and/or 2, proof of concept:** | | | | |
| **Phase 3 clinical trial:** | | | | |
| **Population Analyses -** | | | | |
| **Data rich:** | X | 1<br>1 | | Population PK analysis of data from 4 studies.<br>Exposure-toxicity analysis of data from 2 phase 2 studies. |
| **Data sparse:** | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| **Solution as reference:** | | | | |
| **alternate formulation as reference:** | | | | |
| **Bioequivalence studies -** | | | | |
| **traditional design; single / multi dose:** | | | | |
| **replicate design; single / multi dose:** | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | X | 6 | | |

| Filability and QBR comments | | |
|---|---|---|
| | "X" if yes | Comments |
| Application filable? | X | |
| Comments sent to firm? | Yes | Please submit the bioanalytical report for assay of platinum in plasma and PUF for the phase 2 study ARD 5530. |
| QBR questions (key issues to be considered) | Population PK analysis of oxaliplatin in pediatric patients.<br>Comparison of PK between pediatric and adult patients.<br>E-R for toxicity measures. | |
| Other comments or information not included above | | |
| Primary reviewer Signature and Date | Roshni Ramchandani | |
| Secondary reviewer Signature and Date | Brian Booth | |

CC: NDA 21-492, HFD-850 (Electronic Entry), HFD-150 (CCottrell),
HFD-860 (ARahman, BBooth, RRamchandani), CDR (Biopharm)

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

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/s/
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Roshni Ramchandani
12/22/2006 07:34:39 AM
BIOPHARMACEUTICS

Jogarao Gobburu
12/22/2006 07:36:25 AM
BIOPHARMACEUTICS

Brian Booth
12/22/2006 09:11:43 AM
BIOPHARMACEUTICS