CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 21-492

Medical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FDA MEDICAL OFFICER AND BIOMETRICS REVIEW OF A NEW DRUG APPLICATION

NDA NUMBER:	**21-492**
DRUG NAME:	**Eloxatin® (oxaliplatin for injection)**
INDICATION:	**Treatment of advanced colorectal cancer**
SPONSOR:	**Sanofi-Synthelabo**
CLINICAL REVIEWERS:	**Amna Ibrahim, M.D. (Efficacy review)**
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The Executive Summary of the Primary Clinical Review

1 Recommendations

1.1 Recommendations on Approvability

We recommend the approval of oxaliplatin in combination with infusional 5-FU/LV under Subpart H accelerated approval regulations for the following indication:

"For the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy of the combination of bolus 5-FU/LV and irinotecan therapy"

This recommendation is based on the review of the clinical data, which shows a statistically significant improvement in tumor response and an improvement in time to tumor progression (in an interim analysis) in comparison to an infusional regimen of 5-fluorouracil and leucovorin. The population for whom this treatment will be approved has no effective therapy available to them.

1.2 Recommendations on Postmarketing Studies

There are several post-marketing commitments agreed upon as a condition for accelerated approval of Eloxatin. They include submission of mature survival data and analysis in a final study report of EFC 4584, the major study submitted for this NDA, for review by the second quarter of 2004. Additionally completion, analysis and study reports of the following studies are required as demonstration of "due diligence" in the evaluation of potential clinical benefit from oxaliplatin treatment:

- EFC 4585 (Multi-center, Randomized, Two Arm Study of Irinotecan versus the Combination of Oxaliplatin with Irinotecan as Second Line Treatment of Metastatic Colorectal Cancer),
- EFC7462 (Randomized, Phase 3 trial of Combinations of Oxaliplatin, 5-Fluorouracil and Irinotecan as Initial Treatment of Patients with Advanced Adenocarcinoma of the Colon and Rectum),
- L8125 (Randomized Trial Evaluating Oxaliplatin Combined with Two Different 5-Fluorouracil Regimens in Patients with Previously Untreated Advanced Colorectal Cancer),
- Adjuvant treatment study EFC3313 (Multicenter International Study of Oxaliplatin/5FU/LV in the Adjuvant Treatment of Colon Cancer – MOSAIC TRIAL),
- Adjuvant treatment study EFC7112 (Clinical Trial Comparing 5-FU plus Leucovorin and Oxaliplatin with 5-FU/LV for the Treatment of Patients with Stage 2 and 3 Carcinoma of the Colon).

Other commitments made by the applicant are:

- A study to examine the safety of 85 mg/m2 of oxaliplatin in combination with infusional 5-FU/LV, in patients with renal impairment,
- Submission of all medication errors that occur in the United States with oxaliplatin for two years following the date of approval,
- Redesigning of the product packaging to reduce errors,
- Completion, and submission of study reports of EFC 4759 (Single Arm Phase 2 study of Oxaliplatin as Third-Line Treatment of Metastatic Colorectal Carcinoma) and EFC 4760 (Randomized, Phase 2 Trial of Infusional 5-FU versus Infusional 5FU/Oxaliplatin in 3rd line Treatment of Metastatic Colorectal Carcinoma).

The details of the post-marketing commitments can be found in section 8 of the clinical review.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

Oxaliplatin is an antineoplastic agent, a platinum analogue, that is administered intravenously. An accelerated approval is sought for the combination regimen of oxaliplatin with infusional 5-FU and leucovorin for treatment of patients with advanced metastatic colorectal carcinoma who have recurred or progressed after first-line therapy with a combination of irinotecan (Camptosar) and bolus 5-FU and leucovorin. The single trial submitted for efficacy evaluation, EFC4584, was a multicenter, open-label, prospectively randomized, 3-arm study that enrolled 463 patients. Safety data on a total of 1874 patients from 4 studies, published reports and compassionate use programs were submitted.

2.2 Efficacy

EFC4584 was a single large, multicenter, randomized trial that compared the response rate of three treatment arms in patients with metastatic colorectal carcinoma who had recurred or progressed during or within 6 months of completion of first-line therapy with the irinotecan, *bolus* 5-FU and leucovorin. The schedule and regimens of the three treatment arms are described in Table 1 below. This trial forms the basis for accelerated approval sought by the applicant in this refractory population.

Table 1: Schedule and regimen of the three arms in EFC4584

ARM	DRUGS	DAY	REGIMEN
A	5-FU/LV	1 & 2	LV 200 mg/m^2 IV infusion over 120 min., followed by 5-FU 400 mg/m^2 IV bolus (2 to 4 min.), followed by 5-FU 600 mg/m^2 IV infusion in 500 mL D5W(recommended) over 22 hrs **(de Gramont regimen)**
B	Oxaliplatin	1	85 mg/m^2 IV infusion in 250-500 mL D5W over 120 min
C	Oxaliplatin + 5-FU/LV	1 1 & 2	85 mg/m^2 IV infusion in 250-500 mL D5W over 120 min LV 200 mg/m^2 IV infusion over 120 min., followed by 5-FU 400 mg/m^2 IV bolus (2 to 4 min.), followed by 5-FU 600 mg/m^2 IV infusion in 500 mL D5W(recommended) over 22 hrs **(FOLFOX4 regimen)**

LV:leucovorin

The three arms of the study are infusional 5-FU/LV (Arm A), single agent oxaliplatin (Arm B) and a combination regimen of *infusional* 5-FU/LV and oxaliplatin (Arm C), all administered every 2 weeks. The patients in this study had received bolus 5-FU as part of the first-line therapy, and because infusional 5-FU has shown activity in such patients, *bolus* 5-FU/LV served as the control arm.

The primary endpoint of the study is overall survival (OS). However, the survival data were not mature at the time of the cut-off date for analysis of response rate, the prespecified endpoint for potential accelerated approval. Response rate (RR) should be considered the primary endpoint for this NDA. Time to progression (TTP) and proportions of patients with symptom improvement were also analyzed as secondary endpoints. The prespecified primary comparison was between the 5-FU/LV regimen and the 5-FU/LV/oxaliplatin combination regimen (Arms A vs. Arm C). The null hypothesis was tested at the two-sided level of 0.05, using the log-rank test. The treatment could have been continued for up to a year. However, a maximum number of 18 cycles (16 on the oxaliplatin combination arm) were administered on study.

Response Rate:
Responses were evaluated using the 'Response Evaluation Criteria in Solid Tumors'[39] (RECIST), except that 6 target lesions instead of 5 could be chosen, and duration of stable disease that was required for a designation of SD was not predefined. An independent consulting group reviewed the radiological studies. This group's response assessment, based on radiographic measurements, was pre-specified in the analysis plan as the basis for the primary analysis of response rate. Investigator assessment of response rate was not utilized. The independent reviewer was blinded to the treatment arm of the patient and investigator's assessment of response (including investigator choice of target

lesions). The investigators' assessments of response were also submitted to the NDA, but not as the primary analysis of the RR endpoint. The FDA reviewed the electronic datasets of tumor measurements (both investigator and independent consulting group datasets) and selected the radiographic studies from all patients designated as responders by the independent reviewer for secondary review by a FDA radiologist consultant. The results of the FDA analysis are summarized in Table 2 below.

Table 2: FDA Analysis of Response Rate

Best Response	Arm A N=151	Arm B N=156	Arm C N=152
CR	0	0	0
PR	0	2 (1%)	13 (9%)
P value	0.0002 for Arm A vs. Arm C		
95%CI	0-2.4%	0.2-4.6%	4.6-14.2%

Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin

A small improvement in response rate for the combination regimen of oxaliplatin and infusional 5-FU with leucovorin, over that of single agent oxaliplatin or 5-FU and leucovorin was observed (p = 0.0002).

Time to tumor progression (TTP):

TTP was a secondary endpoint. This endpoint was evaluated in two separate analyses, one based on investigator data (counting radiographic and clinical progression events as well as death as events) and the other limited to radiographic data for progressive disease as assessed by an independent radiology group. The latter analysis, the pre-specified primary analysis of TTP, counted only radiographic progression as an event. With approximately 50% of the potential TTP events recorded an improvement in TTP of almost 2 months was noted for the oxaliplatin combination Arm C over the 5FU and leucovorin control Arm A by both the sponsor and FDA analyses. However, this analysis excluded 82 (18%) patients by censoring them at time zero. Twenty-five of these patients had radiographic assessments performed beyond baseline by the investigator, but those radiographs were either not submitted for independent radiologist review or were not deemed evaluable by the radiologist. The other censored patients did not have radiographic assessment beyond baseline.

Table 3: FDA Analysis of Time to Radiographic Tumor Progression*

Arm	A N=151	B N=156	C N=152
No of Patients Progressing	74	101	50
Median TTP (months)	2.7	1.6	4.6
95% C.I	1.8-3.0	1.4-2.7	4.2-6.1

Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin

P value: < 0.0001 for the comparison of Arm A vs. Arm C by Log-Rank test

* This is not an ITT analysis. Events were limited to radiographic disease progression documented by independent review of radiographs. Clinical progression was not included in this analysis, and 18% of patients were excluded from the analysis based on unavailability of the radiographs for independent review.

Other Secondary Endpoints:

The statistical analysis plan included a plan for examining secondary endpoints of treatment impact on signs and symptoms of disease. The pre-specified primary analysis for this evaluation was time to symptomatic worsening (TTSW). At the cut-off for analysis of response rate, less than 50% of events had occurred for the TTSW analysis. Because the TTSW data were not mature, they were not analyzed. The applicant presented another secondary analysis in this sign/symptom category in the NDA that was referred to as 'clinical benefit assessment', a composite endpoint consisting of KPS, pain, analgesic requirement and weight. FDA review of the data supporting this endpoint raised concerns regarding the validity of its analysis. The review issues included discordant percentages of KPS recorded by patients and their physicians for the same visits and factors that could have caused weight gain other than tumor control.

2.3 Safety

More than 1,500 colorectal cancer patients have been treated with oxaliplatin as a single agent and in combination with fluoropyrimidines in the context of phase 1/2/3 clinical trials, expanded access protocols or single patient INDs. Overall, the oxaliplatin/ fluoropyrimidine combination is a tolerable regimen. Neurotoxicity is most often dose limiting. Nephrotoxicity, cardiotoxicity, and ototoxicity are uncommon.

The principal hematologic toxicity associated with oxaliplatin is neutropenia. While grade 4 neutropenia did not occur in patients receiving oxaliplatin alone in the submitted randomized study (Study EFC4584), 26 patients (17%) on Arm C (5-FU/LV/oxaliplatin) had Grade 4 neutropenia. Grade 3/4 febrile neutropenia occurred in 9 (6%) Arm C patients. Grade 4 thrombocytopenia did not occur in Arm C patients (Grade 3 occurred in 5%).

Oxaliplatin treatment induces nausea and vomiting. This side effect can be controlled with 5-HT3 receptor antagonists and/or dexamethasone. The addition of oxaliplatin to 5-FU tends to enhance 5-FU-related diarrhea. Grade 3/4 diarrhea occurred in 11% of patients on arm C (5-FU/LV/oxaliplatin), 4% on Arm B (oxaliplatin alone) and 3% on Arm A (5-FU/LV alone).

Neurotoxicity associated with oxaliplatin infusion is common and in general is reversible and does not interfere with activities of daily living, although adjustments and compensations may have to be made while the neurotoxicity is manifest. The study population was patients with metastatic colorectal cancer that relapsed or was refractory to a first line colorectal regimen and therefore represents a poor prognosis group. The number of cycles of the combination of oxaliplatin, 5-FU, and leucovorin administered in this study may not represent the exposure in clinical practice and therefore extrapolation of findings may be limited.

Prior categorization of neurotoxicity described events based on a combination of symptom cluster and duration with an acute component consisting of cold sensitive spasms and loss of sensation and a chronic component characterized by progressive paraesthesia and dysesthesia, loss of proprioception, and impairment of daily living that was proportional to cumulative dose. The data submitted did not support this schema because either type of symptom could occur as either an acute or persistent event and there was not a demonstrated threshold of cumulative oxaliplatin dose for an event to occur.

In the current analysis, neurotoxicity was categorized as either acute (lasting less than 2 weeks) or persistent (duration of 2 weeks of greater). The onset of persistent neurotoxicity can occur at any cumulative dose and is not necessarily preceded by any episodes of acute toxicity. The spectrum of symptoms included numbness, tingling, pain, dysesthesia, paraesthesia, or sensitivity in the distal extremeties, legs, hip, arm, eye, jaw, throat, mouth, gums, lips, or tongue that may or may not be exacerbated or induced by contact with cold temperature including beverages, foods, or objects. About 2% of patients had pharyngo-laryngeal spasms that may be accompanied by a sense of loss of air, shortness of breath, or, as one patient stated, "bees in the throat" that can occur without warning. All patients in the study survived the laryngospasm toxicity, which had a median duration of 7 days.

In any given cycle at least 30% of patients will have a neurotoxic event. Having an event in one cycle is not predictive of subsequent events, although there were patients who had events with every cycle. The population of patients having an event varied, so that over the course of the study about 75% of all patients had at least one neurotoxic event. The mean number of acute neurotoxic events per patient was 3 with a range of 1 to 12. Of patients that have neurotoxic events, the acute events tend to occur in the earlier cycles. Persistent events and high grade events may occur during any cycle with the net result that proportionately more patients have persistent events during the later cycles.

Data are inadequate to determine whether dose adjustment, dose delay, or increasing infusional time are useful to decrease or abrogate neurotoxicity. Patients should avoid exposure to cold temperature, objects, or liquids such as ice for easing the pain of mucositis.

The safety profile of oxaliplatin combined with infusional 5-FU appears to be predictable and manageable and is not expected to limit the usefulness of this drug combination.

2.4 Conclusion:

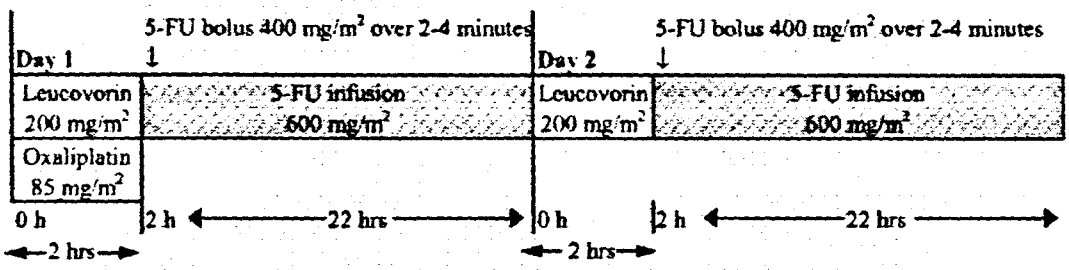
EFC4584 is a well-designed, well-conducted phase 3 trial in a refractory patient population of patients who had metastatic colorectal cancer that had progressed after first-line therapy. There has been no effective therapy found for these patients. A small but statistically significant improvement of response rates was observed in the combination arm of oxaliplatin with infusional 5-FU and leucovorin, and the 95% C.I was non-overlapping for the comparison of response rates between the 5-FU/LV control arm and the oxaliplatin combination arm. Data has been previously reviewed by the FDA for the combination of oxaliplatin + 5-FU and leucovorin for first-line therapy in patients with advanced MCRC. Although the combination regimen evaluated in the first-line setting was somewhat different in dose and regimen for one of two of the trials from the regimen evaluated in the current application, improvements in RR and PFS were observed in these previously reviewed trials. Those two trials support the improvement in response rates observed in EFC4584, the major study presented in this NDA.

2.5 Dosing, Regimen, and Administration

The recommended dose of oxaliplatin in combination with infusional 5-FU/LV is 85 mg/m^2 intravenously over 2 hours in 250-500 mL of D5W. Leucovorin 200 mg/m^2 is administered by an intravenous infusion simultaneously over 2 hours in a separate bag using a Y-line. 5-FU follows the oxaliplatin and leucovorin, first as a bolus injection over 2-4 min in a dose of 400 mg/m^2, followed then by administration of 600 mg/m^2 (5-FU) as a continuous infusion in D5W 500 mL over 22 hours. Leucovorin is repeated on Day 2 of the cycle **without oxaliplatin**. The 5-FU 400 mg/m^2 bolus and 22 hour infusion of 600 mg/m^2 is repeated on Day 2 after completion of the Day 2 leucovorin infusion. The cycle is repeated every 2 weeks.

Figure 1: Dose and Administration Schedule of the Oxaliplatin, 5-FU and Leucovorin Combination Regimen

Applicant Figure (8.8.4.1.1) 2 from Study report



No prehydration is required. Antiemetics including 5-HT3 blockers, with or without dexamethasone are recommended.

Some combinations of oxaliplatin and *bolus* 5-FU may be associated with excessive toxicity as observed in the NCCTG study 9741 (discussed in the literature section) and a phase 2 study comparing oxaliplatin as a single agent with the combination of oxaliplatin with 5-FU/LV as administered in the Mayo Clinic regimen[40].

2.6 Drug-Drug Interactions

The pharmacokinetics of platinum from oxaliplatin are not affected by 5-FU, nor are the pharmacokinetics of 5-FU affected by oxaliplatin at a dose of 85 mg/m^2. At a dose of 130 mg/m^2, oxaliplatin appears to increase the plasma concentration of 5-FU by approximately 20%. *In vitro*, platinum was not displaced from plasma proteins by the following medications: erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel. *In vitro,* oxaliplatin is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes. No P450-mediated drug-drug interactions are anticipated in patients.

2.7 Special Populations

Age

The age of patients on the combination arm (oxaliplatin and infusional 5-FU with leucovorin) of the major study that was submitted for review in this NDA ranged from 22 to 88 years (54 patients were ≥ 65 years of age). Among the responders on the oxaliplatin combination arm, the age range was 30 to 80 years, with a median of 56 years.

For the more commonly occurring AE's in the 5/FU/LV/oxaliplatin arm, patients < 65 were compared to patients ≥ 65 years of age. The younger age group had more frequent (all grades) paresthesias, 78% vs. 67%, nausea, 70% vs. 56%, vomiting 46% vs. 29%, and sensory disturbance, 59% versus 42%, and less frequent fatigue 6% vs. 75%, and

diarrhea, 62% vs. 75%. Fever was comparable in the two age groups, 27% and 28%, respectively.

In addition to the higher incidence of diarrhea and fatigue in patients ≥65 years old, dehydration (4% in <65 years old vs. 15% in ≥ 65 for overall grades and 2% vs. 6% grade 3/4), hypokalemia (7% <65 years old vs. 13% in ≥65 years old for overall grades), and Grade 3/4 granulocytopenia (32% <65 years old vs. 38% in ≥65 years old) occurred more frequently in this older population.

Four of 7 deaths that occurred within 30 days of administration of the oxaliplatin and 5-fluorouracil/leucovorin combination regimen were in patients ≥65 years old. (36% of patients on the oxaliplatin combination treatment arm were ≥65 years old.)

Sex
Of the 13 responders in Arm C (oxaliplatin combination arm), 5 were females and 8 were males. There do not appear to be any differences in efficacy based on sex.

Females had a higher incidence of dizziness, stomatitis, headaches, anemia, urinary tract infections, nausea and vomiting pharyngitis, mucositis, granulocytopenia (42% grade 3/4 in females vs. 28% in males), conjunctivitis, and skin exfoliation (hand-foot syndrome). Rates of diarrhea, paresthesias, and sensory disturbances were similar between males and females.

Thrombocytopenia was reported more frequently in oxaliplatin combination regimen-treated males than in females (4% vs. 0.03% for grade 3/4), as was anorexia and dehydration. Three of the 7 patients who died within 30 days of treatment in the oxaliplatin and 5-fluorouracil/LVcombination regimen were female. (43% of the oxaliplatin combination treatment arm were female).

Race
There were only a limited number of patients not considered Caucasian per arm (Arm A -19, Arm B -22, Arm C -17), which makes a meaningful analysis of differences in efficacy and safety among races impossible.

Renal impairment
There was a limited number of patients per arm with renal impairment (elevated baseline serum creatinine) (Arm A -3, Arm B -5, Arm C -9). Therefore, no assessment was possible.

Hepatic impairment
There did not appear to be an increased number of adverse events in patients with elevated hepatic enzymes or bilirubin, but numbers of patients were small. Only 3 patients receiving 5-FU/LVOxaliplatin had grade 3,4 hepatic enzyme and/or bilirubin elevation.

Clinical Review Section

1 Introduction and Background

1.1 Established and Proposed Trade Name of Drug, Drug Class, Applicant's Proposed Indications, Dose, Regimens, Population

Generic Name:	Oxaliplatin
Proposed Trade Names:	Eloxatin
Established Trade Name:	Eloxatin
Chemical Name:	cis-[(1R,2R)-1,2-cyclohexanediamine-N,N] [oxalato(2-)-O,O]platinum
Pharmacological Category:	Antineoplastic agent
Drug Class:	Platinum analogue
Route of Administration:	Intravenous
Dose and regimen:	Oxaliplatin: 85 mg/m^2 IV infusion in 250-500 mL D5W over 120 min <u>on Day 1 only</u>, Leucovorin (LV) 200 mg/m^2 IV infusion over 120 min., followed by 5-FU 400 mg/m^2 IV bolus (2 to 4 min.), followed by 5-FU 600 mg/m^2 IV infusion in 500 mL of D5W (recommended) over 22 hrs on Day 1 & 2
Population studied:	Patients with metastatic colorectal carcinoma who progressed on or after treatment with the Saltz regimen (irinotecan and bolus 5-FU/LV combination regimen).

1.2 State of Armamentarium for Indication

The following drugs are approved for the treatment of metastatic colon cancer:

<u>First-line treatment for metastatic carcinoma:</u>

a- Irinotecan (Camptosar) with 5-fluorouracil and leucovorin (Leucovorin).
b- Capecitabine (Xeloda) when treatment with fluoropyrimidine alone is preferred.
c- 5-fluorouracil with leucovorin.

<u>Second-line treatment for metastatic colorectal carcinoma after 5-FU-based therapy:</u>

a- Irinotecan.

1.3 Important Milestones in Product Development

The IND —— for oxaliplatin was initially filed by Axiom, Inc. in February 1993. It was then transferred to Debiopharm SA, and finally to Sanofi–Synthelabo in April 1995. The IND was placed on clinical hold due to chemistry manufacturing and control issues and the hold was lifted in May 1997.

A registration application was submitted for oxaliplatin as NDA # 21063 in February 1999 for treatment of advanced colorectal cancer in combination with infusional 5-fluorouracil-based therapy in previously untreated patients. Data from two randomized studies, i.e., EFC 2961 (n=100/arm) and EFC 2962 (n=210/arm) were submitted. Neither trial was designed with overall survival as the primary endpoint. EFC 2961 was powered to show a difference in tumor response and EFC 2962 was powered to show a difference in disease-free survival (DFS). The regimen used in EFC 2961 was different from that used in the current study. The 5-FU and LV in EFC2961 were administered as a chronomodulated infusion for 5 consecutive days with or without oxaliplatin on day 1 of each 21 day cycle. The chronomodulated infusion of 5-FU and LV (given from 10 PM to 11 AM with peak at 4 AM) was administered using a multi-channel portable pump. The oxaliplatin combination regimen in EFC 2962 was identical to that used in the current study, EFC 4584.

The FDA medical reviewer's comments from NDA # 21063 are as follows:

"Of the two trials submitted one, study #2961, did not show a survival advantage or even a trend towards a better survival for the oxaliplatin arm. The second study, 2962, did not show a survival advantage in the primary unadjusted analysis using the Log Rank test".

The following two tables (table 1 and 2) reporting the results of primary endpoints of the two studies have been taken from the Medical Officer's Review:

Table 1: Response Rates in Study EFC 2961 (NDA 21-063)

Response	5-FU/LV ARM (N=100)			L-OHP* + 5-FU/LV ARM (N=100)		
	Investigator	expert	FDA	investigator	expert	FDA
RR	13%	12%	14%	39%	34%	37%

$p < 0.001$: investigator's, expert's, and FDA's analyses
chronomodulated, infusional 5-FU was used in both treatment arms.
*L-OHP: oxaliplatin

Table 2: Progression-free Survival of Patients in Study EFC 2962 (NDA 21-063)

ITT Population		Arm A N = 210	Arm B N = 210	p-Value*
Investigator assessment	Median (months)	6.2	8.8	p = 0.0001
	95 % CI (months)	[5.5 - 7.3]	[7.9 - 9.5]	
Expert assessment	Median (months)	6.0	8.2	p = 0.0003
	95 % CI (months)	[5.5 - 6.5]	[7.2 - 8.8]	

Arm A: infusional 5-FU/LV
Arm B: oxaliplatin + infusional 5-FU/LV

The findings of the two major studies in the application were presented to ODAC in March 2000. At the same ODAC meeting, data on two well-controlled studies for first-line treatment of metastatic colorectal cancer (MCRC) with irinotecan was presented, and a survival advantage associated with irinotecan was demonstrated. This indication was the same as that pursued for oxaliplatin. Analysis of the survival data did not show a survival advantage for oxaliplatin in studies EFC 2961 and 2962. The ODAC members did not recommend oxaliplatin for approval. Sanofi-Synthelabo withdrew the NDA on May 19th 2000.

In the year 2000 Sanofi-Synthelabo had several End-of-Phase 2 (EOP2) meetings with the Division of Oncology Drug Products regarding four protocols for second- and third-line use of oxaliplatin in patients with metastatic colorectal cancer. Oxaliplatin was granted fast-track designation for the development plan that included evaluation of the regimen of oxaliplatin + 5-FU/LV in patients recurring or progressing on 5-FU and irinotecan based regimens (Protocol EFC 4584).

Excerpts from EOP2 Meeting – August 25, 2000

1- Does the Division agree that a comparison of the single agent oxaliplatin arm (Arm B) to the 5-FU/LV alone arm (Arm A), and the comparison of the oxaliplatin alone arm (Arm B) to the 5-FU/LV + oxaliplatin arm (Arm C) does not need to be performed to support the potential submission for conditional approval?

FDA RESPONSE:

- *Yes.*

- *Survival is a clinical endpoint and an improvement in survival for this endpoint would suffice for full approval. Conditional approval is not anticipated.*

2- Does the Division agree with the use of this minimization technique for treatment allocation?

FDA RESPONSE:

- *Because a patient's known characteristics may dictate which treatment they will receive, minimization (particularly when Center is used as stratification factor) can lead to bias with respect to non-stratified factors. If a patient's characteristics dictate that they will be in the control group, they may be dissuaded from entering the study (they can always receive this treatment without being on study). As a stratification factor, we prefer country/region instead of center.*

3- Does the Division agree that the prior dosing information does not need to be collected in this randomized Phase III study?

FDA RESPONSE:

- *Yes. However, the following should be collected: Start and stop dates for prior therapy, whether response was achieved and the date of response, and date of progression of disease.*

4- Does the Division have any additional comments regarding this protocol and the statistical analyses proposed?

FDA RESPONSE:

- *We recommend that the final analysis be performed based on a pre-specified total number of deaths between the 5-FU/LV arm and the combination arm.*

- *Informative censoring (censoring subjects who receive second-line therapy) violates the censoring assumptions needed for the log-rank (Wilcoxon) test and Kaplan-Meier estimation. Such results will not be interpretable – p-values and estimates are calculated based on assumptions that do not hold.*

- *Cause and effect relationships cannot be drawn from adjusting one response variable (survival) by another response variable (second-line treatment included as a time dependent covariate).*

- *Subgroup analyses are strongly discouraged. All subgroup analyses should be pre-specified with multiplicity adjustments, not post-hoc – determined by baseline factors associated with higher or lower probabilities of receiving second-line therapy.*

- *Definition of time to worsening for Clinical Benefit: Death without worsening should be censored and not counted as an event.*

- *In Table 2, 4/8,* (for clinical benefit assessment) *worsening must persist for 4 weeks or until death or Disease Progression. However, improvement must persist for 4*

weeks without death or progressive disease.

- *Each component of clinical benefit response should be analyzed separately in addition to the combined components.*

- *Cross-over design will not be acceptable to review the protocol for survival as an endpoint (discussed at the meeting with NCI).*

- *In the event of Grade IV diarrhea, dose modification should occur with the next cycle. (refer to section 5.1.5.1.2, page 28/102 of protocol)*

- *Because of propensity for diarrhea, electrolyte panel could be included in the routine laboratory blood work. Abnormal electrolytes could possibly affect performance status by causing weakness and lethargy.*

- *Suggest including the duration of adverse event in section 9.3.3 when evaluating safety.*

5- ***A) Does the Division agree with this proposal?***
B) Does the Division have any recommendations regarding how best to address this as an alternative endpoint for full approval in the protocol and/or statistical analysis plan?

FDA RESPONSE:

- *There can be only one primary endpoint. Classically, survival benefit has been the primary endpoint for approvability. Clinical benefit response assessment can be a secondary endpoint. Clinical benefit has not been the basis for marketing approval for any drug for this use. However, it may be used to demonstrate approvability if clinical benefit is shown in case the primary endpoint of survival is not met, provided:*

- *It is supported by better RR and TTP.*

- *It is a very large effect or confirmed in a 2nd randomized, controlled trial.*

- *Clinical benefit is subjective and the trial is not blinded. The clinical benefit response assessment endpoints must be pre-specified in the protocol. Symptoms to be used to show this clinical benefit must also be pre-specified. These have been provided by the sponsor in the second meeting package.*

6- A) Does the Division agree that this is adequate to support this endpoint as an alternative endpoint to support full approval?

FDA RESPONSE:

- *The detailed analysis methods should be included in the statistical analysis plan, which is submitted prior to the randomization of the first patient to treatment.*

7- Would the Division require pre-specified null and alternative hypotheses for the clinical benefit response rate and time to worsening?

8- FDA RESPONSE:

- *Yes.*

OTHER COMMENTS

- *TTF should be removed as a secondary endpoint.*

- *Please refer to the NCI discussion where correlations for time to disease related symptom progression were addressed.*

Excerpts from FDA response to questions posed by Sanofi in a letter dated September 8, 2000.

- *The FDA is willing to consider a NDA for accelerated approval based on tumor response rate in the proposed randomized trial in advanced colorectal cancer patients who have failed on the Saltz regimen.*

- *The FDA agrees that the main analysis is a comparison of Treatment Arm A with Treatment Arm C. However, a comparison of Treatment Arm B (single agent oxaliplatin) with the other two Treatment arms is also important. We do not want to recommend that patients receive the FU/LV in conjunction with Oxaliplatin if it is not necessary.*

- *If the main analysis comparing Treatment Arm A with Treatment Arm C shows Treatment Arm C is better, the subsequent comparisons can be performed as sequential analyses without any inflation of Type One Error.*

- *Tumor progression should be based on objective measurements of the tumor, not on clinical deterioration.*

The FDA has the following additional comments regarding the revised protocol.

- *The FDA strongly recommends that eligibility be limited to patients who have had tumor progression while receiving the Saltz regimen. Patients who have had tumor progression during the 6 months following the Saltz regimen should not be eligible.*

We do not believe there will be many such patients. If there are many such patients, it will add a heterogenity to the study that may not be equally distributed by the randomization. In either case, such patients are best excluded from the study.

- *Protocol section 9.2 should indicate that the primary efficacy analysis will be Intent to Treat.*

Reviewer's comment:
Eight patients (1.7%) had progression of disease beyond 6 months of completion of therapy.

Excerpts from PreNDA clarifications to the applicant dated 12/17/2001

Regarding time to event endpoints the FDA would like this information submitted for each individual patient. If more than 50% of the patients have had an event, a statistical analysis should be submitted. If patients, investigators and Sanofi are still blinded to this information, the FDA will make every effort not to disclose it publicly, e.g. in relation to a Public Advisory Committee meeting.

If a statistical analysis is done for the DSMC, a statistical adjustment must be made for subsequent analyses.

On April 11th, 2002, oxaliplatin received a fast track designation because the response rate reported by the applicant with this oxaliplatin regimen was better than that with available treatment(s) for metastatic colorectal carcinoma that has progressed after treatment with irinotecan and 5-FU/LV (Saltz regimen) first-line.

1.4 Other Relevant Information

Registration status

As of 31 December 2001, oxaliplatin has been approved for marketing in 60 countries and is pending approval in an additional 9 countries. The dates of submission or approval and indications for the individual countries are listed in Tables (3.1.1) 1 and (3.1.2)1 of the foreign marketing history section of the summary provided by the applicant.
The most common approved indication has been metastatic colorectal cancer (MCRC), often for first-line therapy. Oxaliplatin has not been denied approval, nor has it been withdrawn from the market in any country (other than USA).

1.5 Important Issues with Pharmacologically Related Agents

There are two other platinum compounds approved by the FDA. Renal toxicity, neurotoxicity, ototoxicity and myelosuppression are the main side effects of cisplatin. Carboplatin has thrombocytopenia as its most prominent adverse reaction. Oxaliplatin

does not share the marked renal, hematological or ototoxicity of these two other platinum drugs.

2 Significant Findings From Chemistry, Animal Pharmacology and Toxicology

2.1 Chemistry

The information in this section is obtained from the review of Dr. Haripada Sarker, Ph.D.

The USAN chemical name of oxaliplatin is: SP-4-2-(1R,2R)-(cyclohexane-1,2-diamine-2 N,N'(oxalato(2-)-. 2 O 1 ,O 2]platinum(II). It is a white to off-white powder. Oxaliplatin is an organometalic coordination complex, with the platinum atom chelated with a 1,2-diaminocyclohexane group and an oxalate group. Oxaliplatin is slightly soluble in water, very soluble in methanol, and insoluble in ethanol and acetone. The pKa study on oxaliplatin indicated that the molecule is neutral with no dissociation in solution. Multiple batch records, including the microbiological limits, demonstrate the batch to batch consistency of the oxaliplatin drug substance. Primary and secondary stability studies support the stability of oxaliplatin drug substance in the solid state up to 36 months at normal condition using the commercial container/closure system.

The drug product, oxaliplatin for injection (Eloxatin) is formulated as a sterile lyophilized powder at two strengths 50 mg and 100 mg/vial, for reconstitution with water for injection or 5%. Oxaliplatin lyophilized powder is found to be stable up to 36 months using commercial container/closure systems, and at normal condition. However, the reconstituted drug products are stable up to 24 hours at 2-8°C (36-46° F). After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 24 hours at room temperature and at ambient light.

2.2 Animal Pharmacology and Toxicology

No new findings were noted by the current pharmacology reviewer, Dr. Wendelyn Schmidt, Ph.D. A summary of the major *in vitro* and *in vivo* findings regarding the antitumor activity of oxaliplatin taken from the year 2000 review of the previous NDA by Dr. Hua Zheng, Ph.D. follows:

Oxaliplatin demonstrates broad spectrum *in vitro* cytotoxic or antiproliferative activity against a variety of murine and human tumor cell lines. In general, the cytotoxic and antitumor activity of oxaliplatin is equal or superior to that observed for cisplatin. In an *in vitro* human tumor cloning assay, oxaliplatin and cisplatin had similar activity against several types of human tumors obtained directly from patients. Oxaliplatin also demonstrates *in vitro* cytotoxic and *in vivo* antitumor activity (including curative activity) in several cell lines/tumor models that are resistant to cisplatin. Oxaliplatin was shown to have additive and/or synergistic cytotoxic and antitumor activity in combination with a variety of standard antineoplastic agents, including 5-fluorouracil, SN-38, gemcitabine, or cisplatin. Oxaliplatin as a single agent demonstrated *in vivo* antitumor activity against a variety of murine tumor models and human xenografi model in athymic mice.

Oxaliplatin was more active than cisplatin in the following murine tumors: L1210 leukemia, LGC lymphoma, and MA-16c mammary tumors.

Oxaliplatin was negative in the Ames test, but was positive in all other genotoxicity tests, *i.e.*, mouse lymphoma assay for mammalian cells (TK locus), mouse micronucleus assay, and chromosome aberration assay for human lymphocytes in culture. The relative mutagenicity and clastogenicity of oxaliplatin was comparable to cisplatin within an order of magnitude. Oxaliplatin was mutagenic and clastogenic both in the presence or absence of metabolic activation. Based on net values (≥ 4) obtained from the integrative assessment for assignment of concern, it appears there are significant degrees of concerns for developmental and reproductive toxicity for the endpoints of fertility, developmental mortality, and alterations to growth in humans from the exposure to oxaliplatin at the clinical dose proposed.

The carcinogenicity of oxaliplatin has not been studied in animals. However, based on the similar mechanism of action and genetic toxicity as cisplatin, which has sufficient evidence of carcinogenicity in animals and humans, oxaliplatin should be presumed to be a trans-species carcinogen.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics

The following information is taken from the Dr. Brian Booth's review of oxaliplatin for the Division of Biopharmaceutics.

Using a validated assay, the applicant demonstrated that the pharmacokinetics of platinum from oxaliplatin at a dose of 85 mg/m^2 are described by a three-compartment open mammalian model with $t_{1/2}$'s of 0.43, 16.8 and terminal elimination half-life of 391 hours. The pharmacokinetics of oxaliplatin appear to be linear between 40 and 130 mg/m^2. Oxaliplatin is rapidly hydrolyzed *in vivo* to yield a number of active and inactive platinum species.

The pharmacokinetics of platinum from oxaliplatin are not affected by 5-FU, nor are the pharmacokinetics of 5-FU affected by oxaliplatin at a dosage of 85 mg/m^2. At the dose of 130 mg/m^2, oxaliplatin appears to increase the plasma concentration of 5-FU by approximately 20%. Oxaliplatin is extensively protein bound (approximately 90 to 95 % in vivo), but it did not mediate displacement interactions with erythromycin, salicylate, valproate, granisetron or paclitaxel.

Cytchrome P-450 isozymes do not metabolize oxaliplatin, and the platinum is excreted predominantly via the renal route (over 50% in 5 days). Oxaliplatin is eliminated primarily by renal excretion. Approximately 50 % of platinum is excreted in the urine after a single dose of oxaliplatin. The applicant conducted a study to assess the effect of renal impairment on the pharmacokinetics of single agent oxaliplatin in patients with a

variety of cancers using a dose-escalation scheme and renal impairment criteria that differed from the FDA-promulgated recommendations. Re-analysis by FDA indicated that the $AUC_{0\text{-}48hr}$ of platinum in patients with mild, moderate and severe renal impairment increased 59, 138 and 191% respectively, compared to patients with normal renal function. The pharmacokinetic evaluation of oxaliplatin is based on analyses of total platinum ultrafiltrate, and it is unknown what pharmacokinetic changes actually occur in biologically active platinum moieties. There are no PD data available for evaluation. Because the safety data available from this renal impairment study were limited (limited patient numbers) and only single agent oxaliplatin was administered (the combination of oxaliplatin with 5-FU increases the incidence of some of the toxicities associated with 5-FU), no recommendations regarding the relative safety of administering oxaliplatin to patients with varying degrees of renal impairment could be made on the basis of the phase 1 study. There is also no efficacy or safety data available for administration of reduced doses of oxaliplatin to patients with varying degrees of renal impairment. The product label includes cautionary statements regarding administration of oxaliplatin in patients with renal impairment. The following is taken from the Precautions section:

Patients with Renal Impairment
The safety and effectiveness of the combination of ELOXATIN and infusional 5-FU/LV in patients with renal impairment has not been evaluated. The combination of ELOXATIN and infusional 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate, and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established. (See CLINICAL PHARMACOLOGY)

Age and gender had no apparent affect on the pharmacokinetics of oxaliplatin.

3.2 Pharmacodynamics

Pharmacodynamics data relating efficacy to dose have not been submitted. The only pharmacodynamic correlate to safety is limited information that Cmax may correlate with cumulative peripheral neuropathy.

4 Description of Clinical Data and Sources

4.1 Sources of Clinical Data

The clinical data were submitted by Sanofi-Synthelabo in paper copies in 104 volumes, as well as electronically. Annotated Case Report Forms (CRF), patient profiles developed by the Applicant from the CRFs and electronic datasets were provided. A literature search using MEDLINE was performed. A summary of information from the literature search is presented in Section 4.4.

4.2 Overview of Clinical Trials

Five clinical trials have been submitted as illustrated in Table 3. EFC 4584 is the major study submitted for review. Studies EFC2962 and EFC2961 were submitted and reviewed in a previous NDA. The last 4 studies in Table 3 provide supportive safety data.

Table 3: Clinical Studies Submitted in NDA 21-492

Study No.	Study Design	Population	N	Objective
EFC4584	Phase 3, 3-arm RCT	Second-line therapy for MCRC following Saltz regimen	463	RR (for accelerated approval), OS (primary)
EFC2962	Phase 2/3, 2-arm RCT	First-line therapy for MCRC	420	PFS (primary)
EFC2961	Phase 2/3, 2-arm RCT	First-line therapy for MCRC	200	RR (primary)
EFC2964	Phase 2, multicenter, open-label trial	Second-line therapy for MCRC after progression from one 5-FU/LV regimen	100	RR (primary)
EFC2917	Phase 2, multicenter, open-label trial	Second-line therapy for MCRC after progression from one 5-FU/LV regimen	115	RR (primary)

MCRC: metastatic colorectal carcinoma
RCT: randomized controlled trial
OS: overall survival
RR: response rate
PFS: progression-free survival

4.3 Postmarketing Experience

Given that oxaliplatin is available widely outside the USA, there is a considerable post-marketing experience. Per applicant, oxaliplatin has not been denied approval nor has it been withdrawn from the market in any country (other than USA). The applicant's periodic safety update reports (6 month increments of monitoring), compiled by the Sanofi-Synthelabo Corporate Pharmacovigilance Department located in France from April 1996 to April 2001 were submitted for review in the June 24, 2002 Clinical Data Section submission. This submission also included the NCI IND Annual Report for oxaliplatin, dated December 2001. These documents were reviewed by the medical reviewer to assess completeness of safety data the applicant had provided in the Post-marketing Experience section of the proposed product label. The safety issues that were raised in these documents included hemolytic uremic syndrome, pancreatitis and interstitial pneumonitis. Unique neurosensory events including cranial nerve palsies and fasciculations were reported. Cardiac, thromboembolic and CNS events could not easily

be distinguished in causality from the underlying disease, medical conditions, or concomitant use of 5-fluorouracil, which is associated with coronary events.

4.4 Literature Review

This Literature Review section will describe the incidence of colorectal cancer and the prognostic factors in metastatic disease. The role of chemotherapy, specifically 5-FU as a single agent and in combination with leucovorin will be discussed. Finally a review of the published clinical experience with oxaliplatin will be presented.

Incidence:
Colorectal cancer is the third leading cause of death in both men and women in the United States of America. There was an estimated incidence of 135,400 new cases of colorectal cancers diagnosed in 2001 of which 56,700 are expected to have died from their disease. The incidence is higher in developed countries[1]. Africa and Asia have a relatively low incidence of colorectal cancer, with the exception of Japan. Immigration from a low-incidence to a high incidence environment increases a person's risk. Certain hereditary and other medical conditions also increase the risk of developing this disease.

Prognostic Factors of Metastatic Colorectal Cancer (MCRC):
Massacesi et. al. conducted a trial in patients who had disease progression on first-line 5-FU-based regimens [2]. Right and transverse colon primary, younger age, poor performance status, elevated carcinoembryonic antigen (CEA) and more than one site of metastatic disease reached statistical significance as prognostic factors in this population of patients. In MCRC, performance status and serum CEA are the most consistently reported prognostic factors. Others are number of metastatic sites, disease-free interval, presence of symptoms, WBC count, hemoglobin, albumin, and alkaline phosphatase [3-7].

Tolerance of therapy may be influenced by demographic factors such as sex. A meta-analysis from NCCTG suggests that women experience greater toxicity from 5-FU-based chemotherapy when administered as a bolus injection [8-9].

Chemotherapy:
Chemotherapy has been the mainstay of treatment for advanced colorectal cancer. Palliative chemotherapy can prolong time-to-progression and survival in patients with advanced colorectal cancer. A meta-analysis evaluated 13 randomized trials that enrolled 1365 patients and compared chemotherapy to supportive care. Patients who received chemotherapy had a significantly reduced risk of death (H.R. 0.65, 95% C.I. 0.56-0.76). The median survival was 8 months in the control group vs. 11.7 months in the chemotherapy group [10].

Fluorouracil (5-FU):
The first drug to be approved by the FDA for colorectal cancer was 5-FU in the 1960's. Single agent 5-FU produces overall response rates of approximately 20% and a median survival of about 12 to 18 months. Varying combinations and schedules of this drug have

been investigated. A meta-analysis suggested that 5-FU administered by continuous infusion is superior to 5-FU bolus therapy in patients with advanced colorectal cancer, but the survival difference between the two administration methods was small. The toxicity profile was different, as there were fewer hematological adverse events associated with infusional 5-FU[11]. Due to the marginal survival difference, and the need for catheter insertion for the infusional administration, bolus injection of 5-FU has been the standard of care in the U.S.

The two widely used regimens involving bolus injection of 5-FU have been the Mayo Clinic regimen and the Roswell Park regimen. The doses and schedule in the Mayo Clinic regimen are 425 mg/m^2 of 5-FU, IV bolus on Days 1-5 and 20 mg/m^2 of leucovorin on Days 1-5. The treatment is repeated every 4 weeks [12]. The Roswell Park regimen involves 5-FU 600 mg/m^2 + leucovorin 500 mg/m^2 weekly x 6 weeks, followed by a 2 week rest [13].

5-FU in combination with leucovorin:
There have been several studies evaluating the effect of leucovorin in addition to 5-FU. A meta-analysis of 9 randomized trials reported an improvement of response rates (23% vs.11%) of 5-FU/LV compared to 5-FU alone [14]. An improvement in survival has been reported in other studies [15-18]. Several other studies report an improved response rate and/or progression-free survival, with no difference in survival [19-22].

Oxaliplatin:
Oxaliplatin belongs to the diaminocyclohexane platinum family. Its mechanism of action involves formation of DNA adducts and inhibition of DNA synthesis. Preclinical studies suggested synergy between oxaliplatin and 5-FU [23]. Oxaliplatin may reduce 5-FU catabolism and this may explain the supra-additive interaction between these drugs that has been reported[24]. It has been postulated that a reason for this observed supra-additive effect in vitro is that sequential administration of oxaliplatin followed by 5-FU results in a significant decrease in thymidylate synthase gene expression[25]. In vivo, the trial under review suggests synergy between oxaliplatin and 5-FU/LV.

Oxaliplatin was developed in France, and the initial emphasis was on chronomodulation according to circadian rhythms. This drug has been evaluated mostly in combination with 5-FU, often with leucovorin. Varying dosages and regimens of 5-FU/LV (leucovorin) and oxaliplatin combinations have been used. They are:

FOLFOX1:
Bimonthly high-dose LV (500 mg/m^2 on Day 1 & 2) and high dose 5-FU (2 gm/m^2 on Day 1 & 2) q 2 weeks + oxaliplatin 130 mg/m^2 in alternate cycles [26]

FOLFOX2:
LV 500 mg/m^2, + 5-FU 24-h infusion 1.5-2 g/m^2 Day s1-2 and oxaliplatin 100 mg/m^2 on Day 1, q 2 weeks [27].

FOLFOX3:
LV: 500 mg/m^2, 5-FU: 1.5-2 g/m^2/22 hours, Days 1-2, q 2 weeks, oxaliplatin 85 mg/m^2 q 2 weeks [28].

FOLFOX4:
LV 200 mg/m^2, bolus 5-FU 400 mg/m^2, and CI 5-FU 600 mg/m^2/22 hours, Day1, 2 q 2 weeks and 85 mg/m^2 of oxaliplatin Day 1 q 2 weeks [29]. (This is the combination regimen used in the major study reviewed in this NDA.)

FOLFOX6:
LV 400 mg/m^2 d 1, 5-FU, bolus 400 mg/m^2 followed by a 46-h infusion of 2.4-3 g/m^2 q 2 weeks, and oxaliplatin 100 mg/m^2 q 2 weeks [30].

FOLFOX7:
LV 400 mg/m^2 over 2 hours on Day 1, 5-FU bolus 400 mg/m^2 and a 46-h infusion 2400 g/m^2 , every 2 weeks and oxaliplatin 130 mg/m^2 q 2 weeks [31].

OXAF (Oxaliplatin and PVI of 5-FU):
Oxaliplatin (100 mg m^2) infusion over 2 hours every 2 weeks, 5-FU (300 mg m^2/day) administered as a continuous protracted venous infusion to a maximum of 24 weeks [32].

Oxaliplatin with bolus 5-FU and leucovorin:
5-FU and LV 350 mg/m^2 and 20 mg/m ^{2}, respectively on Days 1-5, oxaliplatin 130 mg/m^2 on Day 1, every 21 days [33].

FUFOX:
Infusional 5-FU and LV, 2000 mg/m^2 over 24 hours and 500 mg/m^2 respectively, and oxaliplatin 50 mg/m^2 on Day 1, 8, 15, 22 q 5 weeks[35].

Two trials were previously submitted to the FDA in an NDA, the summary of which are presented in Section 1.3. Survival was not the primary endpoint in either study and the studies were powered to show a difference in RR and PFS. Recently, two abstracts of phase 3 studies of 5-FU/LV and oxaliplatin as first-line treatment for patients with advanced colorectal cancer were presented at the annual ASCO (American Society of Clinical Oncology) meeting. One of these studies was the NCCTG study[34], in which there were six arms initially. During the study, three arms were discontinued because of safety issues associated with the Mayo irinotecan regimen (Mayo Clinic), Wilke regimen (irinotecan combined with 24 hour infusion of 5FU) and an oxaliplatin bolus regimen. In April 2002, the study was closed early by the DSMB (data safety monitoring board) due to the improved TTP and OS observed in the oxaliplatin combination arm (FOLFOX4)

compared to the Saltz regimen arm. The latter regimen has been a first line treatment standard in the US since the demonstration of survival benefit of the addition of irinotecan to 5-FU/LV in studies that were the basis of irinotecan's approval for first line treatment of advanced colorectal cancer. The second first-line study [35] compared the Mayo Clinic regimen of 5-FU/LV (Mayo bolus regimen) versus weekly high dose 24-hour infusional 5-FU/LV with oxaliplatin (FUFOX). After a median follow-up of 27.3 months, PFS is significantly different, favoring the oxaliplatin and infusion 5-FU/LV arm; 5.3 (Mayo) vs 7.9 (FUFOX) months ($p<0.0001$). Median overall survival (with 73% of events on the Mayo Clinic regimen arm and approximately 61% of the events on the FUFOX arm) is 16.1 months on the Mayo Clinic regimen arm and 20.4 months on the FUFOX arm.

Oxaliplatin has little hematologic toxicity relative to other chemotherapeutic drugs, and the neurotoxicity associated with its use can be reversible. Its safety profile and potential synergy with other drugs makes it amenable for inclusion in combination regimens [36]. In phase 1 studies, nausea and vomiting occurred in a high incidence. In later studies, this adverse event was reduced by addition of prophylactic antiemetics. Laryngeal dysesthesia secondary to cold, and pulmonary fibrosis have been reported. De Gramont et al reported a 41.7% grade 3/4 neutropenia with only a 1% incidence of fever for the combination of 5-FU/LV and oxaliplatin. Grade 3/4 vomiting and mucositis affected 5.8% patients and diarrhea occurred in 11.9%. Sensory neuropathy was cumulative and dose-limiting. Reversible paresthesia occurred in 16.3% and led to withdrawal of drug in 3.8% of patients after treatment for a minimum of 4 months. Median time to response was 2.1 months. In this and other studies, the dose limiting neurotoxicity occurred after the maximum response to therapy had been achieved [37-38].

Some combinations of oxaliplatin with bolus 5-FU/LV have been associated with excessive toxicity [40] although more recently, certain combinations has been used with a tolerable safety profile [33]. Care should be taken when choosing a regimen if oxaliplatin is administered with bolus 5-FU/LV.

5 Clinical Review Methods

5.1 Methodology Used for FDA Review

There was one phase 3 trial (EFC4584) submitted to support efficacy. An additional 4 phase 2 and randomized studies (in first line treatment of metastatic colorectal cancer) provide support for safety. Three primary clinical reviewers were involved. They are

Efficacy review:	Dr. Amna Ibrahim, M.D.
Safety Review:	Dr. Martin Cohen, M.D. and
	Dr. Steven Hirschfeld, M.D., Ph.D.

The study reports and data were reviewed. Electronic datasets were used to verify the applicant's analyses and claims.

5.2 Overview of Materials Consulted in Review

FDA reviewed the original protocols with their subsequent amendments and the study reports submitted by the applicant. Electronic datasets for the individual and combined results of patients on the study were submitted and were used extensively for efficacy and safety analyses. FDA requested additional analyses from the applicant which were prespecified in the original protocol, but not included in the study report during the review process.

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

FDA's Division of Scientific Investigation (DSI) audited selected centers to assess data quality and integrity. Sites that accrued the largest number of patients were selected for DSI audit. Inspections were completed at the sites listed in the table 4. DSI determined that study conduct and data quality from these sites were acceptable.

Table 4: Sites inspected by DSI

Name	City, state	Country	# of Patients	Responders	Responders in Arm C
Ramesh Ramanathan, M.D.	Pittsburg, PA	USA	12	0	0
Stephen A. Bernard, M.D.	Chapel Hill, NC	USA	8	1	1
Al Benson, M.D.	Chicago, IL	USA	8	0	0
Daniel Haller, M.D.	Philadelphia, PA	USA	25	2	0

5.4 Ethical Conduct of trial

The trials were conducted in accordance with the accepted ethical standard.

5.5 Evaluation of Financial Disclosure

The Financial Disclosure Rule states that for NDAs or sNDAs submitted on or after February 2, 1999, the applicant must disclose whether the following financial arrangements were made with the investigators:

- Compensation affected by the outcome of the clinical studies
- Significant equity interest in the sponsor of a covered study (exceeds $50,000 during the time the investigator conducts the study and for 1 year following completion)
- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)
- Significant payments of other sorts (payments to the investigator or the institution of > $25,000, exclusive of study costs during the time the investigator conducts the study and for 1 year following completion)

If these arrangements have been made, the applicant must disclose the arrangements and state what has been done to minimize the potential for bias.

The applicant certified that Sanofi-Synthelabo had not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. All except 19 investigators denied disclosable interests. For the 19 investigators, Sanofi-Synthelabo filed a certificate of due diligence, stating that it has not been possible to obtain the financial information required. A subinvestigator for Dr. Mace Rothenberg, [redacted] did not disclose financial interest. There was 1 response [redacted] out of 7 patients at Dr. Rothenberg's site.

Reviewer's assessment of financial disclosure:
Study EFC4584 was a randomized study, and the tumor response analysis required radiological documentation. Radiographic data were reviewed by an independent consulting group, where reviewing radiologists were blinded to the identity of the patient and the treatment arm. Therefore, it is not expected that the financial interests of those, who did not file financial disclosure, would affect the study results. The submitted information appears to be in compliance with financial disclosure requirements.

6 Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

Efficacy data from one large, phase 3, multicenter, randomized trial (EFC4584) was submitted to support the efficacy of oxaliplatin. This trial was conducted in patients with metastatic colorectal carcinoma whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of 5-FU/LV and irinotecan therapy. The basis for accelerated approval at submission of the NDA was response rate.

A small but statistically significant improvement of response rate (RR=9% on the oxaliplatin and infusional 5-FU/LV arm vs. 0% on the infusional 5-FU/LV control arm; p: 0.0002) was observed in the combination arm of oxaliplatin, infusional 5-FU and leucovorin. Additionally, with approximately half the progression events observed at the time of the cut-off for analysis of response rate, TTP was prolonged by approximately two months, from 2.7 months in the 5-FU/LV arm to 4.6 months in the oxaliplatin/5FU/LV combination arm. The applicant's presentation of a 'clinical benefit assessment' (CBA) in this NDA was not considered valid, and was not the pre-specified major analysis that had been planned by the sponsor for evaluation of treatment impact on signs and symptoms of disease, a grouping of secondary endpoints. These signs and symptoms analyses will not be included in the label.

6.2 Detailed Review of Trials by Indication

Protocol EFC 4584 was submitted as the major trial to support the indication proposed in this NDA. First the original protocol will be described, followed by the patient disposition and results.

Protocol Title:

"A multicenter, open-label, randomized, three-arm study of 5-FU + leucovorin (LV) or Oxaliplatin or a combination of 5-FU/LV + Oxaliplatin as second-line treatment of metastatic colorectal carcinoma."

Study Period:

Date first patient enrolled: 2nd November, 2000.
Date last person completed: 18th December, 2001 (cutoff date)*.
Enrollment completed: 22nd February, 2002.

*Enrollment to the trial continued for an overall survival assessment. The number of patients included in this trial was based on a pre-specified interim analysis of response rate for evaluation for accelerated approval.

Sites:

The study was conducted in Canada and USA.

Objectives:

Primary Objective:

To determine the overall survival (OS) of patients with metastatic colorectal cancer (MCRC) that has recurred following first-line treatment with weekly irinotecan/5-FU/LV who then are randomized to receive 5-FU/LV, oxaliplatin, or 5-FU/LV + oxaliplatin.

Secondary Objective:

To evaluate for each of the 3 treatment arms:

- Response rate (RR)
- Time-to tumor-related symptomatic worsening (TTSW)
- Time to Disease Progression (TTP)
- Onset and duration of responses (CR, PR) and duration of disease stabilization.

Study Design:

This is a multicenter, open-label, randomized, three-arm study of 5-FU + leucovorin or oxaliplatin or a combination of 5-FU/LV + oxaliplatin as second-line treatment of metastatic colorectal carcinoma.

It was performed in two phases, with a prospectively defined and planned analysis for each phase. The first phase was to perform a response rate (RR) analysis that would include all patients randomized up to the date when at least 150 patients were enrolled in each of Arms A (5FU/LV) and C (5FU/LV + oxaliplatin). The second phase planned an overall survival (OS) analysis of the planned, fully accrued sample size of 786 patients.

Reviewer's comments:
As noted in Section 1.3 FDA agreed that accelerated approval may be granted based on an improvement in response rates. The applicant designed the trial so that response rate was evaluated in the first phase of trial. Subsequent to the initial phase, patients with nonmeasurable disease could be enrolled because overall survival is the primary endpoint of the trial.

Study Population:

Inclusion Criteria:

- Histologically or cytologically-proven adenocarcinoma of the colon or rectum.
- Age >18 years.
- Female patients should not be pregnant or lactating. Documentation of negative β-HCG is required for women of child-bearing potential.
- Signed informed consent.
- At least one unidimensionally measurable lesion with a diameter ≥ 20 mm using conventional MRI or CT scans or ≥ 10 mm using spiral CT scans. If a single lesion exists, a histological or cytological confirmation of adenocarcinoma is required.
- Saltz regimen (irinotecan + bolus 5-FU/LV) as the only prior regimen for metastatic disease. Prior adjuvant therapy with 5-FU is allowed.
- Documented PD (by MRI or CT scan) either during or no more than 6 months after the last dose of irinotecan + 5-FU/LV given in the first-line setting.
- Prior radiotherapy is permitted if it is not administered to target lesions, unless progression within the radiation portal is documented, and provided it has been completed at least 3 weeks before randomization.
- Previous chemotherapy must have completed at least 3 weeks prior to randomization and any acute/delayed toxicity must have resolved.
- Serum creatinine ≤ 1.5 x ULN.
- Total bilirubin ≤ 1.5 x ULN.

- SGOT/AST and SGPT/ALT $\leq$2 x ULN unless liver metastases are present. ($\leq$3 x ULN in that case)
- ANC $\geq$ 1.5 x 10^9/L.
- Platelet count $\geq$ 100 x 10^9/L.
- Willing to complete the clinical benefit assessment.

Exclusion Criteria:

- Received an investigational drug within 30 days before beginning treatment with the study drug.
- Concomitant treatment with other investigational agents.
- Chemotherapy agents other than the Saltz regimen as part of first-line therapy for MCRC.
- Irinotecan as part of adjuvant therapy.
- Prior therapy with oxaliplatin.
- Cardiac toxicity secondary to 5-FU/LV in the past or MI within 6 months of therapy.
- Known DPD (dihydropyrimidine dehydrogenase) deficiency.
- History of intolerance to appropriate antiemetics to be administered in conjunction with the protocol-directed chemotherapy.
- Concurrent active cancer originating from a primary site other than colon or rectum.
- Known peripheral neuropathy.
- Interstitial pneumonia or extensive and symptomatic fibrosis of the lung.
- Uncontrolled intercurrent illness: high BP, symptomatic CHF, serious cardiac arrhythmias, NYHAC classification III or IV, diabetes or active infection.

Study Procedures:

Chemotherapy:

All regimens are administered every 2 weeks.

Table 5: Chemotherapy Regimen Dose and Schedule

(adapted from Sponsor protocol EFC 4584)

ARM	DRUGS	DAY	REGIMEN
A	5-FU/LV	1 & 2	LV 200 mg/m^2 IV infusion over 120 min., followed by 5-FU 400 mg/m^2 IV bolus (2 to 4 min.), followed by 5-FU 600 mg/m^2 IV infusion in 500 mL D5W(recommended) over 22 hrs **(de Gramont regimen)**
B	Oxaliplatin	1	85 mg/m^2 IV infusion in 250-500 mL D5W over 120 min
C	Oxaliplatin + 5-FU/LV	1 1 & 2	85 mg/m^2 IV infusion in 250-500 mL D5W over 120 min LV 200 mg/m^2 IV infusion over 120 min., followed by 5-FU 400 mg/m^2 IV bolus (2 to 4 min.), followed by 5-FU 600 mg/m^2 IV infusion in 500 mL D5W(recommended) over 22 hrs **(FOLFOX4)**

LV:leucovorin

Figure 1 The Dosing Schedule of Arm A

Applicant Figure (5.1.1) 1 from protocol

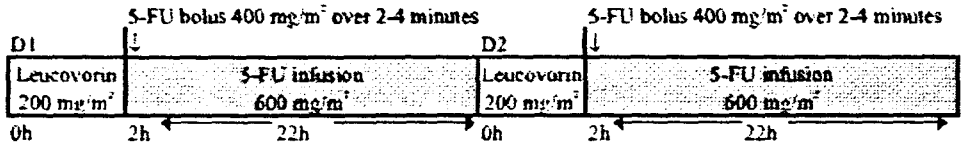
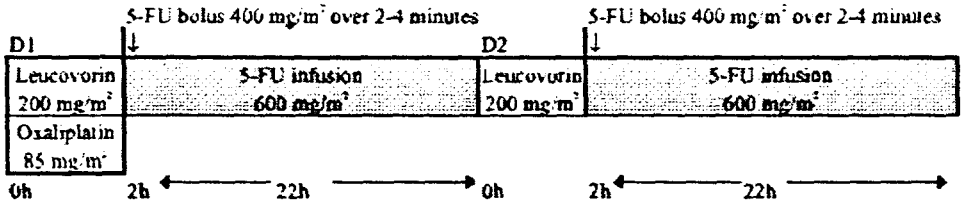


Figure 2: The Dosing Schedule of Arm C

Applicant Figure (5.1.1) 2 from protocol



"Choice of pre- and post treatment antiemetics are at the discretion of the Investigator. 5HT3 antagonists plus dexamethasone are strongly recommended".

Dose Modifications

Toxicity will be graded according to the CTC (Common Toxicity Criteria), Version 2. Neurosensory toxicity will be graded according to the Neurological Toxicity Scale for Oxaliplatin Dose Adjustment as described in Table 6. A plan for dose adjustment for other hematological and non-hematological toxicities were also been submitted in the protocol.

Table 6: Neurological Toxicity Scale for Oxaliplatin Dose Adjustments (for Arm B & C)

Applicant Table (5.1.5.4) 1 from protocol

Toxicity (Grade)	Duration of Toxicity		Persistent between Cycles
	1-7 days	> 7 days	
Paresthesias/dysthesias that do not interfere with function (Grade 1)	No Change	No Change	No change
Paresthesias/dysthesias interfering with function, but not activities of daily living (Grade 2)	No Change	No Change	65 mg/m^2
Paresthesias/dysthesias with pain or with functional impairment that also interfere with ADL (activities of daily living) (Grade 3)	No Change	65 mg/m^2	Stop
Paresthesias/dysthesias that are disabling or life-threatening (Grade 4)	Stop	Stop	Stop
ACUTE: (during or after the 2 hour infusion) Laryngopharyngeal dysesthesia	Increase duration of infusion to 6 hrs	Increase duration of infusion to 6 hrs	Increase duration of infusion to 6 hrs

Dosing Delay:
Treatment will be delayed until:

- ANC is $\geq 1.5 \times 10^9$/L and platelet count is $\geq 75 \times 10^9$/L.
- Recovery from stomatitis or diarrhea to Grade 1 or less.
- Recovery from skin toxicity to Grade 1 or less.
- Recovery from fatigue to Grade 2 or less.

For patients who have dosing delays, all evaluations, including tumor evaluation, will be correspondingly delayed, but not more than 6 weeks, after the initial scan showing a response to treatment.

Duration of Treatment and Follow-up:
Therapy will consist of 2-week cycles for up to 1 year. Patients should be evaluated after 6 months and treatment may be adjusted to a q3w schedule.

Follow-up/observation for treatment-related toxicity will be through day 30 following the last dose of treatment. All patients will be followed for survival. In addition, information will be collected concerning the nature and timing of subsequent anti-tumor therapy.

Study Schema

Table 7: Study Schema

Applicant Table (5.2) 1 from protocol

Evaluation or Procedure	Before Study Treatment[a]	Study Treatment				After Study Treatment	
		Dosing Q2 Weeks			Every 6 Weeks	30-Day Post-Treatment - Evaluation	Follow-Up
		Pre-Dose	Day 1	Day 2			
Informed consent	X						
Medical history	X						
Physical examination	X				X[b]	X[b]	
ECG	X						
Height	X						
Weight		X				X	X
Karnofsky Performance Status (KPS)	X	X[c]				X	X
Hematology	X	X[c,d]				X	
Serum chemistry	X	X[e]			X[f]	X	
CEA	X				X[f]	X[g]	X[h]
TRS Questionnaire	X	X[c]				X[i]	X[i]
Analgesic diary[j]			throughout treatment			X[i]	X[i]
AE assessment[k,l]			throughout treatment			X[l]	
Tumor evaluation	X				X[f]	X[g]	X[h]
Chest X-ray	X				X[f]	X[g]	X[h]
Oxaliplatin[m]			X				
5-FU/LV[n]			X	X			

In each treatment cycle: Day 1 is treatment day for oxaliplatin and/or 5-FU/LV and is the first day of each planned treatment cycle. Procedures indicated for Day1 must be completed at the start of each treatment cycle and before drug administration. Day 2 is the second treatment day for 5-FU/LV for Arms A and C.

a : To be performed within 7 days before randomization and the first dose of study drug(s), except for chest X-rays and tumor evaluation, which must be performed within 21 and 28 days, of the first dose of study drug(s).
b: Significant changes from baseline will be recorded on tumor assessment or AE Case Report Forms (CRFs).
c: Not applicable for Day 1 of Cycle 1.
d: Predose labs may be obtained up to 3 days prior to planned dosing. See Section 5.7 of protocol.
e: At q 2 weeks the only serum chemistry evaluations collected are sodium, potassium, chloride, BUN, and creatinine.
f: CT or MRI scans, chest X-rays, serum chemistry on weeks 6, 12, 18, 24, 30, 36, 42, and 48, and CEA to be performed at baseline and repeated on weeks 6, 12, 18, 24, 30, 36, 42, and 48 if elevated at baseline.
g: CT or MRI scans, chest X-rays, and CEA (if elevated at baseline) to be performed only if progression had not previously been documented.
h: For patients discontinued from study for reasons other than progression, perform every 6 weeks starting from the 30-Day Follow-up Visit until documentation of progression or

13 months after first dose of study drug, whichever comes first. CEA should be performed, if elevated at baseline.
i: The Tumor Related Symptoms (TRS) questionnaire and analgesic diary will be provided to the patient at the last treatment visit and the 30-day post-treatment visit to collect this information up until 3 months after the last study treatment.
j: 2-week diary is provided to the patient at each visit.
k: See Section 7 of protocol.
l: Treatment-related adverse events occurring during study treatment or within 30 days after the last administration of
study drug(s) will be followed until resolution or stabilization.
m: Arms B and C
n: Arms A, B, and C
TRS questionnaire: tumor-related symptom questionnairre

Methodology:
A toxicity assessment, CBC with ANC, and a basic chemistry panel (Na^+, K^+, Cl^-, BUN, and creatinine) will be performed at baseline, 30-day post-treatment evaluation, and prior to each cycle. LFTs (alkaline phosphatase, total bilirubin, LDH, AST and ALT) will be performed at baseline, q 6 weeks and at the end 30-day post-treatment evaluation. CEA will be repeated during study only if elevated at baseline.

Tumor Evaluation:
"Tumor evaluations must consist of a CT or an MRI scan. A chest X-ray is also required at each tumor evaluation to follow non-target lesions or the appearance of a new lesion. For patients with a target lesion in the lungs, a CT or MRI of the chest is required. The CT or MRI must include the liver. If the target lesion is in the colon or rectum, a CT or MRI of the pelvis is required."

"Up to 6 target lesions identified at baseline will be followed throughout the study. At least 1 lesion must be unidimensionally measurable with a diameter of at least $\geq$ 10 mm using spiral CT."

"The RECIST criteria[37] will be used to evaluate response. The same measuring instrument should be used throughout treatment to maintain consistency. After demonstration of a response, a confirmation of response should be performed no less than 4 weeks and no more than 6 weeks later. If a cycle is delayed, confirmation of response will be performed no more than 6 weeks after the previous examination."

The criteria for tumor evaluation, adapted from NCI RECIST (Response Evaluation Criteria in Solid Tumors Group) criteria are illustrated in Table 8, and overall response for all possible combinations of target, non-target and new lesions are given in Table 9 below.

Table 8: Criteria for Tumor Evaluation

Applicant table [5.7.6]1 from protocol

Disease Response	Definition
CR	The disappearance of all known disease determined by 2 observations not less than 4 weeks apart.
PR	30% or more decrease in: • Single lesion: the longest diameter of the target lesion identified at baseline • Multiple lesions: the sum of the longest diameters of target lesions identified at baseline To determine the effect of therapy not less than 4 weeks apart
PD	An increase by at least 20% in: • Single lesion: longest diameter compared to the smallest diameter recorded during treatment • Multiple lesions: an increase in the sum of the longest diameter since treatment of target lesions compared to the smallest diameter recorded during treatment. In addition, the appearance of any new lesions is considered PD.
SD	Neither sufficient shrinkage to qualify for partial shrinkage to qualify for partial response nor sufficient increase to qualify for disease progression can be established, taking as reference the smallest sum of the longest diameter since treatment started. In addition, no appearance of new lesions.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

Table 9:Overall Responses for All Possible Combinations of Tumor Responses

Applicant table (5.7.6) 2 from protocol

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
	Any	Yes	PD

Reviewer's comment:
According to the NCI RECIST criteria, the duration of stable disease required to be documented for assignment of a SD response should be predefined, and this duration should depend on the clinical relevance of the tumor type involved. Such a period was not included in the original protocol, making it technically impossible to perform an analysis of and to to distinguish between best response of stable disease (SD) vs. progressive disease (PD).
RECIST criteria also recommend that up to 5 target lesions should be chosen. The applicant prospectively allowed up to 6 target lesions per patient.

Clinical Benefit Assessment
"Clinical Benefit Assessment" will be assessed by 4 parameters: pain, Karnofsky Performance Status (KPS), weight, and analgesic consumption. Patients will record the assessment of pain and KPS in the Treatment Related Symptoms (TRS) questionnaire and complete the diary for analgesic use. Analgesic use during the 7 days prior to treatment will be recorded in the medical records. Weight and KPS will also be assessed independently by the study site personnel at baseline and at each cycle.

Clinical benefit assessment will be performed every 2 weeks throughout the study. It will include the TRS questionnaire on pain intensity and KPS, and the analgesic diary. Weight and KPS assessment will be recorded by the study site personnel every 2 weeks.

Discontinuation from study drugs:
- Death.
- PD.
- Treatment-limiting toxicity.
- Intercurrent medical problems.
- Noncompliance.
- Voluntary withdrawal.
- Completion of treatment.

Follow-up (off treatment):
Patients will be followed for survival until death with CT or MRI for progression every 6 weeks, or for 13 months, whichever comes first. Patients will be followed for clinical benefit assessment every 2 weeks for 3 months after last study dose. CEA will be followed until documented progression.

After the last treatment cycle, patients will be followed every 3 months for survival. No crossover from Arm A or B to C, or from Arm B to C will be allowed on protocol.

Patients withdrawn from study treatment due to any adverse event (AE) will be followed up at least until the outcome is determined, even if this implies that the follow up

continues after the patient has left the study, and, where appropriate, until the end of planned period of follow up.

Statistical Analysis:

A short statistical analysis plan was submitted with the original protocol. Subsequently, the complete plan was submitted on the 19th of December, 2000. The salient points from both are given below.

Analysis of survival in the intent-to-treat (ITT) population will be done. A "principal efficacy analysis" will also be done and will include all eligible patients with colorectal cancer who enter the study and receive study drugs. Patients included in the latter efficacy analysis will be classified in the treatment arm corresponding to the treatment actually received. The cutoff date for the primary survival analysis is defined as the date when the total number of deaths reaches 393 in the control arm and the combination (oxaliplatin + 5-FU/LV) arms (75% of the events for the two arms). Minimum follow up of all patients for survival is up to the cut-off date. In the primary analysis, survival experience for patients who live beyond the cut off will be censored at that date. Patients who are unable to be followed to the cut off date will have their survival censored at the date of last contact.

All patients who receive at least one dose of study drug(s) will be analyzed for safety.

Major Deviations were defined as follows:

- "Receipt of any anticancer agent other than the allocated treatment.
- Follow-up for survival stopped prior to study cutoff.
- Subject not treated.
- Delay of more than 30 days from baseline tumor assessment to randomization.
- Less than 3 weeks from last chemotherapy treatment to randomization."

Minor deviations were defined as follows:

- ">26 cycles of study therapy.
- >10% above the maximum of 85 mg/m^2 oxaliplatin in any cycle (>93.5 mg/m^2).
- >10% above the maximum of 400 mg/m^2 5-FU in any bolus (>440 mg/m^2).
- >10% above the maximum of 600 mg/m^2 5-FU in any continuous infusion (>660 mg/m^2).
- Escalation of oxaliplatin dose to within 90% of starting dose after once receiving a reduced dose of less than or equal to 75% of the starting dose.
- Dose reduction or delay not according to protocol guidelines.
- Study assessments not done according to schedule."

Efficacy:

This trial randomizes patients to 3 treatment arms with the intended sample size of 262 in each arm.