Efficacy

Table 38. Efficacy Evaluations and Protocol Specified Statistical Analyses, Study

ENDPOINT	DEFINITION/TEST	STATISTICAL ANALYSIS
Survival	•from date of randomization to death	• analysis on intent-to-treat population • Kaplan-Meier estimates • stratified by study center and PS • other prognostic factors to be studied retrospectively
Quality of Life	•comparison of PS •weight change •EORTC QLQ-C30	• statistical analysis plan to be filed before the database is finalized

[a]age, performance status, visceral; involvement, number of metastatic sites, intent of and response to prior chemotherapy

Reviewer's comment: *The following retrospective evaluations were included in the final study report:*

1. *Stratified logrank analysis and stepwise Cox modeling of other prognostic factors such as sex, weight loss 3 months before baseline, hepatic metastases at inclusion, site of colorectal cancer, hematologic and serum biochemical parameters at baseline such as CEA*
2. *Best response to previous 5-FU treatment in patients having received a palliative treatment, prior bolus/non prior bolus 5-FU regimen*
3. *White blood cell counts, hemoglobin, platelets , for biochemical parameters at baseline and percent of the upper normal range*
4. *For the clinical benefit parameters, WHO performance status and weight evolution were compared.*

Survival

The study cut-off date for data analysis was initially assigned on March 3, 1997; at which time approximately 183 patients (number of deaths required to demonstrate a significant difference in one-year survival rates) have already died. The study was closed on July 14, 1997.

Reviewer's comment: Survival Analysis if Sponsor vs. FDA

The sponsor's analysis of survival in the final study report was based on the study close date of 7/14/98.

Reviewer's comments: Censoring

The most common reason for censoring was patients being alive by the cut-off date. There were 44 (34%) and 32 (25%) living patients in Arms A and B, respectively. Two patients in Arm A and five patients in Arm B were lost to follow-up.

Review of electronic data showed the additional results:

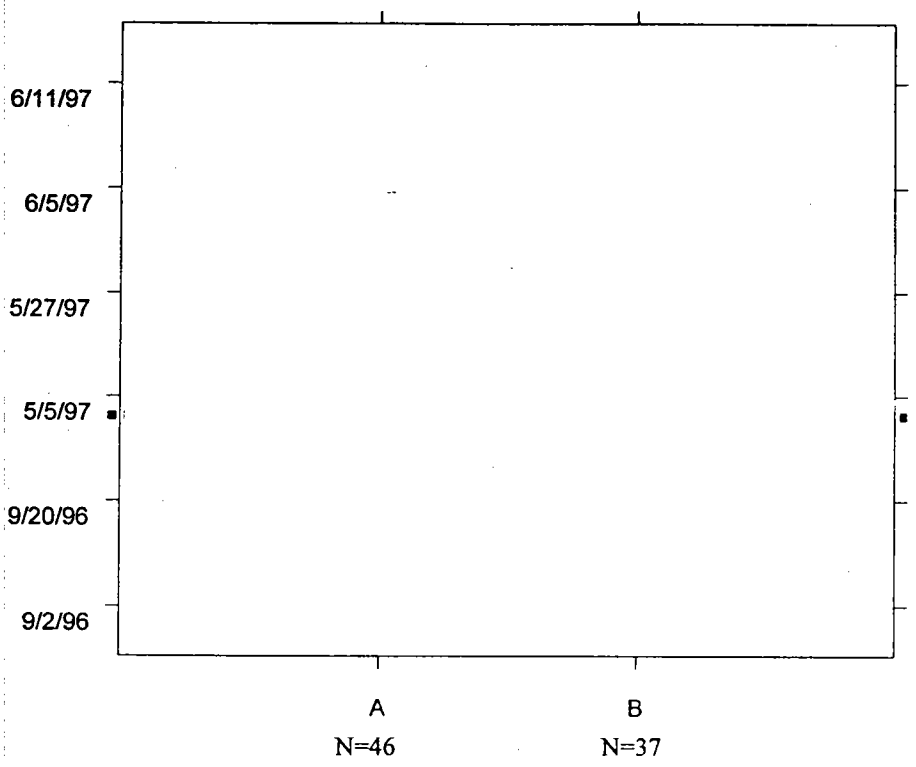
Table 39. FDA Summary Table of Censoring Dates for Survival

Treatment Arm	*Arm A*		*Arm B*	
	N	*%*	*N*	*%*
Number of Patients	*133*	*100*	*134*	*100*
Dead by cut-off date (3/5/97)	*87*	*65*	*97*	*72*
Censored	*46*	*34*	*37*	*28*
• *Before 3/5/97*	*2*	*2*	*5*	*4*
• *On 3/5/97*	*44*	*33*	*32*	*24*
- *Still alive on 7/14/97*	*33*	*25*	*27*	*20*

A total of 87 (65%) patients in Arm A and 97(72%) patients in Arm B were dead while the rest were censored for survival on the cut-off date. A majority of the patients in both Arms who were censored for survival on 3/5/97 were still alive on the last follow-up on 7/14/97 (more than four months after censoring!).

The following box and whisker graph shows the interquartile range (shaded areas) of patients censored in both arms to be 3-4 months beyond the assigned censor date. On last follow-up (7/14/97), 25% and 20% of the patients in Arms A and B, respectively were still alive.

Figure 10. FDA Analysis: Box and Whisker Plot for Censoring

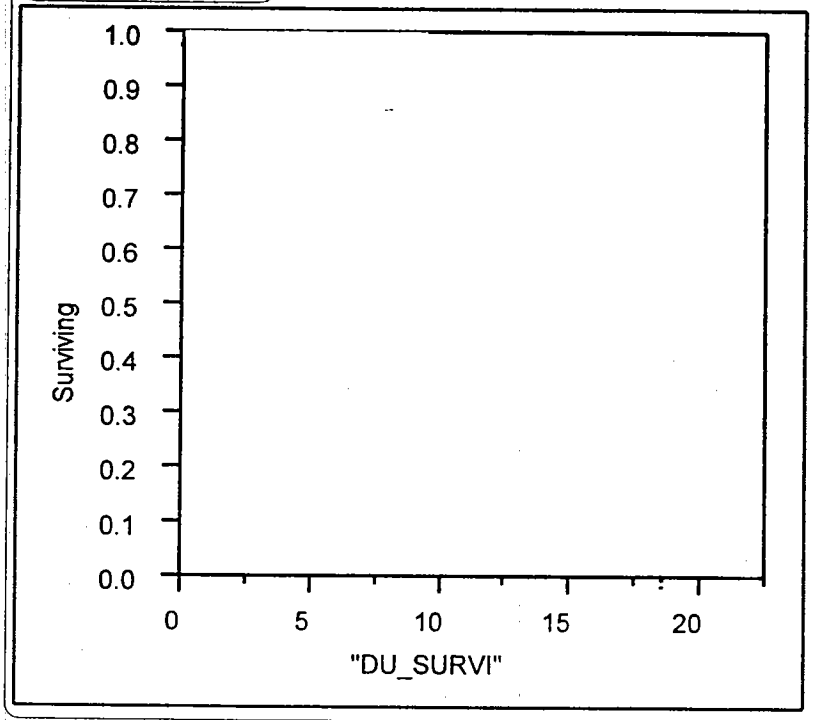


This graph also shows that patients in both arms were followed consistently and similarly for a significant duration of time. The assignment of the censor dates may have placed patients in Arm A at a disadvantage compared to Arm B since there were numerically more patients in Arm A who were alive on 3/5/97. This is reflected in the FDA reviewer's Kaplan-Meier survival curves, which showed less significant differences in survival between the two arms, compared to the sponsor's analysis, which used a later cut-off date.

Figure 11. FDA Reviewer's Survival Curves (3/5/97 Cut-off Date), (A= CPT-11 +BSC Arm; B=BEST 5-FU Arm Arm)

ensoring Variable: "JMP"

Survival Plot



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	3.6485	1	0.0561
Wilcoxon	3.5544	1	0.0594

Table 40. Sponsor vs. FDA Reviewer's Survival Analysis

	SPONSOR		*FDA*	
	Arm A (N=127)	Arm B (N=129)	*Arm A (N=127)*	*Arm B (N=129)*
Cut-off/Censor Date	7/14/97		*3/5/97*	
Median Survival (months)	10.8	8.5	*10.25*	*8.38*
Range				
p-value (log-rank)	0.03		*0.056*	

More complete follow-up of patients who were initially censored at the cut-off date was invaluable in showing a statistically significant difference in survival in favor of Arm A.

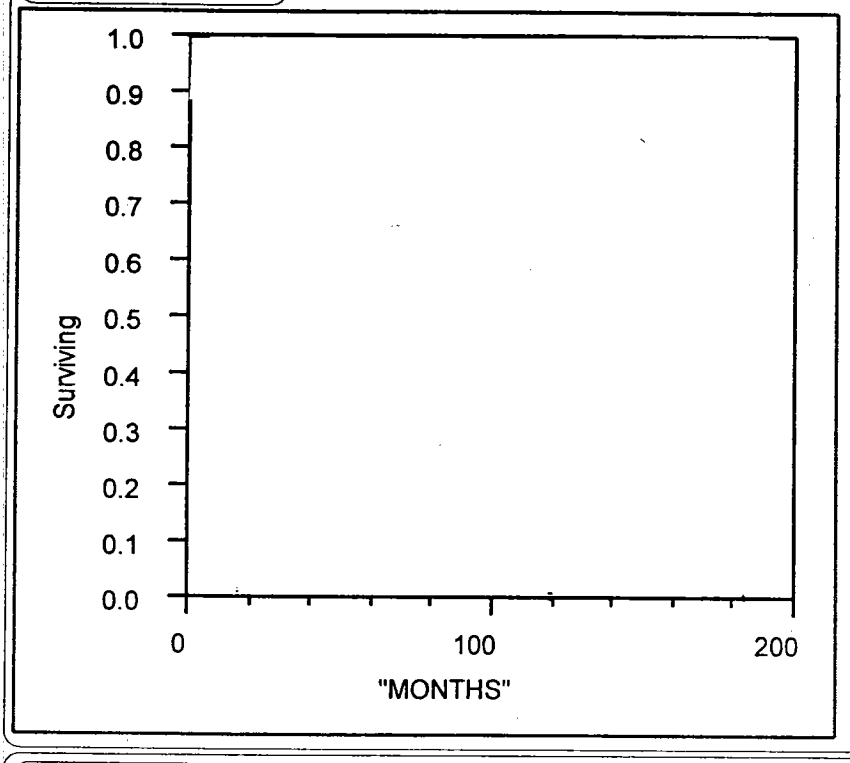
According to the sponsor, the likelihood of being alive at 6, 9, and 12 months is increased by 78%, 63% and 49% in the CPT-11 compared to 65%, 47%, and 32% in the 5-FU arm. This is equivalent to a 1.4x increase in one year survival.

Reviewer's comment: *As noted in Table 36, the median time from diagnosis to randomization of patients in Arm A was similar (19.3 months) to patients in Arm B (17 months). Median survival was calculated from the time of diagnosis of colorectal cancer. An unadjusted analysis showed a significant difference in survival in favor of patients in Arm A (p=0.008) with a median survival of 33.8 months (28.682, 36.567) and 26.6 months for Arm B (21.585, 31.573).*

Figure 12. FDA Analysis of Survival from Date of Diagnosis

ensoring Variable: "jmp"

Survival Plot



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	4.4435	1	0.0350
Wilcoxon	3.7318	1	0.0534

Table 41. FDA Analysis of Survival from Date of Diagnosis

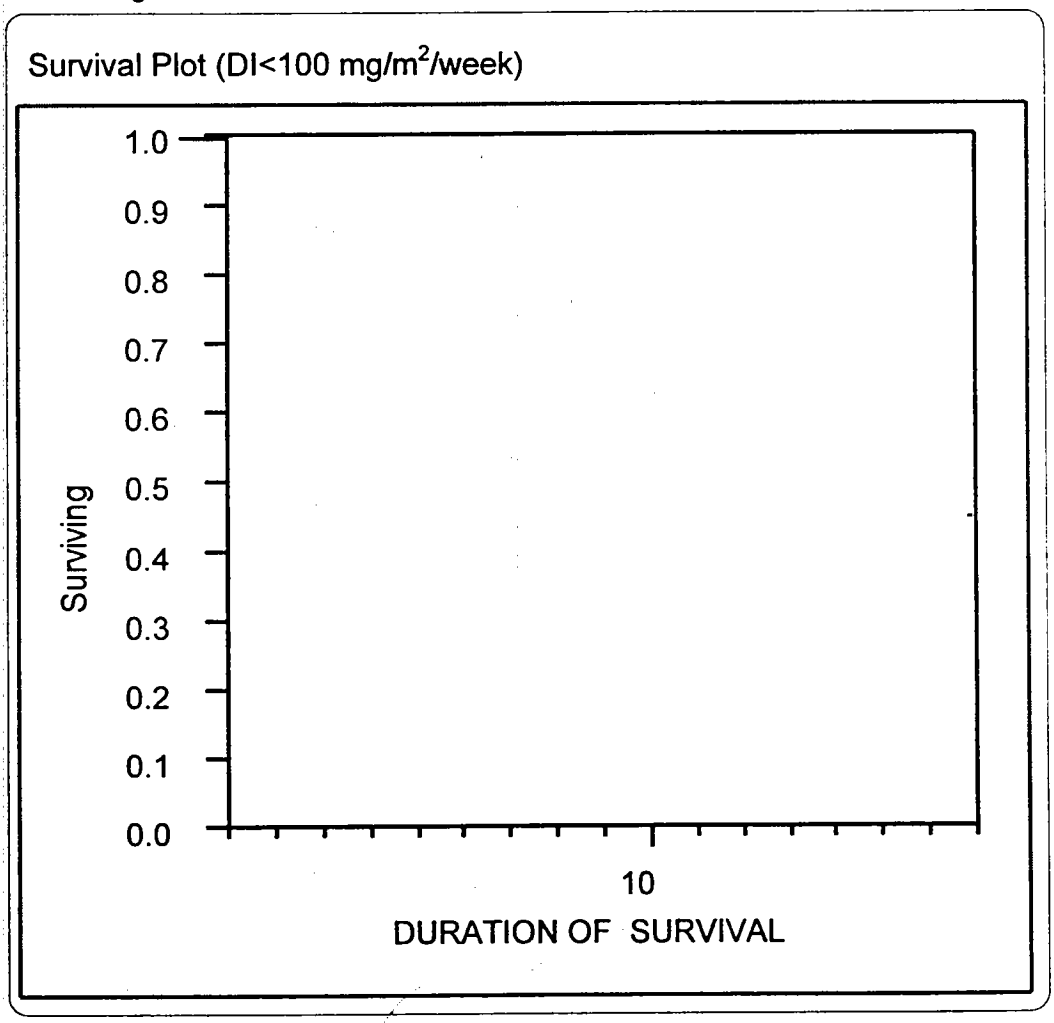
	Arm A (N=127)	*Arm B (N=129)*
Cut-off/Censor Date	*3/5/97*	
Median time from diagnosis to randomization (months)	*15.7*	*15.4*
Median Survival (months)	*32.9*	*27.4*
Range	*4.46-120.3*	*6.36-183.8*
p-value (log-rank)	*0.035*	

***Reviewer's comment**: Case report forms for monitoring subsequent therapies were available for study (chemotherapy, radiotherapy and surgery); but the data were not included in the NDA submission. Data listings on concomitant therapies showed that 9 patients received radiation therapy (3 patients in Arm A And 6 patients in Arm B). Nineteen patients (11 patients in Arm A and 8 patients in Arm B) received heparin or low molecular weight derivatives such as fraxiparin and fragmin (may have an effect on survival?). Because of the small number and equal distribution between the treatment arms, their effect on survival was probably insignificant.*

Reviewer's comment: *The following survival curves were plotted from JMP for patients in study who received a total dose intensity of ≤100 mg/m^2/week (N=45 patients). The median survival is 11.6 months (range 1.51-16.99). This indicates that dose adjustments for DLT, age >70 and PS =2 probably do not worsen the survival of patients treated with CPT-11.*

Figure 13. FDA Analysis: Survival Curve for Patients treated with a Lower Dose Intensity of CPT-11

Censoring Variable: "JMP"



Clinical Benefit

Clinical Benefit was also analyzed retrospectively in study There was no statistically significant differences between the following treatment arms: (1) Symptom-free survival (p=0.23), (2) Pain-free survival (p=0.0586), (3) Survival without PS deterioration (p=0.18), (4) Survival without weight loss >5% over baseline(p=0.23).

Quality of Life

According to the sponsor's review, there were no significant differences in terms of either functional or symptoms scores between the two arms in surviving patients. Diarrhea and nausea and vomiting were higher in the CPT-11 arm.

Table 42. Sponsor's Analysis of QOL with Significant Results

Change from Baseline	p-value (favored arm)	Worst Score	p-value (favored arm)
Cognitive Function	0.001 (B)	Nausea/vomiting	0.007 (B)
Nausea/Vomiting	0.001 (B)	Diarrhea	0.030 (B)
Diarrhea	0.009 (B)	Financial Impact	0.045 (B)

The FDA statistical reviewer analyzed three subscales and found a significant difference favoring the CPT-11 among the dropouts (p<0.001) and completers (<0.001). There was no difference with regard to pain, nausea and vomiting.

Safety

A descriptive analysis of adverse events was performed on the randomized population for both treatment arms according to the NCI common toxicity criteria. There were 91 serious adverse events reported in 52 patients in Arm A and 77 in 53 patients in Arm B. In Arm A, 28 of the 91(31%) were assessed by investigators as probably related to CPT-11; while it was only 8 of the 77 (10%) in Arm B.

The following table shows the frequency of **Grade 3 and 4** adverse events in the study as reported by the sponsor (rounded to the nearest whole number). Except for hematologic toxicities, only Grade 3+4 toxicities with an incidence of >5% are shown; and those where there is a significant difference between the treatment arms are in bold font. Cutaneous toxicity of 5-FU reported as "Hand and Foot Syndrome" and "other cutaneous signs" has only been reported in Arm B.

Table 43. Sponsor's Summary of Grade 3 and 4 Toxicity

	ARM A (N=127) (N/%)			ARM B (N=129) (N/%)		
	Gr 3	Gr 4	Gr3/4	Gr3	Gr4	Gr3/4
Anemia	2(2)		2(2)	1(0.8)		1(0.8)
Leukopenia/neutropenia	**8(6)**	**8(6)**	**16(13)**	1(1)	2(2)	3(2)
Thrombocytopenia	1(1)	1(1)	2(2)			
Fever + neutropenia	2(2)	3(2)	5(4)		1(1)	1(1)
Neutropenia + Infection		1(1)	1(1)			
Nausea	**11(9)**		**11(9)**	5(4)		5(4)
Vomiting	**9(7)**	**4(3)**	**13(10)**	1(1)		1(1)
Diarrhea	**18(14)**	**8(6)**	**26(20)**	7(5)	3(2)	10(8)
Cholinergic symptoms	**2(2)**		**2(2)**			
Asthenia	9(7)		9(7)	2(2)		2(2)
Alopecia	**13(10)**		**13(10)**			
Mucositis	2(2)		2(2)	**6(5)**	**1(1)**	**7 (5)**
Hand and foot syndrome				**6(5)**		**6(5)**

(Final Study Report, p.81)

Reviewer's comment: *More patients in the CPT-11 arm had severe hematologic and gastrointestinal toxicities, cholinergic symptoms, asthenia and alopecia. More patients in Arm B experienced severe mucositis and hand and foot syndrome. This is consistent with studies in previously untreated patients with colorectal cancer who were randomized to infusional or bolus 5-FU.*[13]

Actual laboratory values were submitted electronically only at baseline/before treatment; therefore adverse events such as neutropenia, anemia, etc. could not be verified. Findings of the FDA review using data listings for Grade 4 neutropenia and febrile neutropenia were similar to that of the sponsor.

Reviewer's comment: Cholinergic Symptoms

Cholinergic symptoms include 15 different symptoms and were defined in the protocol as "early diarrhea, sweating, hypersalivation, visual disturbances, cramps, lacrimation, etc.". It was difficult to make an assessment of its incidence since they were recorded as a variety of symptoms. However, an incidence of 2% at doses used

in this study is not consistent with the incidence of cholinergic symptoms described in previous studies..

A review of atropine use provided indirect evidence of its incidence; however, it was also difficult to make a distinction whether atropine use was therapeutic or prophylactic. A total of 25 out of 127 patients (20%) in Arm A who were given atropine for acute cholinergic symptoms during the first and 32 patients (25%) during the second treatment cycle. Nineteen patients (10%) received atropine on both cycles presumably for preventive treatment during the second cycle. Beyond cycle 2, atropine was administered in a total of 197 cycles, some of which extending as far as the 31st.

For the purpose of labeling, the sponsor should reevaluate the incidence of cholinergic symptoms . This should include the incidence of any symptom such as diarrhea only, and a review of atropine use both for therapeutic and prophylactic intent.

Reviewer's comment: Diarrhea

It is not clear which patients in Arm A experienced "early" and which experienced "late" diarrhea. The incidence of diarrhea in derived from the data listings are as follows:

Table 44. FDA Review: Diarrhea

	ARM A (N=127) (N/%)	ARM B (N=129) (N/%)
Grade 3+4 only	29(23)	14 (11)
Grade 1-4	108(85)	55 (43)

The overall incidence of diarrhea (all grades and Grade 3+4) in the CPT-11 is approximately twice compared to treatment Arm B.

Reviewer's comment: Vomiting

The electronic database was queried for the incidence of "vomiting" in both treatment arms. The FDA reviewer's findings were similar to the sponsor's. For treatment Arm A, there were 14 out of 127 patients (11%) and 6 out of 129 patients (5%) in Arms A and B respectively, who experienced Grade 3 or 4 vomiting.

Death within 30 Days of Treatment (Arm A)

There was a difference in the number of deaths between the sponsor and the FDA review of the electronic data. Case report forms and summaries were provided by the sponsor only for those patients who died within 30 days by their review; therefore, the cause of death in the other patients cannot be determined. Additional information regarding these deaths will be requested from the sponsor.

Table 45. Deaths within 30 Days of Treatment

	PATIENT NUMBER	
Treatment Arm	**SPONSOR**	***FDA***
A	(N=3)	*(N=7)*
B	(N=1)	*(N=3)*

Pt. : 49/F died of pulmonary embolism and pericarditis 20 days after CPT-11

Pt. : 31/M died two weeks after CPT-11in hepatic come, with tumor progression, probably not related to CPT-11

Pt. : 56/M died 15 days after CPT-11 with pancytopenia, diarrhea and renal insufficiency

Pt. : 69/M died 9 days after infusional 5-FU after experiencing severe diarrhea

In the FDA review, there were 7 of 127 (6%) deaths within 30 days of CPT-11 in Arm A and 3 of 129 (2%) in Arm B. The causes of the other deaths and their relationship to study drugs have yet to be determined. The sponsor was asked to respond to the above results.

Hospitalizations

Table 46. Hospitalizations

	Arm A (N=127)	Arm B (N=129)
Number of Patients with at Least One Hospitalization Due to Adverse Events	52 (41%)	50 (39%)
Median Number of Hospitalizations Per Patient	1.0	1.0

Figure 14. FDA Reviewer's Summary of Benefits, Risks and Concerns, Study

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
Study Design and Conduct		
• Large, randomized, well-controlled • Active control arm • Well-balanced patient population with mostly resistant/refractory colorectal cancer	• Unequal frequency of patient follow-up within treatment arm B	
Efficacy		
• Well-controlled and appropriate censoring • Statistically significant median survival advantage (from date of randomization) favoring CPT-11 using later cut-off date • Statistically significant median survival (from date of diagnosis) favoring CPT-11 • Lower dose intensity (<100 mg/m^2/wk) possibly no detrimental effect on survival		• Earlier, prospectively determined cut off date did not show a statistically significant difference in survival by FDA analysis • Uncertain survival correlation between weekly (approved) schedule and the every three week schedule
Clinical Benefit		
	• Retrospective analysis of pain-free survival, symptom-free survival, survival without performance status deterioration and survival without weight loss	• No significant difference between treatment arms

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
Quality of Life		
• Good patient compliance	• Retrospective analysis • No prospective plan for controlling Type I error to account for multiple subscales • Sponsor's analysis assumed random occurrence of missing data • Significant advantage favoring the 5-FU arm as regards diarrhea, nausea and vomiting per sponsor's comparison to baseline and worst scores • Significant advantage favoring the 5-FU arm as regards cognitive function per sponsor's comparison from baseline scores • Significant advantage favoring 5-FU as regards financial impact per sponsor's comparison of worst scores • FDA analysis of Physical functioning significantly in favor of 5-FU arm	• Analyses of other clinically relevant subscales using the FDA method need to be done
Safety		
• Toxicity profile probably similar to weekly dosing schedule approved in the U.S. • Safety profile well-described in supporting phase I trials • Similar hospitalizations between treatment arms • More mucositis and hand and foot syndrome with 5-FU	• Unequal frequency of monitoring • On-study lab results not available for verification • Greater incidence of leucopenia, neutropenia, fever+neutropenia, nausea, vomiting, diarrhea and cholinergic symptoms and alopecia	• 6% on-study deaths from CPT-11 per FDA review (vs.2% by sponsor) Needs to be verified

VI. SUPPORTING STUDIES

***Reviewer's comment**: Primary data from the following supporting studies were not available for review. The following discussions were summarized from the sponsor's study reports.*

A. Summary of M/6475/0024

Title: A Phase I Trial to Determine the Maximum Tolerated Dose of Irinotecan Hydrochloride (CPT-11) Using a Once-Every-Three Week Dosing Schedule in Patients with Advanced Solid Tumor Malignancies

Clinical Investigator: Henry Pitot, MD

Objectives: determine the MTD, qualitative and quantitative toxicities, PK

Results: A total of 34 patients were treated. Median patient age was 61 years (range). Twenty-one (62%) were male, and 32 (94%) were white. Fourteen patients (41%) had tumor-related symptoms at study entry. Thirty-two patients had colorectal cancer. All patients had received prior 5-FU based chemotherapy. Five patients responded to treatment (16%, 3.0-28.2)

The most common non-hematologic adverse events were gastrointestinal (GI) (nausea, vomiting, anorexia, diarrhea and stomatitis), body as a whole (abdominal pain, asthenia), and alopecia. Grade 3 and 4 leukopenia/neutropenia were the most frequent hematologic events. Two patients (5.9%) had neutropenic fever/sepsis. Three patients received support during treatment. Twenty-one patients (62%) were reported to have had serious adverse events related to GI and myelosuppressive toxicities. One patient died within 30 days of treatment, potentially drug related.

There was a trend toward more frequent occurrence of any cholinergic symptoms at higher starting dose levels, ranging from 33% of patients treated at a dose of 240 mg/m^2 to 83% of patients treated at 340 mg/m^2. (See next section for a detailed review).

Conclusions: The MTD in this trial is 320 mg/m^2 while European phase I MTD was 350 mg/m^2. The results of this study is consistent with demonstration of the safety and activity of doses between 300 and 350 mg/m^2. The dose of 300 mg/m^2 as a

starting dose in patients with prior abdominopelvic radiotherapy, age >70 years and PS =2 seems appropriate.

B. Phase I Study

Title: An Open Label Phase I Study of Irinotecan Hydrochloride Administered as a 30-Minute Intravenous Infusion Once Every Three Weeks to Cancer Patients

Clinical Investigator: J.P. Armand, MD

Objectives: determine the MTD, RP2 dose and antitumor effects of CPT-11

Results: A total of 120 patients were enrolled, 76 men and 44 women with colorectal, head and neck, lung, ovarian, mesothelioma and others. A total of 107 patients received prior chemotherapy, median of two prior regimens. Eighteen objective responses were observed, 4 CR's and 14 PR's. There was promising activity in colorectal cancer, mainly in the highest dose levels.

Leukopenia, neutropenia and diarrhea were the most frequently observed toxicities. Grade 3 to 4 neutropenia occurred in 44% (52/118); however, 24/52 (46%) of the patients received doses of $\geq$ 350 mg/m^2. Neutropenia was complicated by fever and/or infection and led to death in one patient and early withdrawal from study in 10 patients. Neutropenia became life threatening when it occurred simultaneously with Grade 3 to 4 diarrhea. All seven patients who were treated with the 750 mg/m^2 dose had Grade 4 neutropenia associated with late diarrhea. Administration of 350

mg/m^2 resulted in only one serious adverse event. Other events reported were nausea/vomiting (77%), delayed nausea/vomiting (65%), alopecia (86%) mucositis (12%), abnormalities in SGOT (47%), SGPT (33%) alkaline phosphatase (37%), and hyperbilirubinemia (12%). Twenty-five patents developed dyspnea felt to be unrelated to CPT-11.

Conclusion: The MTD of CPT-11 administered as a 30-minute IV infusion once every three weeks was 750 mg/m^2 when high doses of loperamide were given to reduce diarrhea. Neutropenia and delayed diarrhea were considered to be co-limiting toxicities. The recommended dose for Phase II with this schedule was 350 to 500 mg/m^2. Among the 18 objective responses achieved in this study, promising antitumor activity was observed in colorectal cancer.

C. Summary of Phase II Study (I)

Title: A Multicenter, Open-label Phase II Trial with Irinotecan Hydrochloride (CPT-11) in Patients with Inoperable Advanced Colorectal Cancer Previously Treated or Not with Adjuvant or Palliative 5-FU Based Chemotherapy

Principal Investigator: R. Bugat, MD

Objectives: To characterize the objective response rate and time to progression, toxicity, PK/PD of CPT-11

Dose of CPT-11: 350 mg/m^2 as a 30-minute infusion, once every three weeks

Results: Patients were divided into two groups, A with no prior chemotherapy and B with prior therapy. A total of 213 patients were treated, 81 patients in Group A and 132 in Group B. The primary diagnosis in 151 patients was primary colon cancer, all had metastatic disease, 48 (23%) had undergone prior radiation, and 165 (77%) with prior chemotherapy.

Thirty-three of the 213 (15%, 95% CI 11-21%) patients attained an objective response. The response rate in Group A was 20% (95%CI, 11.7-30%) and that of group B was 12% (95% CI 7-18.1%). The overall median survival time was 10.6 months (range).

A total of 97 patients (47%) experienced Grade 3 or 4 neutropenia while on study. Febrile neutropenia occurred in 33 (15%) of patients. Grade 3 or 4 delayed diarrhea was observed in 82 (39%) patients. Other toxicities included fatigue (81%), nausea/vomiting (74%), delayed nausea/vomiting (78%), lacrimation (12%), malaise (12%), salivation (18%), myosis (10%) and alopecia (81%) of patients.

Conclusion: Irinotecan, 350 mg/m^2 IV over 30 minutes once every three weeks could induce regressions in tumors of patients with colorectal cancer. Leukopenia, diarrhea, and vomiting were the primary toxicities.

D. Summary of Phase II Study (II)

Title: Open-label, Confirmatory, Multicenter Phase II Study of Irinotecan Hyrochloride (CPT-11) in Patients with 5-FU Resistant Colorectal Cancer

Principal Investigator: H. Bleiberg, MD

Objectives: To obtain additional data on efficacy of CPT-11 in 5-FU resistant colorectal cancer, further characterize safety, and perform some QOL parameters

Dose of CPT-11: 350 mg/m^2 as a 90-minute infusion, once every three weeks

Results: A total of 107 patients were enrolled, 63 males and 44 females. Fourteen (13%) had received prior radiation , 76 (71%) had only received palliative therapy. Overall response rate was 12.1% (95% CI 7-22%).

Grade 3 or 4 neutropenia occurred in 33 (31%) patients, nausea/vomiting in 19%, asthenia in 8%. There were 72 serious adverse events, 46 possibly related to study drug. There was one on study death related to drug.

Conclusion: Irinotecan at the recommended dose and schedule has antitumor activity in advanced colorectal cancer patients. Neutropenia, diarrhea, cholinergic syndrome and vomiting were the main toxicities observed.

E. Summary of Cholinergic Effects of CPT-11 (from M/6475/0024)

Reviewer's comment: *The following synopsis was included to support a labeling change regarding the incidence, diagnosis and management of cholinergic effects from CPT-11.*

A cholinergic event from CPT-11 is described as a transient episode of symptoms which may include diaphoresis, lacrimation, miosis, increase salivation, rhinitis, vasodilation (flushing), hypotension, bradycardia, abdominal cramping, and hyperperistalis leading to an acute increase in stool frequency (early diarrhea). The timing of these symptoms were consistent with peak CPT-11 serum levels. Symptoms are generally mild with a median duration of 15-30 minutes.

Table 47. Summary of Clinical Data on Cholinergic Symptoms with Different Schedules of CPT-11

	NUMBER OF PATIENTS (%)			
SCHEDULE OF ADMINISTRATION	TOTAL	ALL SYMPTOMS[a]	DIARRHEA	ATROPINE GIVEN
100-125 mg/m^2 wkly x 4, 2 wks rest	166	38 (23)	2 (1)	19 (11)
250 mg/m^2 q 2 wks	92	63 (68)	11 (12)	33 (36)
240-340 mg/m^2 q 3 wks	34	11-28 (33-83)[b]	6 (18)	16 (47)

[a] includes the following symptoms: abdominal pain/cramps, bradycardia, chills, conjunctivitis, dizziness, diaphoresis, early diarrhea, hypotension, increased salivation, malaise, miosis, rhinitis, vasodilation and vision disorder

[b] more symptoms with higher doses

Conclusion: The overall results of this analysis suggest that CPT-11 induced cholinergic symptoms are generally mild, brief in duration, infrequently associated with diarrhea, and readily manageable. The likelihood of occurrence of these symptoms seem greater with higher doses; therefore, personnel should monitor and be able to provide therapeutic support with atropine intravenously or subcutaneously. Prophylactic use of atropine may be warranted for patients receiving higher initial doses.

***Reviewer's comment**: Because of its incidence with the proposed dosing schedule, it would probably be worthwhile to develop a severity grading system of "cholinergic symptoms" similar to the NCI Common Toxicity Criteria. This grading system should incorporate all the symptoms possible and differentiate between those that are potentially life threatening and those which are not.*

VII. CONCLUSIONS

> ***"Approval under Subpart H is subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty to the relation of the surrogate endpoint to the clinical benefit, or of the observed clinical benefit to the ultimate outcome."*** *(Requirements described under Subpart H and the March 1996 Oncology Initiative, "Reinventing the Regulation of Cancer Drugs")*

CPT-11 was granted accelerated approval on the basis of a surrogate endpoint showing significant responses in patients with colorectal carcinoma whose disease has progressed or recurred following 5-FU based chemotherapy. In the current application, data from two large, randomized and well-controlled studies were submitted to comply with requirements for full approval. The control arms in each of the studies are well selected, one having a "no active treatment, best supportive care arm" and the other with a control arm that is known to most clinicians by far as the "most active" comparator arm. Patients mostly having 5-FU resistant disease were carefully selected and balanced between treatment arms in both studies. Regardless of the control arm, CPT-11 consistently showed a statistically significant advantage in overall survival from either time of diagnosis or time of randomization into the study. The method of censoring for survival was careful and balanced between treatment arms. Based on the evaluation of survival, studies seem adequate and well controlled.

Other endpoints of Clinical Benefit such as Symptom-free survival, Pain-free survival , etc. were not as impressive primarily since these endpoints were not prospectively defined. In this particular instance where real and presumed variations occur with frequency of patient visits, patient compliance, symptom reporting and investigator evaluations, the comparability of results between treatment arms is weak. Although the Quality of Life tests used in the studies are validated and patient compliance was good, the methods of analyses by the sponsor were determined retrospectively. Treatment with CPT-11 showed significant overall advantage in cognitive function, global health, pain, dyspnea, appetite loss, and financial impact favoring CPT-11 when compared to baseline. When compared to worst scores, CPT-11 also showed an advantage in physical functioning, role functioning, cognitive function, social function, fatigue, pain, dyspnea, appetite loss and constipation. In addition to the retrospective nature of the sponsors analyses, the FDA reviewer expressed concerns regarding lack of control for Type I errors as a result of multiple subscales used and

lack of appropriate adjustments for the non-random nature of missing data. The FDA reviewer proposed different methods of analysis and obtained different results.

Adverse events were well described in both studies. As expected, treatment with CPT-11 in study resulted in more severe neutropenia leucopenia, diarrhea, nausea, vomiting and cholinergic symptoms. These observations were similar in study
In addition, there was more toxicity such as fever+neutropenia and alopecia associated with CPT-11 but more mucositis and hand and mouth syndrome associated with infusional 5-FU. The toxicity profile is consistent with those observed in the Phase I trials submitted as supporting studies, and to the weekly, FDA approved schedule. There may be a difference in the severity of some toxicities such as cholinergic symptoms. The sponsor submitted additional data to more clearly define this syndrome, and to diagnose and manage the symptoms more appropriately. Changes in the labeling that address this issue are being proposed. In addition, 23% of the total number of courses of CPT-11 administered was also associated with hospitalizations, mostly due to adverse events. However, the incidence of hospitalization due to adverse events was similar on the two arms of study

Updated efficacy data were submitted from the Phase 2 studies that supported accelerated approval of CPT-11 (see Table 8, p.16) given by the weekly schedule. The submission provides updated response rates, one-year survival and overall survival rates with follow-up that included dates of deaths of all patients who were enrolled in the studies. The results of the sponsor's analysis of survival for patients treated with CPT-11 in these phase 2 studies is notable for its similarity to the survival analysis results of the pivotal trials in the current application. The reviewer notes, however, that one cannot make a definitive comparison of survival between the current weekly schedule of CPT-11 and the proposed q 3 week schedule without a randomized controlled trial. Furthermore, the agency has not received or reviewed the survival data from these phase 2 trials. The proposed package insert recommends both the weekly, 125 mg/m^2 x 4 every six weeks and the every-three-week schedule at 350 mg/m^2. A discussion of whether both schedules should be included in the labeling may be warranted.

MEDICAL REVIEWER RECOMMENDATION

CPT-11 was given accelerated approval status in June 1996 for the treatment of patients with metastatic colorectal cancer whose disease has progressed or recurred following 5-FU based chemotherapy. Confirmatory data from two large phase 3 studies were submitted in a timely fashion (2 years) and showed evidence of a survival advantage favoring CPT-11 compared to best supportive care and infusional 5-FU treatment. The quality of efficacy data from these two trials was validated and found to be adequate. Other efficacy endpoints under "Clinical Benefit" and Quality of Life were less convincing and should be discussed further. Adverse events from treatment were expected and well described. After a thorough review of the protocols and data submitted, approval of this application is recommended on the basis of a benefit to risk ratio in favor of CPT-11.

ODAC QUESTIONS AND RECOMMENDATIONS

Two randomized, prospective, multicenter clinical trials in more than 500 patients have examined CPT-11 in colorectal cancer. Study compared CPT-11 plus BSC (Best Supportive Care) to BSC alone, and Study compared CPT-11 to three infusional schedules of 5-FU. There were statistically significant differences in median survival in favor of CPT-11 in both studies.

	CPT-11 (n=189)	**BSC (n=90)**	**CPT-11 (n=127)**	**5-FU (n=129)**
Median Survival (months)	9.2	6.2	10.2	8.4
p-value	p<0.0001		p=0.04	
Hazard Ratio	1.76		1.37	
95% C.I.	1.31-2.36		1.02-1.85	

The incidences of severe neutropenia, fever and neutropenia, nausea, vomiting, alopecia and cholinergic symptoms were greater with CPT-11 than the control arms in both studies, while the 5-FU arm in study v302 had more severe mucositis and hand and foot syndrome. These adverse events are well described and are similar to those seen with the weekly schedule approved in the United States.

The indication sought by the applicant is for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has progressed or recurred following 5-FU based chemotherapy. The applicant's recommendation is that CPT-11 be administered at a dose of 350 mg/m^2 every three weeks (the regimen in studies) or at a dose of 125 mg/m^2 weekly x 4 every 6 weeks, the schedule approved previously based on tumor response studies.

QUESTIONS:

1. Do you agree that studies are adequate and well-controlled trials demonstrating the efficacy and safety of CPT-11, 350 mg/m^2 as a 90-minute infusion every three weeks, for the treatment of metastatic carcinoma of the colon or rectum whose disease has progressed or recurred following 5-FU based chemotherapy?

   7 YES 0 NO ___ ABSTAIN

2. What dosage regimen(s) should be approved?

   a. Approve only the every-3-week regimen used in the studies demonstrating a survival advantage?

      1 YES (Dr. Ozols) 6 NO ___ ABSTAIN

   b. Approve both the every-3-week regimen used in the studies demonstrating a survival advantage and the initially approved weekly X 4 regimen?

      6 YES 1 NO ___ ABSTAIN

MEDICAL OFFICER'S REVIEW OF DRAFT LABELING

Review Date: September 22, 1998

Attached is the first draft of the label for irinotecan on patients with metastatic carcinoma of the colon. The sponsor's proposals and changes by the FDA reviewers (*italicized*) for the corresponding sections of the label are listed below. Please fax the following comments to the sponsor with the attached strikeout version of the label.

PHARMACOKINETICS

CLINICAL STUDIES

DOSAGE AND ADMINISTRATION

RECOMMENDATION

The sponsor should submit a revised label incorporating the above recommendations.

/S/

Isagani Mario Chico, MD

10/2/98

date

I concur with Dr. Chico's recommendations.

/S/

Grant Williams, MD

10/2/98

date

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[13] Rougier P. 5-Fluorouracil continuous intravenous infusion compared with bolus administration. Final results of a randomized trial in metastatic colorectal cancer. Eur. J. Cancer 33:1789-93, 1997

MEDICAL OFFICER'S DRAFT LABELING REVIEW (V.1)

NDA #20-571 **Submission Date:** April 22, 1998

Irinotecan for Colorectal Cancer **Review Date:** September 22, 1998
Applicant: Pharmacia and Upjohn

Attached is the first draft of the label for irinotecan on patients with metastatic carcinoma of the colon. The sponsor's proposals and changes by the FDA reviewers (*italicized*) for the corresponding sections of the label are listed below. Please fax the following comments to the sponsor with the attached strikeout version of the label.

PHARMACOKINETICS

2. PHARMACOKINETICS IN SPECIAL POPULATIONS:

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

DOSAGE AND ADMINISTRATION

RECOMMENDATION

The sponsor should submit a revised label incorporating the above recommendations.