Survival:
Per Applicant:

"The primary comparison of the OS is between the combination of oxaliplatin and 5-FU/LV (Arm C) and 5-FU/LV alone (Arm A). The null hypothesis is that Arm A and Arm C have equal survival. Testing of this null hypothesis will be two-sided at the level of 0.05, using the log rank statistic. The study sample size is based upon this comparison and provides 88% power, under the assumption that median survival is 8 months in Arm A and 11 months in Arm C."

"A secondary comparison is between single agent oxaliplatin (Arm B) and the 5-FU/LV (Arm A) in terms of survival. This comparison will be a two-sided test at the 0.05 level, using the log rank statistic."

"In the event that both oxaliplatin-containing arms are shown to have significantly longer survival than the control arm (A), the combination arm (C) will be compared to the single agent oxaliplatin arm (B), using log rank statistic. This comparison will test the null hypothesis that the survival in Arm C is less than or equal to the survival in Arm B. The level of this one-sided test will be 0.05."

"The cutoff for the primary survival analysis will be the date when the combined total of deaths reaches 393 in the control arm (A) and the combination arm (C). This is approximately the number of deaths expected 25 months after the start of enrollment, assuming enrollment at the constant rate for 1 year, a median survival time of 8 months in Arm A and 11 months in Arm C, and a constant hazards for death."

Reviewer's comment:
Overall survival is the primary objective of this trial. However, these data are not mature. FDA had previously agreed to consider the response rate data from this trial as a basis for an accelerated approval. (See Section 1.3). For this NDA, the statistical analysis plan for evaluating response rates presented below should be followed for the primary analysis of efficacy.

Response rates:
Per Sponsor:

"Comparisons involving the response rate endpoint will be done with Fisher's exact test. Responders will be the group of patients with confirmed PR or CR. Estimated response rates and 95% confidence intervals will be displayed. "

"An analysis comparing the response rates in Arm C and Arm A will be conducted when response determination is complete for the first 150 patients in each of these arms. The statistical comparison will be done at the two-sided 0.05 level, using Fisher's exact test.

The sample size of 150 per group provides greater than 80% power to detect a difference in response rate between 8% in Arm A and 20% in Arm C. "

"An analysis of response rates for the entire study population will also be done."

Per Applicant, the statistical analysis will be based upon the independent review of all imaging performed up to the dates when there is an investigator assessment of PD and when the patient has been off treatment for more than six weeks.

Clinical Benefit:
Per Applicant:

"Primary analysis of clinical benefit will be based on time to worsening of the tumor-related symptoms, as evidenced through pain severity, analgesic use, performance status, and body weight. Comparisons among the three treatment arms will be done pairwise with the log rank test."

" Secondary analyses of clinical benefit will be done comparing the three treatment arms in terms of the proportion of patients who are symptomatic at baseline and who show improvement while on treatment. These analyses will be done with Fisher's exact test."

" Clinical benefit assessments are susceptible to observer bias. As a means of reducing potential bias the detailed methods of analysis and classification of clinical benefit endpoints are described in a separate document."

In the Dec 19th document, a further description of the analysis plan for clinical benefit assessment was submitted. Biweekly assessments of pain severity, analgesic usage, KPS, and body weight were planned. These were recorded at:

- Baseline
- Every 2 weeks during treatment.
- Twice during the 30 day period after going off study.
- Every 2 weeks for the subsequent 2 months.

"The primary clinical benefit parameter is the time to tumor-related symptom worsening (TTSW). TTSW is defined for all patients who are randomized into the trial and is defined as the number of months from the date of randomization until the patient is first observed as worsened for KPS, pain, or analgesic consumption. The date of worsening is defined as the date of first observation of a change which subsequently persists for at least 4 weeks and leads to a definition of worsened."

"The cut off date for the TTSW analysis will be 30 days after the last dose of the study drug for each patient. A patient who has not recorded symptomatic worsening within 30

days of receiving his last treatment will be classified as censored without worsening without worsening."

Reviewer's comment:
The TTSW data were not mature by the cut-off date and will not be analyzed.

Analgesic consumption was to be converted to morphine equivalents as in Table 7.2.1.1 [adapted from Jacox et al Management of cancer pain: Adults Quick Reference Guide. No. 9. AHCPR Publication No 94-0593. Rockville, MD. Dept. Of HHS, March 1994.]".

Table 10: Table of Morphine Equivalents

applicant table 7.2.1.1 of statistical section of the protocol

	ORAL		PARENTERAL	
DRUG	morphine equivalent dose (mg / day)	Conversion factor*	morphine equivalent dose (mg / day)	conversion factor*
Hydromorphone	52.5	4.00	10.5	6.67
Levorphanol	14	15	7	10
Meperedine	3000	0.07	800	0.09
Methadone	70	3.00	35	2.00
Oxymorphone	N/A	N/A	7	10.00
Codeine w/ aspirin or acetaminophen	1330	0.16	910	0.08
Hydrocodone	210	1.00	N/A	N/A
Oxycodone	210	1.00	N/A	N/A

* Multiply average daily dose by this factor to obtain morphine equivalent. Assumes prescribed daily dose of morphine for severe pain to be 210 mg/day oral and 70 mg/day parenteral.

Time to worsening will also be analyzed separately for each of the components of the "Clinical Benefit" endpoint: KPS, pain, and analgesic consumption.

Table 11: Classification of Patients as Improved, Stable, or Worsened while on Study

Applicant table 7.2.1.2 of statistical plan of the protocol.

Parameter	Improved (for symptomatic patients)	Stable	Worsened
KPS	Increase from baseline of 20 or more	Not meeting the criteria for improved or worsened	Decrease from baseline of 20 or more
Pain	Decrease of 2 cm or more	Not meeting the criteria for improved or worsened	Increase of 2 cm or more from baseline
Analgesic consumption	Decrease of at least 50% from baseline	Not meeting the criteria for improved or worsened	Increase of at least 50% from baseline reaching at least 10 mg morphine use, or its equivalent
	Improved	**Not improved**	
Body weight	At least 5% increase from baseline weight	No gain, or less than 5% gain from baseline	

Notes:
•Changes meeting the criterion for "worsened" must persist for at least 4 weeks or be present at the time the patient dies, has progressive disease, or is lost to follow-up.
•Changes meeting the criterion for "improved" must persist for at least 4 weeks, without death or progressive disease.
•For asymptomatic patients, the category "improved" is not applicable.
•For body weight, patients are classified as only "improved" or "not improved".

"A secondary clinical benefit parameter is the proportion of patients who are symptomatic at baseline and who improve on treatment. These patients are termed 'clinical benefit responders'. A patient meeting any of the criteria in table 7.2.1.3 is called symptomatic at baseline.'

Table 12: Classification of Patients as Improved, Stable or Worsened while on Study

Applicant table 7.2.1.3 of protocol

Parameter	Definition for Symptomatic at Baseline
KPS	KPS* less than or equal to 80
Pain	Score greater than 2 cm on a visual analog scale ranging from 0-10 cm.
Analgesic consumption	Consumption of at least 10 mg/day morphine (or its equivalent) for disease-related pain averaged over the 7 days preceding study entry
Body weight	Baseline weight is more than 10% below the usual weight for the patient

* lower of physician and patient assessment

At any evaluation clinical benefit response is determined by a two-step algorithm. In the first step, the parameters KPS, pain, and analgesic consumption are considered. If any of these 3 parameters is "worsened", then the patient is a non-responder. If at least one of these 3 parameters is "improved" and the other 2 are "stable" or better, then the patient is a responder. If all 3 of these parameters are stable, then the patient is a responder only if body weight is "improved".

At any evaluation a patient is a responder if:
1. None of the parameters (KPS, pain, or analgesic consumption) is worsened, and
2. At least 1 of the 3 is improved, and the others are stable or better.

OR

1. All of the parameters (KPS, pain, and analgesic consumption) are stable, and
2. Body weight is improved.

Patients who are responders at any evaluation are classified as clinical benefit responders. In addition, clinical benefit response status will be determined for each of the 4 individual parameters (KPS, pain, analgesic usage, and body weight) separately.

The following points were communicated to the Applicant at the August 25th, 2000 meeting:

- "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, 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".

Reviewer's Comment:
Symptomatic worsening may actually represent a combination of worsening due to disease as well as toxicity from study drugs. Symptomatic improvement would reflect improvement from treatment, or supportive care measures.
Clinical Benefit assessment is a composite endpoint. As pointed out by the applicant, it may be subject to bias because it was conducted in an unblinded trial. See section 6.3.9

Other Secondary Parameters

"The secondary endpoints of time to progression, time to onset of response, duration of response, and duration of stable disease will be analyzed using Kaplan-Meier methods. Treatment comparisons will be done with the log rank test."

The secondary endpoints are defined as follows:

•Response rate is the number of confirmed responders (PR or CR) divided by the number of patients randomized.
•TTP is the number of months from the date of randomization until the earliest of death or disease progression. (This is also called progression-free survival.)
•Time to onset of response is the number of months from the date of randomization until the first observation of tumor shrinkage qualifying for CR or PR, which is confirmed at a subsequent assessment at least 4 weeks later.
•Duration of response is the number of months from the first observation of response until disease progression or death.
•Duration of stable disease is the number of months from the date of randomization until disease progression or death among patients whose best response to treatment is stable disease.

The cutoff date for TTP will be 13 months after the date of randomization for each patient. Patients with documented lack of disease progression after at least 13 months of follow-up will be classified in the analysis as censored without progression at 13 months. Patients without evidence of disease progression who do not have tumor assessments after 13 months will be classified as censored without progression at the time of the latest tumor evaluation demonstrating lack of progression. No cutoff date will be employed for time to onset of response, duration of response, and duration of stable disease.

Reviewer's comment:
There should be an indefinite follow-up for time to disease progression. However, in this study, follow-up for TTP is cut off at 13 months.

Analysis of response rate, TTP, time to onset of response, duration of response, and duration of stable disease will be done for both investigator and independent assessments. In the analysis of investigator assessment, progression may be declared based upon clinical evidence. However, for the independent assessment only objective evidence (CT, MRI, etc.) will be used to determine disease progression.

Safety
Per Applicant:
The following safety and exposure endpoints will be examined:

"Adverse Events:
- Occurrence of treatment-limiting toxicity.
- Occurrence of one or more adverse events in a patient.
- Overall distribution of intensity of adverse events.
- Occurrence of particular adverse events and their intensities.
- Duration of adverse events."

"Clinical laboratory parameters:
- Occurrence of laboratory toxicities as graded by the NCI Common Toxicity Criteria."

"Dosing utility as assessed by:
- Dose intensity, expressed as the amount of 5-FU, LV, and oxaliplatin administered divided by the duration of treatment.
- Percentage of intended dose delivered for 5-FU/LV or oxaliplatin.
- Delays in the scheduled dosing.
- Dose reductions."

"Hospitalizations – reasons, duration, and outcome."

Sample size calculation:
Per Applicant:

"A total of 262 patients per arm will be randomized in to the trial. This sample size will provide 88% power to detect an increase in median survival from 8 months in the control arm to 11 months in the oxaliplatin and 5-FU/LV arm."

Reviewer's Comment:
Clinical studies of oxaliplatin have been conducted mostly in combination with 5-FU and LV based on preclinical data suggesting synergy between these drugs. This well-designed 3-arm protocol will evaluate not only the contribution of infusional 5-FU/LV to the combination with oxaliplatin, but provides evidence regarding synergy of the components of the combination through the inclusion of the single agent oxaliplatin arm.
The sample size for this submission is adequate for the analysis of RR. Nearly 50% of the events had occurred for the TTP analysis. The data on overall survival was not mature by the cut-off date and will not be evaluated for this NDA.

Amendments:

There were three amendments noted in the study report as listed below. They were made to improve accrual of patients in to the protocol. (First patient enrolled in trial on November 2, 2000)

Protocol Amendment (not noted in study report)
Date: March 09, 2001
Per Applicant:
"The log rank test, stratified for KPS 50-60 versus 70-100, will be used to determine the statistical significance of planned survival. The randomization balances for 3 factors KPS (50-60 versus 70-100), number of metastatic organs involved (1 versus $\geq$ 2), and LDH ($\leq$ 1.5 x ULN and > 1.5 x ULN), and this defines 8 (2^3) strata."

Protocol Amendment 1
Date: March 14th, 2001
Inclusion criteria for alkaline phosphatase levels were changed to $\leq$ 5 x ULN from $\leq$ 3 x ULN for patients with liver metastases.

Protocol Amendment 2
Date: July 17th, 2001.
Implemented: June 29th, 2001.
This amendment allowed inclusion of patients who had variations of the irinotecan containing Saltz regimen. The amendment changed the inclusion criteria wording regarding prior therapy to:

- "Have received one and only one (first-line setting) chemotherapy regimen for metastatic disease and **progressed during or within 6 months of completion of therapy with irinotecan in combination with 5-FU/LV (Saltz Regimen). Prior adjuvant therapy with 5-FU/LV is permitted.**
- **Have relapsed within 6 months of the last irinotecan + 5-FU/LV (Saltz Regimen) dose given in the adjuvant setting.**
- **Have received irinotecan + 5-FU/LV (Saltz Regimen) in the adjuvant or first-line setting is as follows:**

- **Starting dose: 100-125 mg/m^2 irinotecan given as a 90- minute infusion + 400 to 500 mg/m^2 5-FU bolus (+LV) given weekly for 4 weeks as part of a 6- week regimen, with the dose reductions according to the camptosar package insert. The following Saltz Regimen variations are also permitted:**
  - **Weekly dose of irinotecan and 5-FU/LV for 3 weeks as part of a 4-week regimen.**
  - **Weekly doses of irinotecan and 5-FU/LV for 2 weeks as part of a 3-week regimen."**

Protocol Amendment 3
Date: September 10th, 2001.
The inclusion criteria were modified in order to include patients with non-measurable disease.
Per Applicant:
"After recruitment of 450 patients to evaluate response rate, patients with non-measurable disease will be eligible for the trial. These patients will be followed for safety, Progression Free Survival (PFS), and Overall Survival (OS)."

6.3 Efficacy Results:

Patient Disposition:
A total of 463 patients were randomized in 110 study sites in USA and Canada. Of these, 18 patients did not receive the study drug. Four patients were not included in the ITT analysis. Per Applicant these 4 patients included 1 patient each on Arm B and C who did not have colon cancer, 1 patient in Arm A who did not have a written informed consent and 1 in Arm A who had not received prior Saltz regimen.

Reviewer's comment:
These patients who were randomized but excluded, were censored in the FDA efficacy analysis. The number of these patients is small and did not impact the study results.

Table 13: Patient Disposition

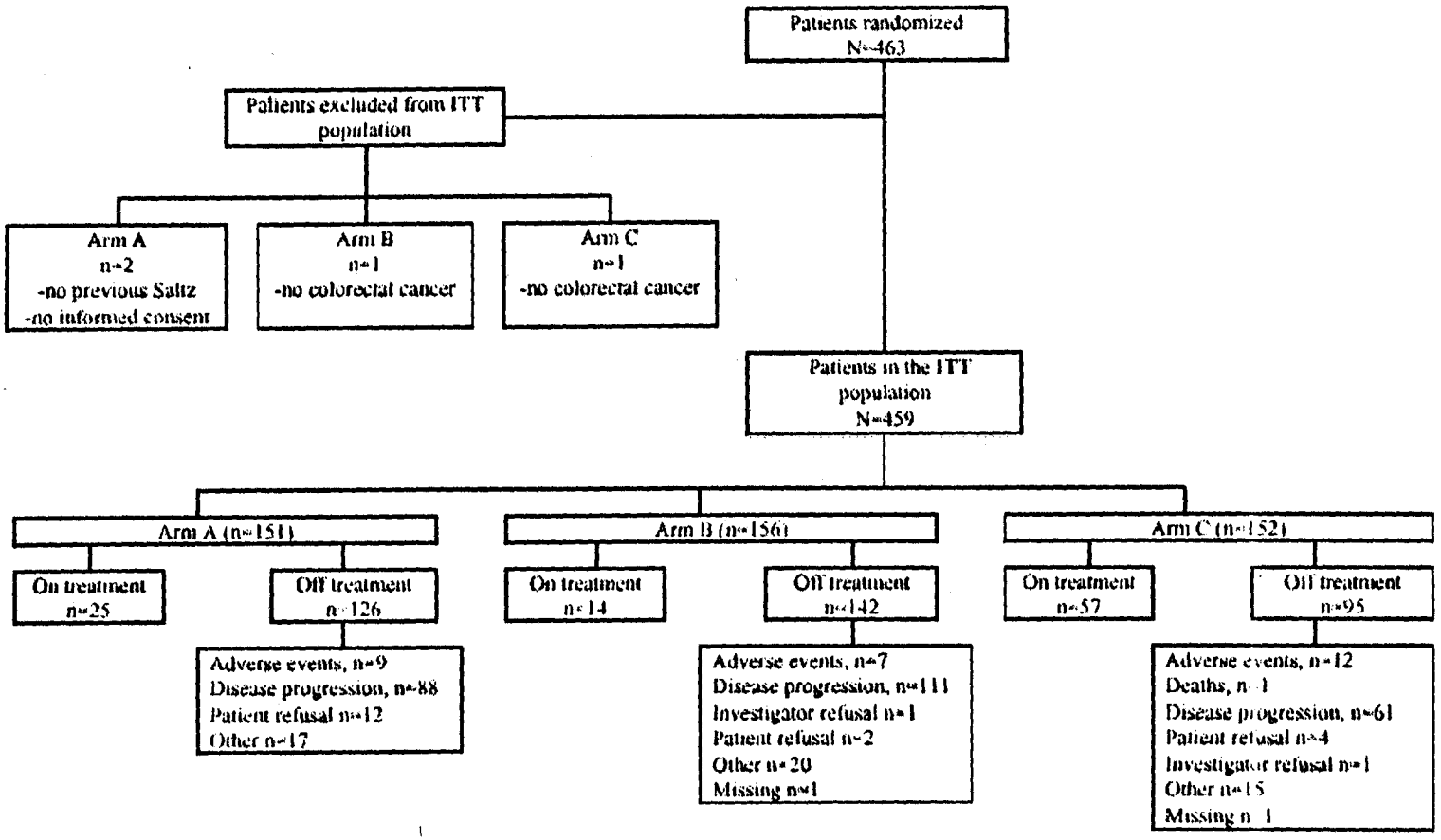
Applicant Table (8.9.1) 1 of Study Report

	Arm A	Arm B	Arm C	Total
No. randomized	153	157	153	463
No. not treated	11	4	3	18
No. receiving any study drug	142	153	150	445
No. in intent to treat population	151	156	152	459
No. in safety population	142	153	150	445

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

Figure 3: Summary of Patient Disposition for Response Rate Analysis

Applicant Figure (8.9.1) of Study Report



Eighteen patients who were randomized, were not treated. The reasons are listed below in Tables 14 and 15. Most of the patients who were randomized and not treated were randomized to the 5-FU/LV control arm (N=11), and most of those patients (7/11) refused therapy, presumably because they had hoped to be randomized to an oxaliplatin arm.

Table 14: Summary of Reasons Off Treatment

Number (%) of Patients Randomized but not Treated
Applicant Table (8.9.1) 2

Category	Arm A (N=11)	Arm B (N=4)	Arm C (N=3)
Death	0(0.0)	0(0.0)	0(0.0)
Adverse Events	1(9.1)	0(0.0)	1(33.3)
Disease Progression	0(0.0)	0(0.0)	0(0.0)
Investigator Refusal	0(0.0)	0(0.0)	0(0.0)
Patient Refusal	7(63.6)	1(25.0)	1(33.3)
Other -- Clinical Progression	3(27.3)	3(75.0)	1(33.3)
Still On Study	0(0.0)	0(0.0)	0(0.0)

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

Table 15: Reasons for not Treating Patients who were Randomized by Study Arm.

Applicant Table (8.9.1) 4 from Study Report

Randomized Treatment Arm	Patient ID	Reason	Comments
A	04584 C105 0002	Patient Refusal	Patient was randomized to 5 FU & leucovorin only. Patient withdrew consent since he did not receive oxaliplatin
	04584 C119 0002	Other	Did not enter study, patient did not consent
	04584 C119 0004	Patient Refusal	No reason given by patient for refusing treatment
	04584 C161 0002	Patient Refusal	Patient declined study drug & or clinical trial following randomization
	04584 C166 0002	Patient Refusal	Patient withdrew consent, she did not like the treatment she was randomized to
	04584 C166 0005	Patient Refusal	Patient withdrew consent
	04584 C166 0006	Patient Refusal	Patient refused secondary to treatment arm she was randomized to
	04584 C166 0007	Other	Patient's labs did not allow her to start treatment
	04584 C187 0003	Other	Patient misrandomized. Patient eligible for the EFC4585 protocol never received study medication
	04584 C199 0001	Adverse Event	GI hemorrhage after randomization and prior to study treatment
	04584 S101 0002	Patient Refusal	Patient refused because randomized to Arm A
B	04584 C155 0003	Other	Between eligibility and treatment visit, patient performance status declined to the point patient was no longer eligible to participate in the study
	04584 C157 0002	Other	After screening and prior to receiving study drug, the patient had clinical progression and was referred to hospice
	04584 C198 0008	Other	Declining performance status. Never treated with drug; canceled treatment (dehydration) SAE filed
	04584 S124 0001	Patient Refusal	Did not like arm he was randomized to
C	04584 C112 0009	Patient Refusal	Decreased PS made patient unable to participate; withdrew from study
	04584 C133 0005	Adverse Event	Myocardial infarction after randomization and prior to study treatment
	04584 0154 0004	Other	Patient never started the treatment due to rising bilirubin. The patient was taken off study

Protocol Violations:

There were several violations of the inclusion and exclusion criteria that are listed below in Table 16. The results of this applicant table were verified by the FDA reviewer.

Table 16: Inclusion/Exclusion Criteria Deviations (%)

Applicant table (8.9.2.2) 1 from study report

Type	Description	Arm A	Arm B	Arm C
Inclusion	A. Carcinoma of the appendix	0 (0.0)	2 (1.3)[a]	1 (0.7)
Inclusion	D. Pregnancy test not done	1 (0.7)	2 (1.3)	1 (0.7)
Inclusion	E. Signed written informed consent not obtained prior to study entry	1 (0.7)	0 (0.0)	0 (0.0)
Inclusion	F. Major surgical procedure (s) within 4 weeks of randomization..	0 (0.0)	1 (0.6)	0 (0.0)
Inclusion	H. Uni-dimensionally measurable lesion with a diameter ≤20 mm using conventional CT or MRI scans or ≤10 mm using spiral CT scans.	0 (0.0)	1 (0.6)	0 (0.0)
Inclusion	I. More than 1 prior chemotherapeutic regimen for metastatic disease	6 (3.9)	10 (6.4)	7 (4.6)
Inclusion	J. Documented PD either during or more than 6 months after the last dose of Irinotecan + 5-FU/LV using the Saltz regimen given in the first-line metastatic setting.	2 (1.3)	2 (1.3)	3 (2.0)
Inclusion	K. Prior radiotherapy administered to target lesions identified for this study without documented progression within the radiation portal.	1 (0.7)	1 (0.6)	0 (0.0)
Inclusion	L. Previous chemotherapy for metastatic disease less than 3 weeks prior to randomization.	2 (1.3)	2 (1.3)	0 (0.0)
Inclusion	N. Total bilirubin ≥1.5 x the institution's ULN	0 (0.0)	3 (1.9)	0 (0.0)
Inclusion	O. SGOT/AST and SGPT/ALT ≥2 x ULN, unless liver metastases are present and documented at baseline by CT or MRI scan (≥5 x ULN in that case)	1 (0.7)	0 (0.0)	0 (0.0)
Inclusion	P. Alkaline phosphatase, ≥2 x ULN unless liver metastases are present and documented at baseline by CT or MRI scan (≥5 x ULN in that case)	3 (2.0)	3 (1.9)	3 (2.0)
Inclusion	P.1 Alkaline phosphatase, ≥2 x ULN unless liver metastases are present and documented at baseline by CT or MRI scan (≥5 x ULN in that case)	3 (2.0)	1 (0.6)	0 (0.0)
Inclusion	R. Platelet count ≤100 x 10^9/L	0 (0.0)	1 (0.6)	0 (0.0)
Exclusion	A. Received any investigational drug within 30 days before beginning treatment with study drug	1 (0.7)	1 (0.6)	0 (0.0)
Exclusion	B. Concomitant treatment with other investigational agents	0 (0.0)	1 (0.6)	0 (0.0)
Exclusion	C. Chemotherapeutic agents other than Irinotecan + 5-FU/LV as part of first-line therapy for advanced metastatic disease	1 (0.7)	3 (1.9)	2 (1.3)
Exclusion	D. Irinotecan as part of adjuvant therapy	0 (0.0)	0 (0.0)	1 (0.7)
Exclusion	I. Concurrent active cancer originating from a primary site other than colon or rectum	0 (0.0)	0 (0.0)	1 (0.7)
Exclusion	J. Known peripheral neuropathy. Absence of DTRs as the sole neurologic abnormality does not render the patient ineligible	1 (0.7)	2 (1.3)	1 (0.7)

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

a One patient was indicated as not having histologically- or cytologically-proven adenocarcinoma of the colon or rectum in the inclusion/exclusion criteria panel at randomization. However, further review of the pathology by the investigational site confirmed the diagnosis of cecal carcinoma.

Reviewer's comments:
Of the inclusion and exclusion criteria deviations, the ones most serious are incorrect histological diagnosis, no signed informed consent, more than one prior chemotherapeutic regimen for metastatic disease and chemotherapeutic agents other than those in Saltz regimen as part of first-line regimen. The number of these deviations is similar across the 3 arms and would not be expected to affect the overall results.

Protocol-defined deviations:
Major Deviations were defined as receipt of any anticancer agent other than the allocated treatment, 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.

Major deviations
Major deviations were pre-specified in the original protocol. (see Section 6.3.9). The applicant's analysis of major deviations is shown below in Table 17, and is identical to the FDA analysis. The numbers below in the applicant's analysis are based on all the randomized population, and changed little for the ITT population as defined for the primary efficacy analysis by the applicant. Four patients were excluded, as discussed earlier in this section who either did not have colon cancer, written informed consent, or prior treatment with the Saltz regimen. The population on which the FDA based its Major Deviation analysis presented in the FDA table below (total N in each column heading differs from applicant table based on these 4 patients).

The major deviations in the study are given in table 17 (applicant's analysis) and table 18 (FDA analysis). Eighteen patients were not treated, as described earlier in this section and 5 patients had a delay of more than 30 days from baseline tumor assessment to date of randomization. Patients with these delays were distributed evenly across arms. One of these patients was classified as a responder in Arm C. The time interval between tumor evaluation and randomization for that patient was border-line at 31 days. Twenty-eight patients were less than 3 weeks from completion of first-line therapy to date of randomization. Three of these patients were classified as responders on Arm C. Progression of disease after first-line chemotherapy was confirmed for all of these 3 patients. The time interval between end of first-line therapy and start of the study drugs was 22 days, 25 days and 16 days for these patients.

Table 17: Major Deviations. (Applicant analysis)*

	Arm A N=153	Arm B N=157	Arm C N=153
Other anticancer therapy	3_a	0	5_b
Subject not treated	11	4	3
Delay of more than 30 days from baseline tumor assessment to randomization	2	1	1
Less than 3 weeks from last chemo treatment to randomization	11	8	11

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

$_a$: patients received leuprolide for prior prostate cancer, raloxifene and tamoxifen

$_b$: three patient received capecitabine post –study, and two were receiving raloxifene.

*Analysis was done on the randomized population

Table 18: Major Deviations (FDA analysis - ITT)

	Arm A N=151	Arm B N=156	Arm C N=152
Other anticancer therapy	3	0	5
Subject not treated	11	4	3
Delay of more than 30 days from baseline tumor assessment to randomization $_a$	2 (33d & 40d)	1 (35 d)	2 (31 & 36d)
Less than 3 weeks from last chemo treatment to randomization $_b$	10 (7-20d) median 17 d	7 (7-20d) median 18.5d	11 (12-20d) median 18d

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

$_a$ Three patients (0108 0002, 0126 0002, 9105 0001) who were responders on Arm C stopped first-line therapy between 12 to 16 days of randomization

$_b$ Data missing for 20 of 463 patients for time from end of first-line therapy to randomization.

Progression of disease after first-line chemotherapy was confirmed for all of the 3 patients who were responders and had received oxaliplatin/5-FU/LV (see footnote $_a$ above).

Reviewer's comment:
The number of patients with major deviations is small and equally distributed in all 3 arms. The specific agents that were identified as concomitant neoplastic therapy used during the study would not be expected to affect the tumor response in colon cancer because the drugs used are either hormonal therapy or, in patients who were treated with capecitabine, administered after the patient went off study. The latter would only be anticipated to impact TTP (if it had not yet been documented when the patient went off study) or survival. The major deviations would not change the study results.

Per applicant, analysis of minor deviations is as follows:

1- >26 cycles of study therapy: 0 patients
2- >10% above the maximum of 85 mg/m^2 oxaliplatin in any cycle: 0 patients
3- >10% above the maximum of 400 mg/m^2 5-FU in any bolus (>440 mg/m^2): 2 patients in Arm C. Neither patient had a response.
4- >10% above the maximum of 600 mg/m^2 5-FU in any continuous infusion: 0 patients
5- 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: 1 patient in Arm C
6- dose reduction or delay not according to protocol guidelines, study assessments not done according to schedule: not done

Population enrolled:

The applicant has submitted the analysis on the first 463 patients enrolled. All responders are within the first 450 patients randomized.

The baseline characteristics of the patients are presented in the tables below. Patients were divided equally in all arms, based on their characteristics. Median age ranged 59-61 years across the three arms. Most patients (62%) had a Karnofsky Performance Status (KPS) of 90% or greater.

The patients were stratified according to KPS, LDH and # of metastatic organ sites involved. The distribution of patients by stratification factors is shown in Table 19. They were similar across arms.

Table 19: Distribution of Patients by Stratification Factors

Factor	Arm A (N=151)	Arm B (N=156)	Arm C (N=152)	Total (N=459)
KPS				
70 - 100	143(94.7)	144(92.3)	145(95.4)	432(94.1)
50 - 60	4(2.6)	7(4.5)	3(2.0)	14(3.1)
Missing	4(2.6)	5(3.2)	4(2.6)	13(2.8)
Number Of Metastatic Organs Involved				
1	41(27.2)	49(31.4)	39(25.7)	129(28.1)
≥2	109(72.2)	106(67.9)	113(74.3)	328(71.5)
Missing	1(0.7)	1(0.6)	0(0.0)	2(0.4)
LDH				
≤1.5 X ULN	76(50.3)	76(48.7)	80(52.6)	232(50.5)
>1.5 X ULN	65(43.0)	71(45.5)	58(38.2)	194(42.3)
Missing	10(6.6)	9(5.8)	14(9.2)	33(7.2)

Applicant table (8.10.2.2) 2 from Study Report
Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin
(percentages appear in parentheses)

Table 20: Baseline Characteristics of the ITT Population

Applicant table (8.10.2.1) 1 from study report

Parameter		Arm A (N=151) N (%)	Arm B (N=156) N (%)	Arm C (N=152) N (%)
Age (Years)	N	151	156	152
	Mean	58.5	59.0	58.6
	Median	60.0	61.0	59.0
	St. Dev.	11.6	10.7	12.2
	Min	21.0	27.0	22.0
	Max	80.0	79.0	88.0
Age	<65	99(65.6)	105(67.3)	98(64.5)
	≥65	52(34.4)	51(32.7)	54(35.5)
Sex	Male	82(54.3)	95(60.9)	87(57.2)
	Female	69(45.7)	61(39.1)	65(42.8)
Race	Caucasian	132(87.4)	132(84.6)	135(88.8)
	Black	12(7.9)	11(7.1)	9(5.9)
	Oriental	2(1.3)	4(2.6)	4(2.6)
	Other	5(3.3)	9(5.8)	4(2.6)
KPS	100	45(29.8)	49(31.4)	48(31.6)
	90	40(26.5)	54(34.6)	50(32.9)
	80	37(24.5)	26(16.7)	27(17.8)
	70	21(13.9)	15(9.6)	20(13.2)
	60	4(2.6)	7(4.5)	2(1.3)
	50	0(0.0)	0(0.0)	1(0.7)
	<50	0(0.0)	0(0.0)	0(0.0)
	Missing	4(2.6)	5(3.2)	4(2.6)
Weight (kg)	N	143	151	148
	Mean	79.3	79.3	83.8
	Median	77.1	79.0	82.9
	St. Dev.	20.6	19.7	19.6
	Min	41.4	42.0	38.6
	Max	147.7	135.5	160.0
BSA (m^2)	N	143	151	149
	Mean	1.90	1.90	1.95
	Median	1.89	1.94	1.96
	St. Dev.	0.26	0.27	0.25
	Min			
	Max			

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

Prognostic Factors:
The major prognostic factors in metastatic colorectal carcinoma (MCRC) are age, months since initial diagnosis prior to first-line therapy, KPS, number of organs involved, CEA, LDH and alkaline phosphatase (ALP). Some articles in the literature also report hemoglobin and WBC as prognostic factors.

The age, KPS, ALP, months since initial diagnosis, number of organs involved in metastatic disease, and CEA were similar across the treatment arms and are presented in Tables 19-21.

Table 21: Description of Initial Diagnosis and Baseline Disease Status

Applicant Table (8.10.2.2) 1 of Study Report

Parameter		Arm A (N=151)	Arm B (N=156)	Arm C (N=152)
Initial Diagnosis				
Primary Site	Colon/Rectum	16(10.6)	16(10.3)	23(15.1)
	Colon	106(70.2)	110(70.5)	100(65.8)
	Rectum	29(19.2)	29(18.6)	29(19.1)
	Other	0(0.0)	0(0.0)	0(0.0)
	Missing	0(0.0)	1(0.6)[a]	0(0.0)
Months Since Initial Diagnosis	N	**151**	**155**	**151**[b]
	Mean	20.8	20.5	20.5
	Median	12.4	13.8	12.9
	St. Dev	20.0	19.1	18.8
	Min			
	Max			
Baseline Disease Status				
Number Of Involved Organs	1	41(27.2)	49(31.4)	39(25.7)
	2+	109(72.2)	106(67.9)	113(74.3)
	Missing	1(0.7)	1(0.6)	0(0.0)
Involved Organs	Liver Only	34(22.5)	40(25.6)	28(18.4)
	Liver + Other	91(60.3)	92(59.0)	81(53.3)
	Lung Only	3(2.0)	4(2.6)	6(3.9)
	Other Including Lymph Nodes	22(14.6)	19(12.2)	37(24.3)
	Missing	1(0.7)	1(0.6)	0(0.0)
CEA	≤10 Ng/Ml	33(21.9)	28(17.9)	33(21.7)
	>10 Ng/Ml	113(74.8)	126(80.8)	119(78.3)
	Missing	5(3.3)	2(1.3)	0(0.0)

Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin
'Months since initial diagnosis' refers to time since patient diagnosis prior to any treatment.

Baseline WBC Count and hemoglobin were well-balanced across the 3 arms.

Table 22: Baseline WBC

	Arm A	Arm B	Arm C
Missing	0	1	1
Range	[redacted]		
Mean	8.4	8.1	7.5
Median	7.9	7.5	7

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

Table 23: Baseline Hemoglobin

	Arm A	Arm B	Arm C
Missing	0	1	1
Range	[redacted]		
Mean	12.2	12.5	12.4
Median	12.3	12.4	12.4

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

Reviewer's Comments:
All evaluated prognostics factors, protocol-specified and otherwise, were generally well-balanced across the treatment arms. Best response to first-line chemotherapy could be considered to be a prognostic factor. Response rate to first-line chemotherapy was slightly higher in Arm C (see First-line therapies administered section below).

Adjuvant Therapy:

The applicant reported that 139 patients received prior adjuvant chemotherapy, as shown in Table 24. They were evenly distributed across the three arms. These numbers are similar to those determined by this reviewer through queries of the electronic database.

Table 24: Previous Anticancer Therapy (Excluding First-Line Treatment of Metastatic Disease)

Applicant Table (8.10.2.2) 3 from Study Report

Previous Therapy		Arm A (N=151)	Arm B (N=156)	Arm C (N=152)
Prior adjuvant chemo-therapy	Yes	43(28.5)	47(30.1)	49(32.2)
	No	108(71.5)	109(69.9)	103(67.8)
If yes:	Adjuvant Saltz	1(2.3)	4(8.5)[a]	1(2.0)
	5-FU	5(11.6)	3(6.4)	10(20.4)
	5-FU/LV	28(65.1)	31(66.0)	32(65.3)
	5-FU/LV + Other	7(16.3)	7(14.9)	6(12.2)
	Other	2(4.7)	2(4.3)	0(0.0)
Prior radiotherapy	Yes	38(25.2)	30(19.2)	38(25.0)
	No	113(74.8)	126(80.8)	114(75.0)
Prior pelvic radiation	Yes	28(18.5)	21(13.5)	32(21.1)
	No	123(81.5)	135(86.5)	120(78.9)
Prior surgery for colon/rectal cancer	Yes	146(96.7)	142(91.0)	140(92.1)
	No	5(3.3)	14(9.0)	12(7.9)

[a]: patient received Saltz regimen for adjuvant as well as first-line treatment.adjuvant
Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin

Table 25: Patients Who Received 5-FU Based Adjuvant Regimens – FDA Analysis

Treatment Arm		5-FU based regimens
A	N=151	40 (27%)
B	N=156	45 (29%)
C	N=152	48 (32%)

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

Given the information that the applicant identified 4 patients in the study (2 each on Arms A and B) who had received non-5-FU based adjuvant therapy, the FDA was able to identify all but two of the patients the applicant had identified as having been treated with adjuvant chemotherapy – 1 on Arm A and 1 on Arm C.

Reviewer's comment:
The number of patients who received any adjuvant therapy was similar across arms. One patient each on arm A and C, and 4 patients on Arm B had received prior adjuvant treatment with the 'Saltz' regimen. The small numbers of patients involved are not expected to affect the overall efficacy results.

First-line therapies administered

According to the original protocol, and an amendment, Saltz regimen doses were pre-defined. Only those patients who received a certain range of doses of irinotecan and 5-FU/LV, could be entered in to the study. However, for 100 patients in the study, no information was available on the doses of the prior first-line 'Saltz' regimen. Due to this missing data, this reviewer will not evaluate the number of patients who received the pre-defined Saltz regimen.

The applicant's analyses of relative distribution of duration of prior first-line therapy, best response to first-line therapy, and time intervals between stopping first-line therapy or documentation of PD on first-line therapy and study entry among the study arms are presented in Table 26.

Per Applicant:

"The patients enrolled in this trial were refractory/resistant to a first-line Saltz regimen as indicated by the fact that all patients had progressed during or within 6 months of completion of the Saltz regimen. Furthermore, 20% of the patients had progressed while on treatment with the Saltz regimen. For this analysis, 4 patients were excluded from the total number of patients randomized to constitute the pre-specified ITT population."

Reviewer comment:
From the electronic database, 8 patients were found who had progressed more than 6 months after completion of first-line therapy. See Table 28.

Table 26: Previous First-line Bolus 5-FU/LV + CPT-11 Weekly Regimen - ITT Population

Applicant table(8.10.2.2) 5 of Study Report

Parameter		Arm A (N=151)	Arm B (N=156)	Arm C (N=152)
Weeks since stop of first-line regimen	N	149[a]	152[b,c]	151
	Mean	10.3	9.7	9.1
	Median	7.4	6.6	5.7
	St. Dev	10.4	8.4	8.5
	Min			
	Max			
Duration (weeks) of first-line regimen	N	149	152	151
	Mean	28.2	31.3	27.7
	Median	25.1	29.4	26.1
	St. Dev	17.7	19.6	15.6
	Min			
	Max			
Weeks since progression on or following first-line regimen	N[e]	147	152	148
	Mean	6.3	6.1	5.5
	Median	4.4	3.7	3.3
	St. Dev	5.2	6.6	6.0
	Min			
	Max			
Response to first-line regimen	CR	3(2.0)	4(2.6)	4(2.6)
	PR	34(22.5)	44(28.2)	42(27.6)
	SD	80(53.0)	70(44.9)	74(48.7)
	PD	32(21.2)	34(21.8)	29(19.1)
	Unknown Not Evaluable	2(1.3)	4(2.6)	3(2.0)

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

a Patient 1990001 on Arm A had a missing date.

b Patient 1550003 withdrew from the study between eligibility and treatment visits due to a decline in performance status.

c Patient 1370007 received both adjuvant and first-line Saltz regimen.

d One patient received Saltz regimen, had a PR, and then received a second Saltz regimen

e The date of progression following first-line regimen was not reported for 4 patients in each arm.

Information on best response to prior to any treatment was available on 452 patients in the electronic datasets and is presented in Table 27. Patients on Arm B and C had a higher responses to first-line chemotherapy. The overall response rate (CR + PR) on each arm was 25% , 31% and 31% for Arm A, B and C, respectively. FDA analysis obtained similar results from the applicant's dataset.

Only three patients received first-line chemotherapy drugs other than those specified in the protocol. The drugs used were capecitabine and floxuridine. These 3 patients were evenly divided across the treatment arms. Of the patients who had a response in the current study, the prior best response to the first-line regimen is given in the table below. Most responders in the trial under review had either a SD or PD as the prior best response.

Table 27: Best response to first-line chemotherapy of patients with PR on current study

Prior Best Response	Arm B N=2	Arm C N=15
Complete response	1	0
Partial response	0	3
Progression disease	1	6
Stable disease	0	6

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

Reviewer's comment:
All patients had received the combination of 5-FU/LV and irinotecan. There is insufficient data to indicate that all patients received the 'Saltz' regimen. Since this study was conducted in USA and Canada, it is likely that the regimens used were what has been usually administered in clinical practice when combining 5-FU/LV with irinotecan.
Patients in Arms B and C had a slightly higher response to the first-line therapy, and may have had disease more responsive to chemotherapy. The results shown in Table 27 do not appear to be consistent with this theory.

Time from first-line treatment to randomization

Per protocol, patients could be enrolled in this study if they had progressed during first-line treatment or within 6 months of completing it. There were 8 patients who progressed after this time period (see table 28).

Table 28: Patients with PD more than 6 months after Completion of First-Line Chemotherapy

ARM	Patients	Range (months)	Median (months)
A N=151	3 (2%)		7.1
B N=156	1 (0.6%)		7.3
C N= 152	4 (2.6%)		7

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

Per sponsor there may have been a further 2 patients on Arm A who had PD documentation longer than 6 months after last chemotherapy. These data could not be verified due to lack of specific dates of disease progression. The FDA reviewer observed that based on the available month of progression, these patients progressed after 6 months of completion of therapy. These data could not be verified from the electronic dataset.

Reviewer's comments:
The number of patients enrolled who had PD more than 6 months after end of first-line chemotherapy is small and similar in Arm A and Arm C, and is not expected to impact the overall response rates. One patient (0167 0004) was classified as a responder by the independent reviewer, — but was not in the FDA's list of responders.

Response Rates
Evaluation by the independent review consulting group was the accepted prespecified analysis of the response endpoint. An independent company, — was hired for the independent review. The electronic data set included both the response analyses by the investigator and the independent reviewer.

Per Applicant:
"An independent radiologic review was carried out in a blinded fashion. The radiologic images of individual patients, (which included CT scans, MRIs, and chest X-rays) were randomly assigned to reviewers. The reviewers were also blinded to the designation of the target and nontarget lesions as assessed by the Investigator and, therefore, could have identified the same target and nontarget lesions, completely different lesions from the Investigator or both. This was done to ensure complete and unbiased radiologic review."

There were 3 CRs by the investigator analysis. However, there were no CRs in the — analysis. The reasons for the discrepancy between the investigator and — CRs are as follows: One patient (0102 0002) in Arm A, had non-measurable lesion per —. According to the inclusion criteria, only patients with measurable disease could have been enrolled. For the other 2 patients (1 each on Arms A and C), the target lesions chosen by the independent reviewer did not resolve completely.

There was no predefined time period for confirming/establishing SD submitted in the original protocol as required by the RECIST criteria. Due to the technical difficulty in distinguishing between a best response of SD and PD without criteria for how long the SD had to have been documented as sustained, the FDA review will report only CRs and PRs.

Copies of CT scans of patients who were responders by — criteria were reviewed by an FDA consultant radiologist, Dr. M. Dubrow, M.D.. This review was performed as an audit and to verify the responses. An attempt was made to identify and follow the target lesions used by — Dr.Dubrow concurred with all responders, except for 2 patients. Patient 0103-0003 was not considered evaluable for confirmation of response and patient 0167-0004 had progressive disease in the lungs.

Table 29: Response Rate Analysis by FDA

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%%
SD & PD	NA	NA	NA

Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin
NA: Not assessable.
* Only CR and PR are reported for the FDA review. Due to absence of definition of duration of SD for confirmation, further classification of responses could not be performed.

Table 30: Response Rates per Applicant*

Applicant table(8.10.3.1.2) 1 of Study Report

Response	Arm A (N=151)	Arm B (N=156)	Arm C (N=152)
Independent Assessment			
Response classification	n (%) (95% C.I.)	n (%) (95% C.I.)	n (%) (95% C.I.)
PR + CR	0 (0.0) (0.0 – 2.5)	2 (1.3) (0.1 – 4.6)	15 (9.9) (5.6 – 15.8)
CR + PR + SD	69 (45.7) (37.5 – 54.0)	63 (40.4) (32.6 – 48.6)	106 (69.7) (61.7 – 77.0)
	n (%)	n (%)	n (%)
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	0 (0.0)	2 (1.3)	15 (9.9)
SD	69 (45.7)	61 (39.1)	91 (59.9)
PD	52 (34.4)	70 (44.9)	21 (13.8)
NA	30 (19.9)	23 (14.7)	25 (16.4)
Investigator Assessment			
Response classification	n (%) (95% C.I.)	n (%) (95% C.I.)	n (%) (95% C.I.)
PR + CR	4 (2.6) (0.7 - 6.7)	5 (3.2) (1.0 – 7.4)	21 (13.8) (8.7 – 20.4)
CR + PR + SD	64 (42.4) (34.3 – 50.7)	62 (39.7) (32.0 – 47.9)	105 (69.1) (61.0 – 76.4)
	n (%)	n (%)	n (%)
CR	2 (1.3)	0 (0.0)	1 (0.7)
PR	2 (1.3)	5 (3.2)	20 (13.2)
SD	60 (39.7)	57 (36.5)	84 (55.3)
PD	60 (39.7)	77 (49.4)	34 (22.4)
CP	9 (6.0)	6 (3.8)	2 (1.3)
NA	18 (11.9)	11 (7.1)	11 (7.2)

* Analysis by the independent reviewer was the prespecified analysis
Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin
CP: Clinical progression
NA: Not assessable.

Time to Tumor Progression
Per Applicant:

"Statistical analysis of time-related parameters in this report was planned if more than 50% of the 459 intent-to treat patients had an event. This criterion was met for Investigator-assessed time to progression (TTP), for which 347 / 459 ITT patients (76%) had events. Although the number of progressors by independent radiological review was slightly less than 50% (225/459 = 49%), this parameter is also summarized in this report."

There were 222 patients who progressed on the three arms (Arm A: 74 patients, Arm B: 101 patients and Arm C: 50 patients). The time to tumor progression analysis performed by the FDA and the independent review were based on the measurements taken by independent review by [redacted] Only the radiological progression (target lesions, non-target lesions as well as appearance of new lesions) were taken in to account. For the investigator's evaluation reported by the applicant, death and clinical progression were counted as progression.

The median time to tumor progression in Arm A was improved by almost 2 months relative to that of Arm C in the FDA analysis and both of the applicant's analyses (Independent and Investigator assessed) with a p value of < 0.0001. The 95% C.I. was non-overlapping. However, as noted by the applicant, only 49% of the events have occurred in this analysis, which was limited to radiographic documentation of PD and did not take into account other clinical evidence of progression. Examination of the data set revealed that 82 (18%) of patients were excluded from the analysis by censoring them at time zero. Twenty-five of those censored 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 remainder had no radiographic assessment beyond baseline. Because of the significant number of patients excluded from the analysis, the analysis could not be considered a valid ITT analysis.

Table 31: FDA Summary of Time to Radiographic Progression*

Arm	A N=151	B N=156	C N=152
No. of Progressors	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.

Table 32: Applicant's Summary of Time to Progression

	Arm A (N=151)	Arm B (N=156)	Arm C (N=152)
Independent Review*			
Number of progressors	74	101	50
Median TTP (months)	2.7	1.6	4.6
(95% confidence limits)	(1.8-3.0)	(1.4-2.7)	(4.2-6.1)
Investigator Assessment**			
Number of progressors	118	140	89
Median TTP (months)	1.9	1.4	4.0
(95% confidence limits)	(1.5-2.7)	(1.4-2.0)	(3.2-4.5)

Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin
* Independent TTP events were limited to radiographic evidence of PD
** Investigator TTP events included radiographic evidence of PD, clinical evidence of PD, and death

Reviewer's comment:
Event numbers are higher for the investigator analysis of TTP because death and clinical progression without radiographic documentation of PD were counted as events in the investigators analysis. Inclusion of death as an event without requirement for documentation of disease progression is a disease free survival or progression free survival analysis. In an unblinded trial such as this, inclusion of clinical progression without radiographic documentation of PD opens the analysis of TTP to bias.

Table 33: Summary of Stratified Log-Rank Tests – Time to Progression

Applicant table (8.10.3.1.2)4 from Study Report

Comparison	Stratified Log-Rank P-value
Independent Review	
Primary: Arm A vs. C	< 0.0001
Secondary: Arm A vs. B	0.03
Conditional: Arm C vs. B	Not applicable[a]
Investigator Assessment	
Primary: Arm A vs. C	< 0.0001
Secondary: Arm A vs. B	0.03
Conditional: Arm C vs. B	Not applicable[a]

[a] Per Statistical Analysis Plan, the conditional analysis was not required.

* Independent TTP events were limited to radiographic evidence of PD (18% of patients were excluded from this analysis).

** Investigator TTP events included radiographic evidence of PD, clinical evidence of PD, and death

Figure 4: Kaplan Meier Curve for Time to Progression: Independent Reviewer's Analysis (based on radiographic evidence of disease progression; and with 82 patients excluded from the analysis)

Applicant figure(8.10.3.1.2)1 from Study Report

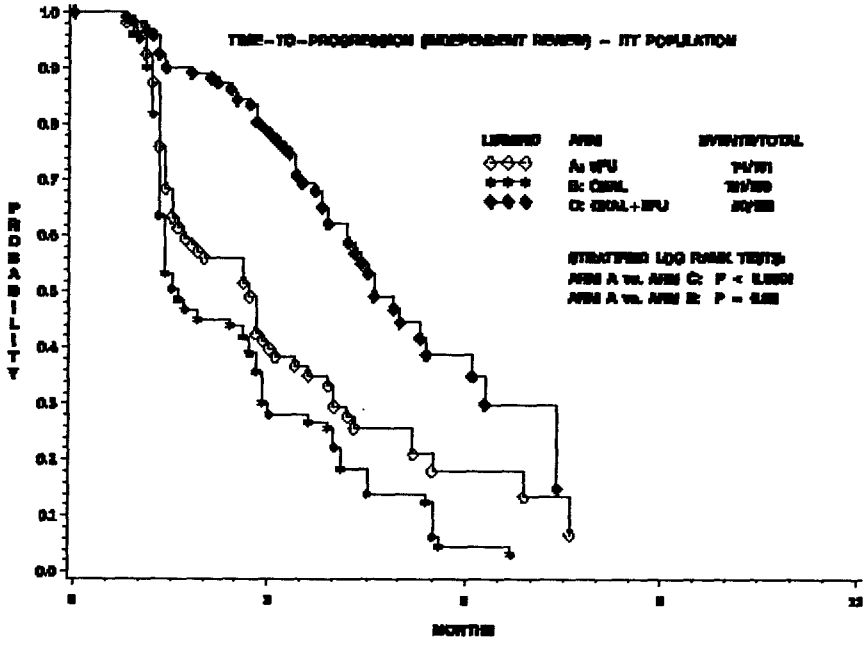
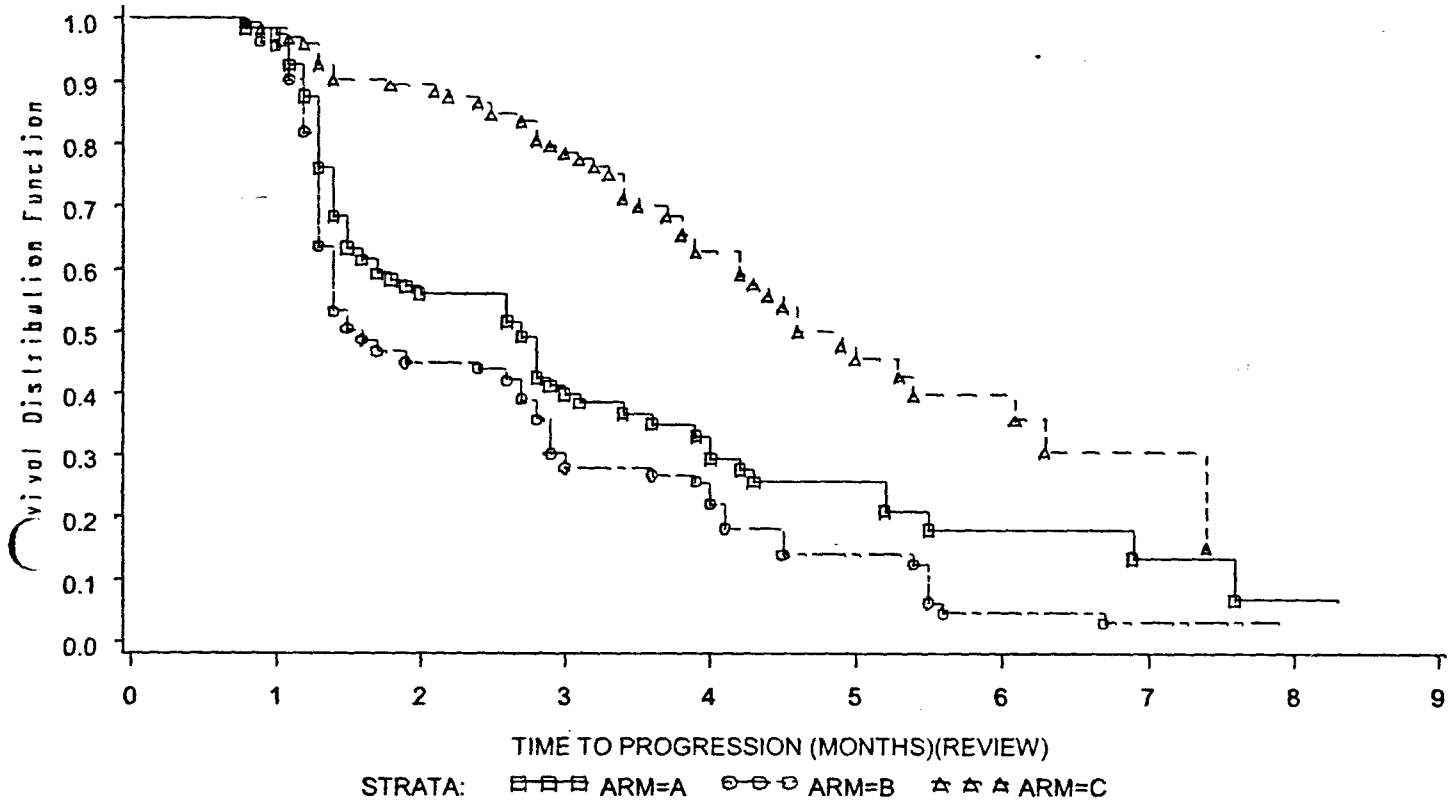


Figure 5: Kaplan Meier Curve for Time to Progression – FDA Analysis

(based on radiographic evidence of disease progression and with 82 patients excluded from the analysis)



Exploratory analysis of Time to Progression

Investigator evaluations were available for several of the patients who were censored at time zero by the independent reviewer, that is, no radiological films were available beyond baseline. A summary of these evaluations by treatment arm is given in the table 34 below. In this exploratory analysis, patients who had PD or SD by the investigator analysis were not censored. Patients who did not have any radiology studies beyond baseline were censored at time zero. These include patients who were either "not evaluable" or were "clinical progressors". The reason for taking 5 patients off-study was 'clinical progression and/(serious adverse event)'. It is not clear whether it was toxicity or actual clinical progression noted in these patients. This lack of differentiation was confirmed during discussions with the applicant. MCRC does not tend to metastasize to areas easily measurable with out radiological assistance, such as subcutaneous nodules.

Table 34: Investigator evaluations for patients without radiological films beyond baseline based on independent review

	Arm A (N=29)	Arm B (N=24)	Arm C (N=29)
PD	7	5	9
SD	0	2	2
CP	4	6	4
NA	18	11	14

Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin
PD: Progressive disease,
SD: Stable disease,
CP: Clinical progression,
NA: Not evaluable

Table 35: Applicant comments[a] for patients without radiological films beyond baseline based on the *independent* review

Reason	Arm A (N=29)	Arm B (N=24)	Arm C (N=29)
Patient refused treatment (prior to 2nd radiological evaluation)	9	2	4
Serious AE (prior to 2nd radiological evaluation)*	6	4	8
Clinical progression (prior to 2nd radiological evaluation)*	5	7	5
CT scans not sent to independent reviewer	3	5	6
Documented PD (prior to 2nd radiological evaluation at 6 weeks)	2	1	2
Problems with randomization. Patient not treated.	2	3	1
Date of PD missing	1	2	1
Non-measurable disease per independent review	0	0	1
Pt transfer to other site	1	0	0
Quality control issues	0	0	1

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

[a] Comments were added by the applicant based on the review of investigator and independent reviewer data, and not directly from the CRFs.

*Patients who had a serious AE and clinical progression were included in the subset of patient taken off study due to AE prior to 2nd radiological evaluation.

Table 36: Applicant comments[a] for patients without radiological films beyond baseline based on the *investigator* review

(exploratory analysis)

Reason	Arm A (N=21)	Arm B (N=17)	Arm C (N=19)
Serious AE prior to 2nd radiological evaluation	5	4	7
Clinical progression prior to 2nd radiological evaluation	5	6	5
Patient refusal	7	2	4
Problems with randomization. Patient not treated.	2	3	1
Date of PD missing	1	2	1
Pt transfer to other site	1	0	0
Quality control issues	0	0	1

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

[a] Comments were added by the applicant based on the review of investigator and independent reviewer data, and not directly from the CRFs.

Twelve percent patients had no radiological evaluation beyond baseline by this exploratory analysis. The Time to Tumor Progression (TTP) improved from 2.6 months to 4.5 months in this exploratory analysis, a difference of 1.9 months. The statistical significance was maintained at this interim analysis. See table below.

Table 37: Time to Progression based on independent reviewer and investigator data

(exploratory analysis)

	Arm A (N=151)	Arm B (N=156)	Arm C (N=152)
Number of progressors	84	109	59
Missing films beyond baseline	22 (15%)	16 (10%)	17 (11%)
Median TTP (months)	2.6	1.5	4.5
(95% confidence limits)	(1.7, 2.9)	(1.4, 2.4)	(3.9, 5.4)

Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin
Log-rank "p" value for comparison of Arm A vs. Arm C: less than 0.0001
Log-rank "p" value for comparison of Arm B vs. Arm C: less than 0.0001
Log-rank "p" value for comparison of Arm A vs. Arm B: less than 0.023

Reviewer comment:
The improvement in TTP is the same as in the prespecified analysis (i.e. by approximately 2 months). This exploratory analysis supports the pre-defined analysis.

Other Secondary Endpoints:

Time to Symptomatic Worsening (TTSW) was the primary predefined analysis of clinical benefit assessment. However, at the time of analysis, only 26% of events had occurred, making these data too immature to analyze. For this reason, there was no statistical analysis of the preliminary TTSW data provided by the applicant in the table below.

Table 38: Summary of Patients who Experienced Symptomatic Worsening by Category

Per Applicant

Worsened for:	Arm A N=151(%)	Arm B N=156(%)	Arm C N=152(%)
KPS	12 (7.9)	17 (10.9)	15 (9.9)
Pain	14 (9.3)	21 (13.5)	12 (7.9)
Analgesic Consumption	26 (17.2)	23 (14.7)	17 (11.2)
Composite*	44 (29.1)	49 (31.4)	35 (23.0)

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

* composite: a patient is a responder if:

1. None of the parameters (KPS, pain, or analgesic consumption) is worsened, and
2. At least 1 of the 3 is improved, and the others are stable or better.

OR

1. All of the parameters (KPS, pain, and analgesic consumption) are stable, and
2. Body weight is improved.

The applicant also presented a secondary analysis of proportion of those patients who were symptomatic at baseline (as defined for KPS, pain, analgesic use, and weight in Section 6.3.9) who improved on study as defined by the applicant in the statistical analysis plan (Section 6.3.9). These data are presented in the table below.

Table 39: Clinical Benefit Assessment (Improvement)

Applicant table (11.2.2)7 submitted electronically during review

Category	No. Symptomatic at Baseline (Arm A)	No. Responders (%) (Arm A)	No. Symptomatic at Baseline (Arm B)	No. Responders (%) (Arm B)	No. Symptomatic at Baseline (Arm C)	No. Responders (%) (Arm C)
KPS	83	2 (2.4)	74	3 (4.1)	65	5 (7.7)
Pain	50	7 (14.0)	58	9 (15.5)	47	19 (40.4)
Analgesic Usage	36	5 (13.9)	38	4 (10.5)	37	14 (37.8)
Weight	35	2 (5.7)	30	1 (3.3)	25	3 (12.0)
Composite	101	12 (11.9)	100	12 (12.0)	95	31 (32.6)

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

P-value for composite (Chi-Square Test) Arm A vs. Arm C: P <0.001 Arm A vs. Arm B: P = 0.98

When evaluating improvement, a patient had to be symptomatic at baseline. When analyzing pain, analgesic use needs to be to evaluated as well, and vice versa, since they both impact the same endpoint of improvement in pain in a patient. For details on the Statistical Analysis Plan of clinical benefit assessment, please see Sections 6.3.7 and 6.3.9.

Reviewer's comments:
Proportion of patients with a 'clinical benefit' improvement was a predefined secondary analysis of a secondary endpoint. These analyses are based on data that are fraught with problems that could affect their validity.
Examples of these problems are as follows:

a- Algorithm for pain scores and analgesic use was not described in detail,

b- Definition of reduction in pain or analgesic use is arbitrary, particularly when dealing with percentages, as in definition for improvement in analgesic consumption. The differences in absolute numbers that are associated with percentages can be too small to be meaningful.

c- It would not be unexpected for pain to worsen until chemotherapy has had its effect. The question arises as to whether there should be a time period, and if so, how long that period should be, after the initiation of treatment during which an initial worsening of pain followed by an improvement would be ignored and not counted as worsening of pain.

d- KPS values were recorded by patients and physicians and were discordant with each other (see Table 41). Since this is an open-label study, evaluations of KPS may be affected by a physician's or patient's bias.

e- Weight of a patient can be affected by medicines or changes in fluid balance such as development of edema or ascites.

Pain:
Applicant evaluation of pain is illustrated in Table 39. Stricter criteria have been used in some other studies when evaluating pain. Patients who had a baseline score of at least 4 cm. out of a possible 10 cm. on a visual scale were evaluated by the FDA. Responders were patients who had a decrease in pain by 50% sustained over at least 4 weeks, without any accompanying increase in analgesic requirement or evidence of PD during that time. The results of this analysis is given in Table 40.

Table 40: Reduction in Pain in Patients with a Baseline Score of 4 cms – FDA Analysis.

	Arm A N (%)	Arm B N (%)	Arm C N (%)
Pain score of at least 4 at baseline	32	34	31
Pain improved by 50%	2 (6.3%)	4 (11.8%)	11 (35.5%)

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

Analgesic use:

When evaluated as defined in the protocol, patients with a baseline requirement of 10 mg of morphine equivalents were considered symptomatic. A 7-day moving average was taken at day 1 and 15 of each cycle. Patients with a sustained decrease of 50% over 4 weeks, without increased pain or evidence of PD during this time, were termed responders. The FDA was informed that the applicant identified inconsistencies in their dataset. The results submitted by the applicant are presented in table 39. FDA did not verify these results because of the questionable validity of the analysis, since the algorithm was not described in detail in the original protocol.

KPS:

Per protocol, the lower value of the physician vs. the patient assigned KPS was to be used in analyses of symptom worsening/improvement. This prespecified analysis is presented in the applicant Table 39. There were physician-patient differences in KPS scores for 282 patients shown in the table below (Arm A: 80 patients, Arm B: 91 patients, Arm C: 110 patients). Since this was an unblinded study, a bias could be present when assigning a KPS score. Patients tended to give themselves lower KPS scores.

There is a difference in absolute values associated with visits in Table 41 across the different arms because the median number of cycles on Arm A and Arm B was 3, and for Arm C was 6 cycles. The percentages were similar in the 3 arms.

Table 41: Differences in KPS Score per Visit between Patient and Physician Assigned KPS

	Arm A	Arm B	Arm C
Median # of cycles	3	3	6
Patients with missing KPS scores	32	42	52
Number of Patients whose KPS Scores Differed from Physician Assigned KPS Scores	80	91	110
Number of Visits with KPS Score Concurrence between Patient and Physician	256 (56%)	277 (58%)	381 (52%)
Number of Visits with Patient Assigning a Lower KPS Score	132 (29%)	130 (27%)	204 (28%)
Number of Visits with Physician Assigning a Lower KPS Score	70 (15%	74 (15%)	141 (19%)

Arm A = 5-FU/LV; Arm B = oxaliplatin; Arm C = oxaliplatin + 5FU/LV

The FDA analysis of KPS according to the patient evaluation is illustrated in Table 42. The analysis by the physician KPS assessment is provided in Table 43. The numbers of patients with improvement are small in all treatment arms in both analyses.

Table 42: FDA Analysis of Improved KPS Score Based on Patient Assigned KPS

Treatment arm	Patients symptomatic at baseline as defined by KPS Score*	Symptomatic improvement defined by KPS score
A	72	4 (5.5%)
B	69	3 (4.3%)
C	56	5 (8.9%)

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

* Symptomatic was defined as KPS ≤80 as evaluated by the patient

Table 43: FDA Analysis of Improved KPS Score Based on Physician Assigned KPS

Treatment arm	Patients symptomatic at baseline as defined by KPS Score*	Symptomatic improvement defined by KPS score
A	61	1 (1.6%)
B	46	3 (6.5%)
C	48	3 (6.2%)

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

* Symptomatic was defined as KPS ≤80 as evaluated by the physician

As pointed out earlier, the validity of each component of clinical benefit assessment is questionable, as is the composite score derived from them (see statistical analysis section 6.2.9)

Reviewer's comment:
Due to the concerns regarding the validity described in the previous comment and in the discussion of the analyses presented above, analysis of proportion of patients with symptom improvement can only be considered exploratory. It should not be included in the product labeling.

6.4 Efficacy Conclusions:

EFC 4584 is a well-designed, well-conducted phase 3 trial that enrolled a refractory patient population with metastatic colorectal cancer that had progressed after first-line therapy with a combination regimen of irinotecan and bolus 5-FU with leucovorin. These patients have no further effective treatment options.

A small but statistically significant improvement of tumor response rate was observed in the combination arm of oxaliplatin, infusional 5-FU and leucovorin. An analysis of radiographic time to progression (TTP), with approximately 50% of events, revealed that TTP was prolonged on the combination arm. This analysis excluded 82 patients (18%) because either the radiographic evaluation was not performed, or the independent reviewer did not receive them or the radiographs were not considered evaluable by the independent radiologist. However, an exploratory analysis was performed, borrowing additional data from the investigator measurements, when present. This exploratory analysis supports the improvement in TTP.

Data from two randomized, controlled trials that studied the combination of oxaliplatin, 5-FU and leucovorin in first-line treatment of colorectal carcinoma have been previously reviewed by the agency. In one study, the 5-FU/LV was administered as a chronomodulated infusion, in a different dose and schedule from that investigated in the major study reviewed in this NDA. The second study used a regimen identical to the one administered in the study reviewed, EFC4584. These two first-line studies demonstrated improvements in RR and PFS for patients with advanced metastatic colorectal carcinoma in comparisons to 5FU/LV. These trials, which were submitted for review in a previous NDA, support the improvement in response rates and the radiographic TTP (evaluable patient analysis, non-ITT) observed in EFC4584, the major study presented in this NDA.

7 Integrated Review of Safety

7.1 Brief Statement of Conclusions (Applicant and FDA)

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. 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 Arm C patients (6%). 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. For every cycle a different population of patients had an event 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.

There are inadequate data to determine if dose adjustment, dose delay, or increasing infusional time are useful to decrease or abrogate neurotoxicity. Absent effective interventions or prophylaxis, the most practical approach will be anticipatory guidance of health care professionals and patients with avoidance of 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.

7.2 Description of Patient Exposure

Table 44 summarizes the number of treatment cycles administered. As indicated, patients in Arm C (5-FU/LV/oxaliplatin) received a median of 6 cycles of treatment, whereas patients in Arms B (oxaliplatin alone) and C (5-FU/LV alone) received a median of 3 cycles. The maximum number of cycles administered per patient ranged between 16 cycles (Arm A and Arm C) and 18 cycles (Arm B).

Table 44: Number of Treatment Cycles Administered (FDA Analysis)

Parameter		Arm A (N=142)	Arm B (N=153)	Arm C (N=150)
Number of cycles administered	Median	3	3	6
	Min			
	Max			
Number of cycles administered, grouped	1-3	76(53.5)	79(51.6)	37(24.7)
	4-6	29(20.4)	39(25.5)	44(29.3)
	7-9	20(14.1)	19(12.4)	42(28.0)
	10-12	10(7.0)	10(6.5)	18(12.0)
	13-18	7(4.9)	6(3.9)	9(6.0)
	>18	0(0.0)	0(0.0)	00.0
	Numbers in parentheses are the proportions of patients per arm that were administered the corresponding range of cycles as the maximum number of cycles on study			

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

Tables 45 and 46 summarize the extent of exposure for 5-FU and oxaliplatin, respectively. The total cumulative dose (mg/m^2) was calculated as the sum of the actual dose administered in all cycles while the patient was on study. The duration of dosing (weeks) was calculated as the [(start date of last cycle) - (start date of first cycle) + 14]/7. The dose intensity (mg/m^2 /week) was calculated as the (total cumulative dose) / (duration of dosing). The relative dose intensity (RDI) (%) was calculated as 100 x (dose intensity)/(planned dose intensity). The planned dose intensities, expressed as mg/m^2 /week, are 1000 for 5-FU, 42.5 for oxaliplatin, and 200 for LV. The extent of exposure for leucovorin was similar in Arm A and Arm C.

As indicated in **Tables 45 and 46** treatment was reasonably well tolerated. Patients in Arm A (5-FU/LV alone) received a median of 99.0% of the protocol specified 5-FU dose intensity and patients in Arm C (5-FU/LV and oxaliplatin) received 88.8% of the projected 5-FU dose intensity. Similarly, patients in Arm B (oxaliplatin alone) and Arm C received a median of 99.6 and 87.8% of the protocol specified oxaliplatin dose intensity, respectively.

Table 45: Extent of 5-FU Exposure in 5-FU Treated Patients (Applicant Analysis)

		Arm A* (N=142)	Arm C (N=150)
Total cumulative dose (mg/m2)	N	142	149
	Mean	9995	12616
	Median	6017	12000
	St. Dev.	6973	6832
	Min		
	Max		
Duration of dosing (weeks)	N	142	149
	Mean	10.7	15.0
	Median	6.9	15.0
	St. Dev.	7.7	8.1
	Min		
	Max		
Dose intensity (mg/m2/week)	N	142	149
	Mean	952.2	863.8
	Median	990.1	888.1
	St. Dev.	79.3	130.4
	Min		
	Max		
Relative dose intensity (%)	N	142	149
	Mean	95.2	86.4
	Median	99.0	88.8
	St. Dev.	7.9	13.0
	Min		
	Max		

Arm A = 5-FU/LV; Arm C = 5FU/LV/oxaliplatin

Table 46: Extent of Exposure to Oxaliplatin (Applicant Analysis)

		Arm B* (N=153)	Arm C (N=150)
Total cumulative dose (mg/m2)	N	153	149
	Mean	431.6	539.1
	Median	255.8	510.0
	St. Dev.	286.2	276.0
	Min	[redacted]	
	Max		
Duration of dosing (weeks)	N	153	149
	Mean	10.5	15.1
	Median	6.9	15.0
	St. Dev.	6.9	7.8
	Min	[redacted]	
	Max		
Dose intensity (mg/m2/week)	N	153	149
	Mean	41.1	36.6
	Median	42.3	37.3
	St. Dev.	3.0	5.5
	Min	[redacted]	
	Max		
Relative dose intensity (%)	N	153	149
	Mean	96.7	86.2
	Median	99.6	87.8
	St. Dev.	7.0	12.9
	Min	[redacted]	
	Max		

Arm B = oxaliplatin; Arm C = 5-FU/LV/oxaliplatin

Table 47 summarizes treatment delays and dose reductions by patient. Per protocol, only 1 dose reduction was permitted and if a patient required a second dose reduction, the patient was taken off the study. Only 5 patients who underwent 1 dose reduction were taken off the study because of adverse events. More patients on Arm C (5-FU/LV and oxaliplatin) experienced delays than the other arms. Additionally, more dose reductions occurred on Arm C than the other arms. Four patients in Arm C and 1 patient in Arm B (oxaliplatin alone) had 1 dose reduction for oxaliplatin and were subsequently taken off study for a second adverse event.

Three of 43 patients in Arm C had oxaliplatin discontinued due to paresthesias between Cycles 9 and 13 and 1 patient in Arm C had oxaliplatin discontinued due to an allergic reaction. However, these patients continued to be treated with 5-FU/LV on study. Four patients in Arm C had 5-FU discontinued, yet continued treatment with oxaliplatin on study - 1 each for allergic reaction, hiccups, angina, and paresthesia. Per protocol, one patient on Arm C switched from an every 2-week to an every 3-week regimen after 6 months of treatment. Overall, 20 patients (13%)on Arm C had adverse events that led to discontinuation of treatment on study, compared to 18% on Arm A and 14% on Arm B.

There is a discrepancy between the applicant and the FDA in **Table 47** regarding the reason(s) for treatment delay in Arm C patients. In both analyses adverse events were the most common reason for treatment delay (90 patients in the applicant's analysis versus 82 patients in the FDA analysis). The category of "Other" included 1 patient in the applicant's analysis and 8 patients in the FDA analysis. The applicant accepted the FDA analysis.

Table 47: Summary of Treatment Delays, Dose Reductions and Reasons for Delay/Reduction by Patient (FDA Analysis)

Parameter	Arm A	Arm B	Arm C
Number of treated patients	142	153	150
Number of patients who could have a delay (dosed more than 1 Cycle)	130	148	145
Number of patients with at least 1 delay (>4 Days)	38(29.2)	22(14.9)	97(56.6)
Reasons for delay (number of patients) *			
Adverse Event	22(16.9)	14(9.5)	82(62.1)
Personal Convenience (PC)	11(8.5)	3(2.0)	7(4.8)
Other	5(3.8)	5(3.4)	8(5.6)
Number of patients with at least 1 cycle of 5-FU administered at a reduced dose ($\leq$ 330 mg/m^2 Bolus or $\leq$550 mg/m^2 Infusion)	12(9.2)	N/A	49(33.8)
Number of patients with at least 1 cycle of oxaliplatin administered at a reduced dose ($\leq$ 71.5 mg/m^2)	N/A	6 (4.1)	43(29.7)

* If a patient had more than 1 reason for delay the following rule was applied: If 1 of their reasons was AE they were classified as AE. If they had PC and Other they were classified as PC.
Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin

7.3 Methods and Specific Findings of Safety Review

Safety data for Study EFC4584 were found in 3 datasets; NSAE, SAE, and TOX. Often these datasets had to be combined to determine the total number of patients having a specific adverse event. In addition, the date of onset of the adverse event had to be compared to the date of randomization to assure that the date of onset of the AE was later than the date of randomization. Laboratory abnormalities were found in the "labhema" and "labchem" datasets. Hospitalizations and deaths were reported in the SAE dataset.

Safety data for the supporting studies EFC2961, EFC2962, EFC2964, and EFC2917 were found in the ISS data base, specifically in data sets AEA, TOX 17, TOX 61, TOX 62, and TOX 64. Laboratory abnormalities were included in the appropriate CLABA dataset and hematology abnormalities were found in the appropriate HLABA dataset. Deaths were found in the DEATHA dataset

7.3.1 Summary of Adverse Events

Adverse events (AEs), by decreasing order of frequency in Arm C (5-FU/LV and oxaliplatin), and with a frequency of $\geq$ 5%, are summarized in **Table 48**. Almost all patients

had at least 1 adverse event (AE). **Table 48** includes all AEs reported in the NSAE, SAE, and Tox databases. In addition, AEs that were present prior to randomization or that only occurred more than 30 days after completion of treatment (cycle 999) were subtracted. AEs and toxicities (worst grade by patient $\geq$ 5%) by decreasing order of frequency in Arm C are summarized by preferred term and grade. Sensory neuropathy occurred in 74.0% of patients in Arm C, 77.1% of patients in Arm B, and 16.2% of patients in Arm A. The FDA's analyses are presented in the table below. There were minor differences between the FDA and applicant's findings, usually higher in the FDA analysis, but only by differences of 1-2%, and these usually occurred in the "All Grades" category in the two control arms. In the combination oxaliplatin arm, the FDA's differences were limited to 1% incremental changes in the "All Grades" categories for hand foot syndrome, peripheral edema, and abdominal pain. The FDA agreed to accept the applicant's findings in product labeling.

Table 48: Adverse Events with an Incidence ≥ 5% Summary (FDA Analysis)

Adverse Event	Arm A (N=142) 5-FU/LV		Arm B (N=153) Oxaliplatin		Arm C (N=150) 5-FU/LV/Oxaliplatin	
	All Grades No. (%)	Grade 3,4	All Grades No. (%)	Grade 3,4	All Grades No. (%)	Grade 3,4
Any Event	139(97.9)	58(40.8)	153(100.0)	71(46.4)	148(98.7)	109(72.7)
Paresthesia	23(16.2)	0(0.0)	118(77.1)	6(3.9)	111(74.0)	7(4.7)
Fatigue	77(54.2)	11(7.7)	96(62.7)	13(8.5)	102(68.0)	10(6.7)
Diarrhea	62(43.7)	4(2.8)	71(46.4)	6(3.9)	100(66.7)	17(11.3)
Nausea	84(59.2)	6(4.2)	98(64.1)	6(3.9)	97(64.7)	16(10.7)
Sensory Disturbance	4(2.8)	0(0.0)	88(57.5)	10(6.5)	79(52.7)	5(3.3)
Vomiting	39(27.5)	5 (3.5)	57(37.3)	6(3.9)	60(40.0)	13(8.7)
Stomatitis	45 (31.7)	4(2.8)	21 (13.7)	0(0.0)	56(37.3)	4(2.7)
Abdominal Pain	46(32.4)	8(5.6)	51(33.3)	10(6.5)	49(32.)	6(4.0)
Constipation	33(23.2)	1(0.7)	49(32.0)	3(2.0)	48(32.0)	1(0.7)
Fever	32(22.5)	2(1.4)	38(24.8)	1(0.7)	44(29.3)	2(1.3)
Anorexia	33(23.2)	4(2.8)	32(20.9)	3(2.0)	44 (29.3)	5 (3.3)
Dyspnea	16(11.3)	3(2.1)	20 (13.1)	10(6.5)	30(20.0)	6(4.0)
Back Pain	22(15.5)	7(5.0)	19(12.4)	1(0.7)	29(19.3)	4(2.7)
Coughing	14(9.9)	0(0.0)	18(11.8)	0(0.0)	28(18.7)	2(1.3)
Headache	12 (8.5)	1 (0.7)	20(13.1)	0(0.0)	25(16.7)	0(0.0)
Rhinitis	6(4.2)	0(0.0)	9(5.9)	0(0.0)	22(14.7)	0(0.0)
Pain	12(8.5)	4(2.8)	21(13.7)	5(3.3)	23(15.3)	3 (2.0)

(continued)

Table 48 - Adverse Events Summary - continued (FDA)

Adverse Event	Arm A (N=142)		Arm B (N=153)		Arm C (N=150)	
	All Grades	Grade 3,4	All Grades	Grade 3,4	All Grades	Grade 3,4
Dyspepsia	14(9.9)	0(0.0)	11(7.2)	0(0.0)	21(14.0)	0(0.0)
Taste Perversion	2(1.4)	0(0.0)	7(4.6)	0(0.0)	21(14.0)	0(0.0)
Dizziness	11(7.7)	0(0.0)	11(7.2)	1 (0.7)	19(12.7)	1(0.7)
Skin Exfoliation (Hand-foot)	18(12.7)	1(0.7)	1(0.7)	0(0.0)	16(12.7)	0(0.0)
Flushing	4 (2.8)	0(0.0)	4(2.6)	0(0.0)	15(10.0)	0(0.0)
Injection Site Reaction	7(4.9)	1(0.7)	20(13.1)	0(0.0)	15(10.0)	4(2.7)
Edema Peripheral	16(11.3)	1(0.7)	9(5.9)	1(0.7)	16(10.7)	1(0.7)
Allergic Reaction	1(0.7)	0(0.0)	5(3.3)	0(0.0)	15(10.0)	1(0.7)
Arthralgia	17(12.0)	4(2.8)	11(7.2)	0(0.0)	15(10.0)	0(0.0)
Upper Resp Tract Infection	6(4.2)	0(0.0)	10(6.5)	0(0.0)	15(10.0)	0(0.0)
Pharyngitis	14(9.9)	0(0.0)	3(2.0)	0(0.0)	14(9.3)	0(0.0)
Rash	7(4.9)	0(0.0)	7(4.6)	0(0.0)	14(9.3)	0(0.0)
Insomnia	6(4.2)	0(0.0)	17(11.1)	1(0.7)	13(8.7)	0(0.0)
Epistaxis	2(1.4)	0(0.0)	3(2.0)	0(0.0)	13(8.7)	0(0.0)
Dehydration	8(5.6)	6(4.2)	8(5.2)	5(3.3)	12(8.0)	5(3.3)
Chest Pain	5(3.5)	1(0.7)	7(4.6)	1(0.7)	12(8.0)	2(1.3)
Mucositis NOS	14(9.9)	2(1.4)	4(2.6)	0(0.0)	11(7.3)	1 (0.7)
Alopecia	4(2.8)	0(0.0)	4(2.6)	1(0.7)	11(7.3)	0(0.0)
Lacrimation Abnormal	8(5.6)	0(0.0)	2(1.3)	0(0.0)	11(7.3)	0(0.0)
Rigors	9(6.3)	0(0.0)	15(9.8)	0(0.0)	10(6.7)	0(0.0)
Hematuria	5(3.5)	2(1.4)	0(0.0)	0(0.0)	9(6.0)	1(0.7)
Febrile Neutropenia	1(0.7)	1(0.7)	0(0.0)	0(0.0)	9(6.0)	9(6.0)
Dysuria	1(0.7)	0(0.0)	2(1.3)	0(0.0)	9(6.0)	1(0.7)
Hiccup	0(0.0)	0(0.0)	3(2.0)	1(0.7)	8(5.3)	1(0.7)
Flatulence	9(6.3)	0(0.0)	4(2.6)	0(0.0)	8(5.3)	0(0.0)
Gastroesophageal Reflux	5(3.5)	0(0.0)	2(1.3)	0(0.0)	8(5.3)	3(2.0)
Thrombophlebitis Deep	2(1.4)	2 (1.4)	2(1.3)	1(0.7)	8(5.3)	7(4.7)

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

7.3.2 Hematology Adverse Events

A summary of hematologic laboratory abnormalities on study by grade and by patient is presented in **Table 49**. The incidence of hematologic abnormalities for each parameter, was higher in Arm C (5-FU/LV/Oxaliplatin) compared with Arm A (5-FU/LV) and Arm B (Oxaliplatin). Considering Grade 3,4 toxicities, all abnormal hemoglobin values were Grade 3 except for a single patient with Grade 4 anemia (# 186004) in Arm B. White blood cell abnormalities were all Grade 3 except for 2 patients (# 150004 and # 91040001) in Arm C who had Grade 4 leukopenia. Grade 3 neutropenia was noted in 40 Arm C patients and Grade 4 neutropenia was found in 26 patients. Corresponding results for Arm A were 5 patients with Grade 3 and 2 patients with Grade 4 neutropenia. Grade 4 thrombocytopenia occurred in 1 patient (# 1560005) in Arm B. All of the otherpatients that fell into the Grade 3/4 thrombocytopenia category had Grade 3 thrombocytopenia. The overall incidence of febrile neutropenia was 6% on Arm C and 1% on Arm A.

Table 49: Hematologic Laboratory Abnormalities (FDA Analysis)

	Arm A (N=142)*		Arm B (N=153)		Arm C N=150)	
Hematology Parameter	All Grades	Grade 3,4	All Grades	Grade 3,4	All Grades	Grade 3,4
Hemoglobin	101(71.1)**	4(2.8)	98(64.1)	3(2.0)	122(81.3)	4(2.7)
White Blood Cell Count	48(33.8)	2(1.4)	20(13.1)	0(0.0)	114(76.0)	29(19.3)
Neutrophils	37(26.1)	7(4.9)	10(6.5)	0(0.0)	110(73.3)	66(44.0)
Platelet Count	28(19.7)	0(0.0)	46(30.1)	4(2.6)	96(64.0)	9(6.0)

* Arm A = 5FU/LV; Arm B = oxaliplatin ; Arm C = 5-FU/LV/oxaliplatin

** Number (%) of Patients

There were minor differences between the FDA and applicant's findings, usually higher in the FDA analysis, but only by differences of 1%, and these usually occurred in the 5-FU/LV control arm. In the combination oxaliplatin regimen arm, the FDA's differences were limited to 1% incremental changes in the "Grade 3/4" categories for anemia and thrombocytopenia. The FDA agreed to accept the applicant's findings in product labeling.

7.3.3 Chemistry Adverse Events

Clinical chemistry abnormalities are summarized in **Table 50**. All ALT abnormalities listed in the Grade 3,4 columns were Grade 3. All AST abnormalities listed in the Grade 3,4 columns were Grade 3 except for 1 Arm B (oxaliplatin) patient who had a Grade 4 abnormality. Bilirubin abnormalities for Arm A (5-FU/LV) patients were 7 Grade 3 and 2 Grade 4. Corresponding numbers for Arm B were 4 and 3 and for Arm C (5-FU/LV/ Oxaliplatin), 1 and 1, respectively. All of the Grade 3,4 elevations of serum creatinine were Grade 4.

Table 50: Laboratory Abnormalities (FDA Analysis)

Laboratory abnormalities	Arm A* (N = 142)		Arm B (N = 153)		Arm C (N = 150)	
	All Grades	Grade 3,4	All Grades	Grade 3,4	All Grades	Grade 3,4
ALT (SGPT)	43(30.3)**	5(3.5)	58(37.9)	3(2.0)	48(32.0)	0(0.0)
AST (SGOT)	60(42.3)	5(3.5)	87(56.9)	8(5.2)	71(47.3)	1(0.7)
Total Bilirubin	32(22.5)	9(6.3)	20(13.1)	7(4.6)	19(12.7)	2(1.3)
Creatinine	16(11.3)	0(0.0)	15(9.8)	1(0.7)	18(12.0)	2(1.3)

* Arm A = 5-FU/LV; Arm B = oxaliplatin; Arm C = 5-FU/LV/oxaliplatin

**Number (%) of Treated Patients

There were minor differences between the FDA and applicant's findings, higher in the FDA analysis, but only by a differences of 1-3%, and these usually occurred in the two control arms. In the combination oxaliplatin arm, the FDA's differences were limited to 1% incremental changes in the "All Grades" category for ALT and the "Grade 3/4" category for AST. The FDA agreed to accept the applicant's findings in product labeling.

7.3.4 Neurological Adverse Events

Exposure to heavy metals such as lead, arsenic, or platinum in most animal species leads to toxicity, particularly of cells that are metabolically active and have a relatively high mitochondrial content. Examples of tissues that are metabolically active are nerve, kidney, cardiac muscle, and many types of malignancies. Arsenic and platinum containing compounds are approved for human use and include arsenic trioxide, carboplatin, and cisplatin. These products all contain warnings and precautions in the package insert regarding use. Cisplatin contains warnings for nephrotoxicity, ototoxicity, irreversible parasthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation. Carboplatin contains warnings for peripheral neuropathy, loss of vision, and adverse events of peripheral neuropathy, ototoxicity, sensory side effects, and central neurotoxicity. Arsenic trioxide contains warnings for electrocardiogram abnormalities with conduction changes

Oxaliplatin has been studied for the last decade and multiple publications document neurotoxicity such as paraesthesias, dysesthesias, laryngospasm, pain, temporal mandibular joint spasm, loss of proprioception, ataxia and other infrequent complications such as bladder problems and Lhermitte's sign (painful spinal sensations upon neck turning). Many of the neurologic events are either triggered or exacerbated by exposure to cold temperature, objects, or liquids. Attempts to mitigate the neurotoxicity through dose delay, dose reduction, increasing the infusion time or the use of analgesics, anticonvulsants, or other pharmacologic interventions have not been demonstrated to be successful.

The most common descriptors of the oxaliplatin neurotoxicity have been an acute event that is cold sensitive and a progressive and persistent event characterized by paraesthesia or dysesthesia in the distal extremities and loss of proprioception that is dependent upon cumulative oxaliplatin exposure.