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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-571/S-021

Medical Review(s)

Medical Officer's Review of
Pediatric Exclusivity Request

NDA:	20,571
Drug:	Camptosar (Irinotecan, CPT-11)
Serial no.:	SE8- 021-PM
Sponsor:	Pfizer Pharmaceuticals
Medical Reviewer:	Amna Ibrahim MD
Team Leader:	John Johnson MD
Letter date:	December 22, 2003

Recommendation:

The Applicant seeks to obtain pediatric exclusivity for irinotecan by submitting study reports in response to a written request. The Applicant has met all the requirements of the written request, except that children younger than one year were not enrolled. This was discussed at the pediatric exclusivity board and was found to be acceptable.

In the Study P9761, 16% (n=3) responses were observed in the Rhabdomyosarcoma subgroup (n=19). The numbers of patients in this stratum are too small to allow definitive conclusions. In the second phase 2 study, D9802, 9 of 21 patients (43%) had a PR as the best response to irinotecan. However, the irinotecan window was closed to accrual due to 14% early deaths. Although irinotecan demonstrates some promise, no overall efficacy was demonstrated.

No efficacy claim is made. Changes to the label have been proposed by the applicant. These include description of the two phase II studies and safety of study COG 9761. There should be no change in the label as no efficacy has been observed. No unexpected adverse event findings have been noted. Biopharmaceutics review is pending at this time.

Executive Summary:

Four phase 1 and two phase 2 study reports have been submitted to support a response to the written request for pediatric exclusivity. Please see table 1. Three schedules were tested in the phase 1 trials. Two of the phase I studies evaluated daily x 5, q 3 weeks schedule (POG 9571 and P9871). Another studied [daily x 5] x 2, q 3 weeks (St. Judes Study). The last one mimicked the adult schedule of weekly x 4, q 6 weeks (H6957). Daily x 5, q 3 weeks schedule and [daily x 5] x 2, q 3 weeks were studied in two phase II trials.

Three phase I studies and one phase II study were completed. Interim reports have been submitted for two phase I studies (H6957, a phase 1 study and P9761, a phase 2 study). One study (P9871, a phase 1 study) was closed early due to insufficient and slow accrual. DSMB closed the single agent irinotecan window for D9802, a phase 2 study because of the numbers of PD and early death.

Studies H6957 (although patients were enrolled after cut-off date), POG 9571 and St. Judes Studies are adequate for analysis of phase 1 studies. The following observations are made after analyzing the phase I studies:

-Twenty mg/m^2 [daily x 5] x 2, q 3 weeks evaluated in the St. Judes study appears to be too toxic, although it was thought to be appropriate as a phase 2 dose by the investigator. This high toxicity was again observed in the phase II trial (D9802) that employed this regimen.

-For heavily treated patients in POG9571, 39 mg/m^2, for less heavily treated patients 50 mg/m^2 and for children less than 6 years of age 30 mg/m^2 administered daily x 5 q 3 weeks is an appropriate phase 2 regimen. The 50 mg/m^2 daily x 5, q 3 regimen was used in phase II study, P9761. The toxicity was acceptable, but the response rate was too low at 5%.

-The investigators of study H6957 concluded that 125 mg/m^2 of irinotecan is an appropriate phase 2 dose, although by FDA assessment, this dose is too high. It should be noted that 125 mg/m^2 was initially thought to be the dose for adult patients. In a large NCI trial, an increased number of early deaths were observed at this dose in adult patients.

-P9871 closed early prior to MTD determination.

Two phase II studies were submitted. Conclusions for the phase II studies are as follows:

-P9761 accrued 170 patients and was ongoing at the time of cut-off date. A 5% RR was observed with acceptable toxicity.

-In the other phase II study D9802, single agent irinotecan (SAI) was administered prior to a multi-agent regimen. The SAI window was closed early due to high rate of early disease progressions and deaths.

Two studies were designed to study the interaction of irinotecan with anticonvulsants (AC). One of them was H6957. The 3rd stratum of this study which was designed to evaluate interaction with anticonvulsants was closed with out accruing any patients. In the second study P9871, a total of 9 patients were accrued to all 3 strata (6 in enzyme-inducing ACs, 1 in valproic acid and 2 in other AC strata). This study was closed early due to slow accrual. The sponsor compared the pharmacokinetics of the EIAC patients to a control group who were not on any anticonvulsants. The control group was from another concurrent study (P9761). The demographics, regimens and pharmacokinetic sampling and analysis methods were comparable between the two studies. In the assessment of the Biopharmaceutics reviewer, Dr. Roshni Ramchandani, the studies appear to fulfill the PK requirements of the Written Request.

Table 1: Summary of results of submitted studies

FDA table

	Schedule	Number enrolled	Study completed	Results
Phase 1 Studies				
H6957	weekly x 4, q 6 weeks	16	Interim report. 8 pts. enrolled after cut-off date	MTD of 125 mg/m^2 probably too high by FDAs definition for strata 2 & 3.
P9871	daily x 5, q 3 weeks	9	Closed early	Study closed early due to slow accrual
POG9571	daily x 5, q 3 weeks	33	Yes	The MTD for stratum 1 =39 mg/m^2, stratum 2 =50 mg/m^2 (<6 years age) stratum 3 = 30 mg/^{2}
St. Jude Study	[daily x 5] x 2, q 3 weeks	22	Yes	55% experienced DLT at the starting dose
Phase 2 Studies				
P9761 Refractory pts. <2 prior Rx	50 mg/m2 qd x 5, q 3 weeks	170	3 strata still open	5% RR with acceptable toxicity
D9802 Newly diagnosed rhabdomyosarcoma	20 mg/m^2 qd x 5, wks 0 & 1, 3&4	21	Yes	High rate of early PDs and deaths. SAI window closed by DSMB

SAI: single agent irinotecan

The applicant states the following in the summary of the clinical document:
"*The results of these phase II studies, confirm that single- agent irinotecan is generally tolerable and provides an early indication of clinical activity in children with refractory tumors (solid tumors or CNS tumors) or with metastatic untreated rhabdomyosarcoma. Combinations of irinotecan with other anticancer drugs are critical for the development of new treatments for the pediatric population.*"

However, the applicant states in the proposed label *"The effectiveness of CAMPTOSAR in pediatric patients has not been formally established."* This reviewer agrees with this preceding statement. A description of PK findings, of the two phase II studies and a table that represents

the adverse events in 170 previously treated patients in the COG 9761 phase 2 study has been included in the proposed package insert. However, because the efficacy of irinitecan has not been demonstrated, and because there is no new, meaningful safety information, no changes should be made to the approved label.

Interim reports from phase I and phase II trials have been submitted instead of final reports. However sufficient numbers of patients were enrolled in the phase I and phase II studies. Other than children over 1 year were enrolled into the studies, instead of over 1 month in age, all conditions of the written request have been met.

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/s/

Amna Ibrahim
6/15/04 03:17:22 PM

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Clinical Review

1 Background:

Irinotecan is a prodrug derivative of camptothecin, an alkaloid obtained from plants such as the Camptotheca accuminata tree. Camptothecins are inhibitors of topoisomerase I. Topoisomerase I is a nuclear enzyme that functions normally during DNA replication to cause transient breaks in a single strand of DNA, releasing the torsional strain caused by synthesis of a new strand of DNA or RNA around the double helix. The camptothecin target this topoisomerase- I- DNA complex, stabilizing it and inhibiting reannealing of the parent DNA. Double-stranded DNA breaks leading to cell death occur when an advancing replication fork collides with the camptothecin- topoisomerase- I- DNA complex.

Camptosar received an accelerated approval for metastatic colorectal cancer (MCRC) in June 1996. A regular approval was given in October 1998 for second-line treatment of MCRC. In April 2000, Camptosar in combination with 5-FU and leucovorin for first-line treatment of MCRC was presented to ODAC. Demonstration of improved survival provided basis of approval in this patient population and it became the new standard for this treatment setting. Approved regimens for single agent irinotecan in adults are as follows:
1- Weekly schedule: 125 mg/m ^{2} IV over 90 min, d 1,8,15,22 then 2-wk rest
2- Once-Every-3-Week Regimen: 350 mg/m ^{2} IV over 90 min, once every 3 wks

A Pediatric Written Request was sent to the Sponsor of Camptosar on October 30th, 2000. In response, ongoing or completed protocols were submitted with the letter dates being August 6, 2002, April 9, 2003, and December 23, 2002, and reviewed. The Sponsor submitted reports from 6 studies to fulfill this request on December 22, 2003.

The written request included newly diagnosed and recurrent childhood tumors. In addition, FDA asked the sponsor to submit results from studies where potential pharmacokinetic interactions with anticonvulsants existed. The applicant has noted that in adult patients with gliomas, the systemic exposure to irinotecan and its metabolite SN-38 were substantially lower in patients receiving concomitant enzyme-inducing anticonvulsants (EIAC) and dexamethasone (compared to prior trials in colorectal cancer patients not receiving these drugs). The patient subgroup on EIACs and dexamethasone also had a lower incidence of severe toxicities, suggesting a drug-drug interaction with irinotecan. Trials with strata of children on anticonvulsants have been submitted.

2 Items of Written Request and their Adequacy

Table 2: Written request Items

Types of studies/ Study Design: **Study 1:** Phase 1: A dose finding study including PK, with doses determined for all appropriate age groups and schedules of treatment. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25. **Study 2:** Phase 2 or pilot studies: Enrollment of at least 14 pediatric patients per trial, in refractory or relapsed tumors. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer. **Study 3:** not requested	**Types of studies:** **Phase 1 Studies** A total of 81 (16+33+9+23) patients consented to the four phase 1 dose finding/PK studies. **Phase 2 Studies** One hundred and ninety seven (176 + 21) patients were enrolled in two phase 2 studies in relapsed and refractory tumors. Studies were conducted by cooperative groups or facilities with experience and expertise in pediatric cancers.
Indication(s) to be studied: 1- Refractory or relapsed pediatric solid tumors (metastatic rhabdomyosarcoma, Ewing's sarcoma, neuroblastoma, osteosarcoma, medulloblastoma, brain stem glioma, and ependymoma) 2- Previously untreated metastatic rhabdomyosarcoma	**Indication(s) studied:** **H6957:** Hepatic, Sarcoma, Leiomyosarcoma, Ewing's Sarcoma, Neuroblastoma, Glioma, Ependymoma, Optic Glioma, Hepatoblastoma, Synovial Sarcoma. All patients had received at least 1 prior chemotherapy or radiation treatment. (16 patients) **P9571:** Solid tumors refractory to conventional therapeutic (33 patients). Following tumor types were enrolled: Astrocytoma, Brain stem glioma, Ependymoma, Glioblastoma multiforme, Neuroblastoma, Pineoblastoma, Clear cell sarcoma, Malignant rhabdoid tumor, Rhabdomyosarcoma, Ewing's sarcoma, Osteogenic sarcoma, Osteosarcoma, Hepatocarcinoma, Hepatoblastoma,

	Colon Adenocarcinoma, Hodgkin's disease, Large cell lymphoma, Adrenocortical tumor, Wilm's tumor **P9871:** Refractory Solid Tumors Who Are Concomitantly Receiving Anticonvulsants. This study enrolled the following tumor types: T-Cell lymphoma, Anaplastic Astrocytoma, PNET, Wilm's Tumor **St Judes Study:** Refractory solid tumors. Patients enrolled had the following tumor types: Carcinoma of larynx, Anaplastic Astrocytoma, Medulloblastoma, Neuroblastoma, Oligodendroglioma, PNET, Rhabdomyosarcoma, Osteosarcoma, PNET. (23 patients) **Phase 2 Studies:** **P0761:** Brain stem glioma, Ependymoma, Ewing's sarcoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, Primitive neuroectodermal tumor, Rhabdomyosarcoma and others **D9802:** Newly diagnosed patients with stage 4 rhabdomyosarcoma
Age group and population in which study will be performed: Infants > 1 month of age to adolescents Study 3: N/A	**Age group and population in which study was performed:** **Phase 1 Studies:** **H6957**: < 2 years - ≥16 years **P9571:** > 1 - < 22 years **P9871:** ≥ 1 and ≤ 21.99 years **St. Judes Study:** < 2 years - ≥16 years **Phase 2 studies:** **P9761:** ≥ 1 and ≤ 21.99 years **D9802:** 0.8 – 19.2 years

Number of patients to be studied or power of study to be achieved: Study 1: The number of patients should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25. Study 2: At least 14 pediatric patients per trial, in relapsed or refractory tumors. Study3: N/A	**Number of patients studied or power achieved:** **<u>Phase 1 Studies:</u>** A total of 81(16+33+9+23) Patients consented to the four phase 1 dose finding/PK studies. **<u>Phase 2 Studies:</u>** One hundred and ninety seven (176 + 21) patients were enrolled in two phase 2 studies in relapsed and refractory tumors.
Entry criteria: None stated	**Entry criteria used:** N/A
Clinical endpoints: The PK study will have maximally tolerated dose (MTD) or BED (biologically effective dose =BED) as a primary endpoint with measurements of blood (or CSF if appropriate) concentrations, clearance, and distribution in body compartments as secondary endpoint. The Phase 2 studies should have a disease-specific surrogate or clinically relevant endpoint.	**Clinical endpoints used:** **<u>Phase 1 Studies:</u>** **H6957:** To determine MTD and DLT **P9571:** MTD **St. Judes Study:** MTD **<u>Phase 2 Studies:</u>** **P9761:** RR **D9802:** RR PK evaluation was included in objectives of all studies.
Timing of assessments: if appropriate Regimen should be as determined by Phase 1/2 studies	**Timing of assessments:**
Drug specific safety concerns: Diarrhea, myelosuppression and potential PK interaction with anticonvulsants	**Drug specific safety concerns evaluated:** **<u>Phase 1 Studies:</u>** **H6957:** Diarrhea and neutropenic fever were DLTs.

	P9571: Myelosuppression, diarrhea and liver impairment were DLTs **St. Jude Study:** Diarrhea and myelosuppression were prominent adverse events observed. **P9871**: vomiting and diarrhea were the commonest events. -Diarrhea, myelosuppression were evaluated in both phase II studies and were common AEs. -PK interaction studies appear to have met the written request conditions
Drug information: • **Route of administration:** Intravenous • **Dosage:** Intravenous • **Regimen:** as determined by Phase 1/2 studies • **Formulation:** Intravenous	**Drug information:** **Phase 1 Studies:** • **Route of administration:** Intravenous • **Dosage:** escalating • **Formulation:** Intravenous **H6957:** • **Regimen:** weekly x 4 weeks, every 6 weeks **P9871:** • **Regimen:** daily x 5 every 3 weeks **P9571:** • **Regimen:** daily x 5 every 3 weeks **St Judes Study:** • **Regimen:** daily x 5 for 2 consecutive weeks every 3 weeks **Phase II Studies:** **P9761** • **Regimen:** 50 mg/m2 daily x 5 every 3 weeks **D9802** • **Regimen:** 20 mg/m2 daily x 5 for 2 consecutive weeks every 3 weeks

Statistical information (statistical analyses of the data to be performed): Descriptive statistics	**Statistical information (statistical analyses of the data to be performed):** Descriptive statistics
Labeling that may result from the studies: Appropriate sections of the label may be changed to incorporate the findings of the studies.	**Did the sponsor submit proposed labeling?** Yes
Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation	**Format of reports submitted:** Interim reports for phase I study H6957, and phase II study P9761 have been submitted.
Timeframe for submitting reports of the studies: On or before December 31, 2003	**Date study reports were submitted:** Submitted on December 22, 2003
Additional Information:	Phase I study P9871 closed early due to slow early, and the irinotecan closed early in the other phase II study D9802 due to PDs and early deaths.

3 Sources of Clinical Data

The submission, NDA 20-571, serial # SE 8- 021 is available electronically at \\CDSESUB1\N20571\S_021\2003-12-22, and consists of labeling with proposed changes marked, pharmacology section, a clinical statistical section, case report tabulations consisting of patient profiles, debarment certification, user fee cover sheet and financial disclosure information. Paper copy of all sections except the patient profiles have been included in this sNDA. Patient profiles for deaths within 30 days of last dose and patients who discontinued due to AE's. There are no datasets provided for the efficacy or safety information. No CRFs or datasets have been submitted.

Per applicant, most of the patient data (RDE modules from Demography, Eligibility, Diagnosis, Prior Therapy, Adverse Events, On Study and Off Study Summary, Course Assessment, Death and Survival) were provided to Pharmacia via SAS datasets. Tumor measurement data for responders were provided to Pharmacia in a Word Document. Paper CRFs ("roadmaps") were used for Study Drug Administration, Laboratory Data, and Vital Signs. Pharmacia contracted _____ to complete data entry of the paper CRFs. Data entered by _____ was provided to Pharmacia as SAS transport datasets. No source document review was conducted by Pharmacia and where feasible, data clean- up was performed by Pharmacia using the available data in- house.

4 Description of Clinical Data

Results from 6 studies have been submitted as basis for this sNDA. Four Phase 1 studies provide data on PK and two Phase 2 studies provide safety, PK and efficacy information in several solid tumors and CNS tumors in children.

The Applicant responded as below when asked about the status of the study reports:

"The data cut off date for the December 22, 2003 submission was December 31, 2002. The study reports included in the December 22, 2003 were final reports. Safety information from the patients included in Study #'s H6957 and P9761 after the data cut off will be included in the Safety Update.

Status of patients entered into individual studies included in the December 22nd submission:

- *Study P9571- no extra patients enrolled and all patients off treatment.*
- *Study P9871 - no extra patients enrolled and all patients off treatment.*
- *St Jude - no extra patients enrolled and all patients off treatment.*
- *Study D9802 - no extra patients enrolled and all single agent patients off treatment. This protocol was amended to initiate an irinotecan plus vincristine 'combination up-front treatment phase'. All the patients treated after cut off date were patients treated with the combination. We informed the FDA on August 6, 2002 that a final report will be written and submitted to include the patients treated with the combination therapy following completion of the study.*
- *Study H6957 - 8 patients were enrolled and treated after the cut off date.*
- *Study P9761 - 3 strata were still open for stage 3 and approximately 10 patients were enrolled after cut off date."*

Phase I Studies:

1- H6957: A Pediatric Phase I and Pharmacokinetic Study of Irinotecan (Weekly x 4 every 6 weeks)

2- P9571: A Trial of Irinotecan in Children with Solid Tumors (Daily x5 every 3 weeks

3- P9871: A Phase I Study of Irinotecan in Patients with Refractory Solid Tumors who are Concomitantly Receiving Anticonvulsants: A COG Study (Daily x5 every 3 weeks)

4- Saint Jude Children's Research Hospital: A Phase I Study of Irinotecan (CPT- 11) in Pediatric Patients with Refractory Solid Tumors (Daily x5, x2 every 3 weeks)

Phase II Studies:

1- P9761: Phase II Trial of Irinotecan in Children with Refractory Solid Tumors: A POG/ CCG Intergroup Study (Daily x 5 every 3 weeks)

Tumor types: previously treated Ewing's sarcoma/ PNET, neuroblastoma, osteosarcoma, rhabdomyosarcoma, and other extracranial solid tumors; and medulloblastoma, glioma, ependymoma, brain stem glioma, and other CNS tumors

2- D9802: A Phase II "Up- Front Window Study" of Irinotecan (CPT- 11) Followed by Multimodal, Multiagent Therapy for Selected Children and Adolescents with Newly Diagnosed Stage 4/ Clinical Group IV Rhabdomyosarcoma: An IRS- V Study (Daily x 5, x 2 every 3 weeks)

Tumor type: previously untreated rhabdomyosarcoma

Table 3: Overview of Phase 1 Trials

Applicant Table (Item 8.3)

Protocol # Institution & Pharmacia	Principal Invest/Chair & Sponsor	Protocol Title	Regimen	IND # & Holder	Source of Study Drug Supplies	Pharmacia Funding	Total # Patients & Age Range	Strata (# Patients)
[redacted]								
H6957 98-6475-178	S. Blaney TCCC	Pediatric phase I and pharmacokinetic study of irinotecan	Weekly x4 Q 6 Wk	57,166 S. Blaney	Pharmacia	Per patient & data-sharing grants	Clinical = 16 PK = 14 4-17 y	1 = Heavily pretreated (9) 2 Less heavily pretreated (7) 3 Anticonvulsant (0)
POG 9571 M-6475-056	S. Blaney POG/COG	A trial of irinotecan in children with solid tumors	Daily x5 Q 3 Wk	42,459 NCI	Pharmacia via NCI CTEP	Grant for data sharing	Clinical = 33 PK = 18 1-20 y	1 = Heavily pretreated (14) 2 Less heavily pretreated (12) 3 1 to <6 y (7)
P9871 CPTAIV-0020-452	A. Moghrabi COG	A phase I study of irinotecan in patients with refractory solid tumors who are concomitantly receiving anticonvulsants: A COG Study	Daily x5 Q 3 Wk	IND exempt	Commercial	Grant for data sharing	Clinical = 9 PK 9 5-19 y	Anticonvulsants: 1 = EIAC (6) 2 = Valproic acid (1) 3 = Other (2)
St Jude CPTAIV-0020-453	W. Furman St Jude Children's Research Hospital	A phase I study of irinotecan (CPT-11) in pediatric patients with refractory solid tumors	(Daily x5) x2 Q 3 Wk	IND exempt	Commercial	Grant for data sharing	Clinical = 22 PK = 23 1-21 y	Not applicable

Table 4: Overview of Phase 2 Trials

Applicant Table (Item 8.3)

Protocol # Institution & Pharmacia	Principal Invest/Chair & Sponsor	Protocol Title	Regimen	IND # & Holder	Source of Study Drug Supplies	Pharmacia Funding	Total # Patients & Age Range	Strata & # Patients
P9761 440E-ONC-0020-222	L. Bomgaars COG	Phase II trial of irinotecan in children with refractory solid tumors: A POG/CCG intergroup study	Daily x5 Q 3 Wk	IND exempt	Pharmacia via NCI CTEP	Grants for trial conduct & data sharing	Clinical = 170 PK = 14 1-23 y	1 = Ewings/PNET (18) 2 = Neuroblastoma (18) 3 = Osteosarcoma (12) 4 = Rhabdomyosarcoma(19) 5 = Other Solid (43) 6 = Medullo/PNET (21) 7 = Brain stem glioma (9) 8 = Ependymoma (10) 9 = Other CNS(20)
D9802 440E-ONC-0020-207	A. Pappo IRSG for COG	A phase II "up-front window study" of irinotecan followed by multimodal, multiagent therapy for selected children and adolescents with newly diagnosed stage 4/ clinical group IV rhabdomyosarcoma: an IRS-V study	Daily x5, x2 Q 3 Wk	IND exempt	Commercial	Per patient grant & grants for PK support & data sharing	Clinical = 21 PK = 7 9 mo–19 y	Irinotecan single-agent (21)

5 Individual Studies

Phase 1 Studies

5.1 Study H6957

A Pediatric Phase I And Pharmacokinetic Study Of Irinotecan (CPT-11): A Preliminary Report

Note: 8 patients were enrolled and treated after the cut off date.

Date first patient enrolled: August 13, 1998
Date last patient enrolled: November 21st, 2002
Date of the Study Report: November 03, 2003
No. of patients enrolled before cut-off:16

Study Design

Primary Objectives

-To estimate the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of irinotecan administered IV over 90 min, weekly x 4, every 6 weeks to children with refractory or progressive solid tumors

- To determine the PK of irinotecan and its metabolites (SN- 38, SN- 38G and APC) following administration of irinotecan IV on this schedule

- To determine the PK of irinotecan and its metabolites (SN- 38, SN- 38G and APC) following administration of irinotecan IV on this schedule in children who were receiving EIACs

Secondary Objective:

To gain information whether irinotecan is beneficial for pediatric patients with refractory or progressive tumors.

Regimen:

administered IV over 90 minutes, weekly x 4, every 6

The planned irinotecan starting dose levels were: 125, 160, 200 and 260 mg/ m^2. If the MTD was exceeded at 125 mg/ m^2, subsequent patients could be enrolled at a dose of 100 mg/ m^2.

Methodology:

Per study report:
The study was an open-label, uncontrolled, dose-escalation, phase I trial conducted in 2 centers in the US. Sequential cohorts of 3 patients were enrolled to receive progressively higher starting dose levels of irinotecan. If 1 of 3 patients at a dose level developed Cycle 1 DLT, an additional 3 patients were to be treated at that dose level. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), Version 1.

Initially 2 enrollment strata were planned in anticipation that the DLT might be myelosuppression in patients who had received prior intensive therapy or diarrhea in patients who had received prior abdominal or pelvic radiation. The 2 defined strata were:

- Stratum 1: Heavily pretreated patients

- Stratum 2: Less heavily pretreated patients

Less heavily pretreated pediatric patients were defined by determinants of bone marrow reserve, including a maximum of 2 prior chemotherapy regimens, no prior bone marrow transplantation, no prior abdominal, pelvic or central axis radiation, and no known bone marrow involvement by tumor. If either myelosuppression or diarrhea were dose limiting in Stratum 1, that stratum was to be closed and accrual to Stratum 2 was to be initiated.

- Stratum 3 was created for patients who were receiving concomitant EIAC (enzyme-inducing anticonvulsants).

Up to 3 patients had to be enrolled and observed for DLT for at least 3 weeks from the first day of treatment before new patients could be enrolled at the next higher dose level.

Definition of Dose- Limiting Toxicity (DLT):
Per protocol, DLT was defined as the occurrence of any of the following adverse events (AEs) during Cycle 1:
- Grade 4 neutropenia lasting > 7 days
- Grade 4 thrombocytopenia
- Grade 4 diarrhea despite maximal antidiarrheal support
- Grade 4 nausea and/ or vomiting despite maximal antiemetic support
- Grade 4 asthenia
- Grade 4 fever
- Grade 4 anorexia
- Grade 4 hepatic toxicity
- Any irinotecan- induced grade 3 or 4 toxicity that did not return to grade 1 prior to the planned start of the next cycle

FDA Recommended Definition of DLT:
FDA's comments to the protocol in October 2002 were: "Grade 3 toxicities, including hepatic dysfunction, nausea/ vomiting and diarrhea (despite appropriate treatment) should constitute DLT in your phase 1 studies".

Per sponsor, "In addition to the AEs defined prospectively in the protocol, the occurrence of DLT was also evaluated using these additional AEs: grade 3 ANC with fever, grade 3 diarrhea, grade 3 nausea, grade 3 vomiting and grade 3 hepatic dysfunction. Because the duration of grade 3 ANC and details of supportive therapy were not always available, the Sponsor counted any occurrence of these grade 3 AEs as a DLT."

[redacted] happened that the sponsor chose a more restricted FDA recommended definition of DLT than what FDA comments had suggested however all major toxic non-hematalogical toxicities were included by the sponsor.

Determination of MTD:
The MTD was based on the DLTs observed in Cycle 1. The MTD was defined as that dose at which 0 or 1 of 6 patients experienced irinotecan- related DLT with the next higher dose level provoking DLT in 2/ 3 or 2/ 6 patients.

Results:

Disposition of Patients:
As of 31 December 2002, 9 patients were enrolled into Stratum 1 (heavily pretreated patients) and 7 into Stratum 2 (less heavily pretreated patients). No patients have been enrolled into Stratum 3 (patients with concomitant EIAC) and accrual to Stratum 3 is closed. **Stratum 2 is open to accrual** and results from these patients will be summarized by the investigators.

MTD Determination:
One of six patients had a DLT at dose level 125 mg/m^2 (G4 ANC, G3 diarrhea). 2 of 8 patients at dose level of 160 mg/m^2 (G3 ANC, Neutropenic fever and G4 diarrhea) and 1 of 2 patients at dose level 200 mg/m^2 had a DLT (Neutropenic fever). Per sponsor, using the FDA's expanded definition for DLT, 2 patients (ML101192, and GA012882) experienced a Cycle 1 DLT of grade 3 diarrhea. These patients also had DLT AEs per the protocol definition. Using the FDA's expanded definition for DLT, 2 patients (MD121091 and BF080282) experienced DLTs during Cycle 1 in stratum 2. With this definition of DLT, the 160 mg/ m2 dose level was too toxic; and a cohort of 3 patients should have been treated at the 125 mg/ m2. No patients should have been accrued at the 200 mg/ m2 dose level. For less heavily pretreated patients, the MTD has not yet been established by the applicant's definition, as of the data collection cut-off of 31 Dec 2002.

In summary, using the DLTs defined in the protocol, the study investigators established the MTD for heavily pretreated patients at 125 mg/ m^2 weekly for 4 weeks every 6 weeks, and that for stratum 2 has not been established by the cut-off date. Using FDA's definition, the DLT should have been lower than 125 mg/m^2 in stratum 1 and more patients should have been treated at 125 mg/m^2.

Adverse Events:
All 16 patients had at least 1 AE; the most common nonhematologic AEs were gastrointestinal disorders (nausea, vomiting, diarrhea, abdominal pain). Hematologic toxicity was the second most frequent adverse event, experienced by 93.8% of the patients overall. The most frequent grade 3- 4 AEs were hematologic (56.3% of patients) and grade 3- 4 diarrhea 25% of patients).

Table 5: Serious Adverse Events for Study H6957

Applicant table

Patient #. (Stratum)	Starting Dose (mg/m^2)	Cycle	SAE	Inv Opinion Related to CPT-11?	Sponsor Opinion Related to CPT-11?
AR040382 (1)	125	1	G3 Viral infection	No	No
AS111182 (1)	125	1	G3 Malignant melanoma in situ	No	No
BF080282 (2)	160	1	G4 Convulsions	No	No
BZ070493 (1)	125	3	G4 Neutropenia	Yes	Yes
		4	G3 Aspiration pneumonia	Yes	Yes
		Off Study	Death	No	No
GA012882 (1)	160	1	G4 Neutropenia G4 Anemia G4 Leucopenia G4 Diarrhea	Yes	Yes
MD121091 (2)	160	1	G4 Lethargy G4 Headache G5 Respiratory arrest	No	No
ML101192 (1)	125	1	G4 Neutropenia	Yes	Yes
		1	G4 Bloody stool G4 Abdominal pain	No	No
		1	G4 Benign colon polyp	No	No
		1	G4 Condition aggravated	No	No
MS072793 (2)	200	1	G4 Neutropenia	Yes	Yes

Discontinuations and Deaths Due to Adverse Events:

One patient may have withdrawn from this study due to an irinotecan- related AE. This patient (BF080282) with malignant glioma experienced grade 3 diarrhea (drug- related) and grade 4 convulsions (disease- related) 1 day after her Cycle 1 Week 2 dose. The investigator recorded that the patient recovered from these events and the "action taken" was "drug permanently withdrawn" on the CRF. However, on the Off Study CRF the patient was documented as removed from study due to PD.

One patient with a diffuse pontine glioma died within 30 days of receiving the study drug. After cycle 1, week 3, the patient experienced sudden nausea, vomiting and mental status change and died despite attempts to resuscitate. The cause of her death was PD and considered not related to irinotecan by the investigator and the sponsor.

Efficacy:

No patients were observed to have a response in this phase 1 study of previously treated patients.

Table 6: Best Overall Tumor Response of Study H6957

Applicant table

Patient #	Tumor Type	Stratum	Dose Level (mg/m^2)	# of Cycles	Best Overall Response
AS111182	Ewing's Sarcoma	1	125	2	SD
BZ070493	Ependymoma	1	125	4	SD
AM091987	Undifferentiated Hepatic Embryonal Sarcoma	1	125	1	PD
AR040382	Leiomyosarcoma	1	125	1	PD
ML101192	Hepatoblastoma	1	125	1	PD
RW011086	Synovial Sarcoma	1	125	1	PD
BC120794	Neuroblastoma	1	160	1	PD
GG110788	Alvedar Rhabdomyosarcoma	1	160	3	SD
GA012882	Ewing's Sarcoma	1	160	2	PD
DS010997	Optic Nerve Glioma	2	160	1	PD
RD121592	Ependymoma	2	160	1	PD
RS102984	Embryonal Rhabdomyosarcoma	2	160	1	PD
MD121091	Pontine Glioma	2	160	1	NE
BF080282	Malignant Glioma	2	160	1	NE
MS072793	Metastatic Secretory Breast Carcinoma	2	200	1	SD
SB022696	Pontine Glioma	2	200	1	PD

[redacted]

Patients with documented refractory solid tumors were to be enrolled in H6957. The age ranged from 4 years to 17 years. The Applicant has submitted an interim report of this phase 1 study. This study was to have 3 strata depending on the prior treatments. Stratum 3 (for patients on concomitant anticonvulsant therapy), was closed prior to enrollment. Stratum 2 with less heavily pretreated patients (1-2 prior regimens) was open at the time of the study report. The results from stratum 1 (patients who received more than 2 multi-agent chemotherapy regimens) have been submitted for this interim report. P9871 has been submitted in place of the H6957 stratum 3, which did not enroll any patients.

Using the DLTs defined in the protocol, the study investigators established the MTD for heavily pretreated patients at 125 mg/ m^2 weekly for 4 weeks every 6 weeks, and that for stratum 2 has not been established by the cut-off date.

Using FDA's definition, by this reviewer's assessment, the DLT should have been lower than 125 mg/m^2 in stratum 1 and more patients should have been treated at 125 mg/m^2 for stratum 2. It should be noted that 125 mg/m^2 was initially thought to be the appropriate irinotecan dose to administer to patients. Subsequently, in an NCI trial, an increased number of early deaths were observed at this dose in adult patients. Adverse event observed in H6957 were the expected ones

5.2 Study P9871

A Phase I Study Of Irinotecan In Patients With Refractory Solid Tumors Who Are Concomitantly Receiving Anticonvulsants: A COG Study

Studied Period:
15 January 2001 to 13 December 2002.

Data cut-off date:
31st December, 2002

Patient enrolled: 9

Primary Objectives:
- To estimate the maximum tolerated dose (MTD) of irinotecan administered daily x 5, every 3 weeks to children with refractory solid tumors who are concomitantly receiving ACs
- To determine the dose- limiting toxicity (DLT) of irinotecan given on this schedule
- To characterize the PK behavior of irinotecan in children with refractory solid tumors who were receiving concomitant ACs

Secondary Objectives:

- To gain preliminary information on the antitumor activity of irinotecan within the confines of a phase I study

Study Design:
The study was an open- label, uncontrolled, dose- escalation, phase I trial sponsored by the COG at 54 cancer centers in the US and Canada. Eight centers accrued and treated patients.

At registration patients were stratified according to their anticonvulsant therapy:

- Stratum 1: Patients receiving enzyme- inducing anticonvulsants (EIAC)
- Stratum 2: Patients receiving valproic acid (VAL)
- Stratum 3: Patients receiving other anticonvulsants (Other AC)

[EIACs include phenytoin, (Dilantin), phenobarbital, primidone (Mysoline) and carbamazepine (Tegretol)]

Toxicities were graded by the investigators according to the National Cancer Institute Common Toxicity Criteria (NCI CTC)

Regimen:
60 min IV infusion daily x 5 repeated every 3 weeks.

Table 7: Dose Escalation in Study P9871

1	100	30	50
2	130	39	65
3	170	50	85
4	220	65	110
5	285	85	140

Definition of DLT:

Nonhematologic Dose Limiting Toxicity: Any irinotecan- related grade 3 or 4 nonhematologic toxicity except:

- Grade 3 nausea or vomiting
- Grade 3 transaminase (AST/ ALT) elevation which returned to grade = 1 prior to the planned start of the next cycle
- Grade 3 fever or infection

Hematologic Dose Limiting Toxicity: Any grade 4 neutropenia or grade 4 thrombocytopenia lasting >7 days, which required transfusion therapy on > 2 occasions in 7 days or which caused a delay of = 14 days beyond the planned interval between treatment courses.

FDA- Recommended Definition of DLT: In addition to the AEs defined prospectively in the protocol (see above), the occurrence of DLT was also evaluated using these additional AEs: grade 3 ANC with fever, grade 3 diarrhea, grade 3 nausea, grade 3 vomiting and grade 3 hepatic dysfunction. Because the duration of grade 3 ANC and details of supportive therapy were not always available, the Sponsor considered any occurrence of these grade 3 AEs in Cycle 1 as a DLT.

Results

Nine patients enrolled at 8 sites. The distribution of patients at different dose-levels and reason for discontinuation from study is given below.

Table 8: Distribution of patients at dose levels and reason for discontinuation

Applicant Table

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
N	4	2	6	1	1	2	2	9
PD	2 50.0	2 100.0	4 66.7	-	-	1 50.0	1 50.0	5 55.6
Protocol Deviation	-	-	-	-	-	1 50.0	1 50.0	1 11.1
Consent Withdrawn	-	-	-	1 100.0	1 100.0	-	-	1 11.1
Still on Treatment	2 50.0	-	2 33.3	-	-	-	-	2 22.2

EIAC: Enzyme-inducing Anticonvulsant
VAL: Valproic acid
AC: Anticonvulsants

Table 9: Distribution by Age and Tumor Type

Applicant Table

		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Age Group									
N %		4	2	6	1	1	2	2	9
2 - <12 y		1 25.0	-	1 16.7	-	-	1 50.0	1 50.0	2 22.2
12 - <16 y		-	2 100.0	2 33.3	-	-	1 50.0	1 50.0	3 33.3
≥16 y		3 75.0	-	3 50.0	1 100.0	1 100.0	-	-	4 44.4
Initial Diagnosis									
Lymphoma	**T-Cell**	-	1	1	-	-	-	-	1
CNS	**AA**	1 25.0	-	1 16.7	1 100.0	1 100.0	-	-	2 22.2
Bone	**PNET**	-	1 50.0	1 16.7	-	-	1 50.0	1 50.0	2 22.2

Renal	**Wilm's Tumor**	-	-	-	-	-	1 50.0	1 50.0	1 11.1

DLTs:
No DLTS were reported in stratum 2 and 3 by dose levels 30 mg/m^2 and 50 mg/m^2. The DLTs in stratum are summarized in the table below. MTD has not been defined for any strata.

Table 10: DLTs in Stratum 1 in Study 9871

Patient #	**(mg/m^2)**	**Protocol**	**per FDA**	**Action Taken**
706662	100	No	No	None
700986	100	No	G3 ANC Febrile neutropenia	Dose reduction
713444	100	No	No	None
715722	100	No	No	None
574963	130	No	No	None
721659	130	No	No	None

Reviewer's Comments:
Refractory solid tumors patients who are concomitantly receiving anticonvulsants were enrolled in this trial. This study was closed early by COG due to slow accrual. Relatively few patients (N=9) have been enrolled in all 3 strata (age range 5-19 years). One DLT has been observed in stratum 1 and none in stratum 2 and 3. The MTD has not been defined. This study should be excluded from exclusivity analysis.

Please see the biopharmaceutics review by Dr. Roshni Ramchandni for the PK analysis of the interaction with anticonvulsants in this study.

5.3 Study POG9571

A Trial Of Irinotecan In Children With Solid Tumors: A Pediatric Oncology Group (POG) Phase I Cooperative Agreement Study

Study period:
14 August 1996 to 03 June 1999.

Study Center:
19 centers participated n US and Canada. The coordinating center was:

Texas Children's Cancer Center
Houston, Texas

Primary Objectives:
- To estimate the maximum tolerated dose of irinotecan administered in children with refractory disease to standard therapy.

Secondary Objectives:
- To evaluate acute and chronic dose- limiting toxicities (DLTs) and describe cumulative toxicity in patients treated with multiple doses
- To determine the pharmacokinetics of irinotecan and its active metabolite SN- 38 as well as other metabolites and to correlate the pharmacokinetic data with toxicity

Study Design:
The study was an open-label, uncontrolled, dose-escalation, phase I trial.

Sequential cohorts of 3 patients were enrolled to receive progressively higher starting dose levels of irinotecan as a 60 minute IV infusion, daily x 5 every 3 weeks. If 1 of 3 patients at a dose level developed Cycle 1 DLT, an additional 3 patients were to be treated at that dose level. Toxicities were graded by the investigators according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), Version 2.

Based on the intensity of preprotocol treatment, 2 enrollment strata were included in the anticipation that the primary DLT would be myelosuppression secondary to intense prior treatment. In the event that myelosuppression was a DLT in heavily pretreated patients (Stratum 1), this stratum was to be closed and the protocol would continue to accrue less heavily pretreated patients into Stratum 2. Exclusion criteria for Stratum 2 patients included > 2 prior chemotherapy regimens and patients who had received any prior central axis radiation (skull, spine, pelvis or ribs) or a bone marrow transplant. Patients on anticonvulsants were also excluded.

While the study was ongoing, in February 1997, the eligibility criteria were revised to remove the exclusion criteria of craniospinal radiation therapy (XRT) and or = 50% XRT of the pelvis. .

Initially the age criteria were = 6 years to < 21 years of age. In March 1997, the protocol was amended to allow inclusion of patients aged > 1 to < 22 years. Children > 1 to < 6 years were entered in Stratum 3 and were to start treatment at 1 dose level below the level that children > 6 years were being treated at the time of study entry.

The MTD and DLTs were assessed in the context of specific supportive care recommendations. Dexamethasone and other antiemetics were to be given for prophylaxis of nausea and vomiting. Patients who developed diarrhea were to receive therapy with loperamide. Patients with cholinergic symptoms were to be treated with atropine 0.01 mg/ kg (maximum 0.4 mg) IV.

Throughout therapy, patients were evaluated for clinical and laboratory adverse events (AEs). Blood samples for PK sample analysis were collected on Day 1 of Cycle 1. For children with body weights = 20 kg, samples were also collected on Day 4 of Cycle 1. Repeated tumor measurements were to be obtained to assess response to therapy.

Regimen:
Irinotecan delivered daily for 5 days every 3 weeks.

Definition of DLT:
following adverse events (AEs) during Cycle 1: - Hematologic DLT was defined as any grade 4 neutropenia, anemia or thrombocytopenia lasting > 7 days. - Nonhematologic DLT was defined as any grade 3 or 4 nonhematologic toxicity with the exception of: Grade 3 nausea and vomiting of brief duration Grade 3 hepatic toxicity that returns to grade 1 prior to the next planned cycle Grade 3 fever

FDA Recommended Definition of DLT:
In addition to the AEs defined prospectively in the protocol, the occurrence of DLT was also evaluated using these additional toxicities: grade 3 ANC with fever, grade 3 diarrhea, grade 3 nausea, grade 3 vomiting and grade 3 hepatic dysfunction. Because the duration of grade 3 ANC and details of supportive therapy were not always available, the Sponsor counted any occurrence of these grade 3 toxicities as a DLT.

Results:
A total of 33 patients were enrolled. 27 had PK studies done. Median age was 9.5 years [range: 1.1 – 20.4 years]. The number of patients in each stratum and age group is given in table below. There were 2 patients less than 2 years old in stratum 3. This stratum was created for age groups 1-6 years. About half ranged from 2-12 years and a quarter were older than 16 years. Across all strata, the median duration of treatment was 1 cycle (range 1-20 cycles) and the median cycle duration was 21 days (range 20-119 days). Very few dose reductions occurred in all strata. Three (9.1%) of the 33 treated patients had irinotecan dose reductions: 1 patient in Stratum 1 and 2 patients in Stratum 2. No dose reductions occurred in the <6 years old stratum. The reason for dose reductions was neutropenia. Ten patients (30.3%) had a delay >24 days in 31 cycles before starting the next planned cycle. Similarly to the dose reductions, the delays occurred only in the heavily (5 patients) and less heavily (5 patients) pretreated patients.

Table 11: Age of patients by stratum for Study P9571

N , %		14 (100.0)	12 (100.0)	7 (100.0)	33 (100.0)
Age	1 months - <2 y[a]	-	-	2 (28.6)	2 (6.1)
	2y - <12y[a]	7 (50.0)	6 (50.0)	5 (71.4)	18 (54.5)
	12 - <16 y	3 (21.4)	2 (16.7)	-	5 (15.2)
	≥16 y	4 (28.6)	4 (33.3)	-	8 (24.2)

Thirty-one of 33 patients had received prior therapy. The following tumor types were enrolled in the trial:

Table 12: Tumor types in P9571

[illegible]	[illegible]	Stratum 1	Stratum 2	Stratum 3	All (%)
CNS	Astrocytoma	1 (7.1)	-	-	1 (3.0)
	Brain stem glioma		1 (8.3)	1 (14.3)	2 (6.1)
	Ependymoma	1 (7.1)	-	1 (14.3)	2 (6.1)
	Glioblastoma multiforme	-	1 (8.3)	1 (14.3)	2 (6.1)
	Neuroblastoma	4 (28.6)	2 (16.7)	1 (14.3)	7 (21.2)
	Pineoblastoma	1 (7.1)	-	-	1 (3.0)
Soft Tissue Sarcoma	Clear cell sarcoma	-	-	1 (14.3)	1 (3.0)
	Malignant rhabdoid tumor	1 (7.1)	-	-	1 (3.0)
	Rhabdomyosarcoma	1 (7.1)	1 (8.3)	1 (14.3)	3 (9.1)
Bone	Ewing's sarcoma	1 (7.1)	-	-	1 (3.0)
	Osteogenic sarcoma	-	3 (25.0)	-	3 (9.1)
	Osteosarcoma	1 (7.1)	-	-	1 (3.0)
Hepatic	Hepatocarcinoma	-	1 (8.3)	-	1 (3.0)
	Hepatoblastoma	-	1 (8.3)	-	1 (3.0)
GI	Colon adenocarcinoma	1 (7.1)	-	-	1 (3.0)
Lymphatic	Hodgkin's disease	1 (7.1)	-	-	1 (3.0)
	Large cell lymphoma	1 (7.1)	-	-	1 (3.0)
Renal	Adrenocortical tumor	-	-	1 (14.3)	1 (3.0)
	Wilm's tumor	-	2 (16.7)	-	2 (6.1)
Prior chemotherapy	0 regimen	1 (7.1)	1 (8.3)	1 (14.3)	3 (9.1)
	1 regimen	1 (7.1)	2 (16.7)	1 (14.3)	4 (12.1)
	>2 regimens	12 (85.7)	9 (75.0)	5 (71.4)	26 (78.8)
Prior Therapy	No prior therapy	-	1 (8.3)	-	1 (3.0)
	Chemo + Surgery	3 (21.4)	4 (33.3)	2 (28.6)	9 (27.3)
	Chemo + XRT	-	-	1 (14.3)	1 (3.0)

	Chemo + XRT + Surgery	11 (78.6)	7 (58.3)	4 (57.1)	22 (66.7)

Most patients (82%) discontinued the drug because of disease progression before MTD was reached.

Table 13: Reasons for Discontinuation for study P9571

	30 mg/m^2	39 mg/m^2	50 mg/m^2	All Dose Levels	50 mg/m^2	65 mg/m^2	All Dose Levels	39 mg/m^2	50 mg/m^2	All Dose Levels	All Strata
N %	5	4	5	14	6	6	12	4	3	7	33
Disease Progression	5 100.0	4 100.0	2 40.0	11 78.6	6 100.0	4 66.7	10 83.3	4 100.0	2 66.7	6 85.7	27 81.8
Adverse Event	-	-	-	-	-	-	-	-	1 33.3	1 14.3	1 3.0
Protocol Deviation	-	-	1 20.0	1 7.1	-	-	-	-	-	-	1 3.0
Consent Withdrawn	-	-	-	-	-	1 16.7	1 8.3	-	-	-	1 3.0
Died	-	-	1 20.0	1 7.1	-	-	-	-	-	-	1 3.0
Completed	-	-	1 20.0	1 7.1	-	-	-	-	-	-	1 3.0
Other	-	-	-	-	-	1 16.7	1 8.3	-	-	-	1 3.0

MTD Determination:
Fourteen patients were treated at 3 dose-levels in the heavily pre-treated group. Per the protocol, the MTD was established at 39 mg/ m2 in the heavily pretreated population and myelosuppression was the primary DLT. However, per the protocol, additional patients should have been evaluated before declaring the MTD. In the less heavily pre-treated group, the MTD was established at 50 mg/m^2, and myelosuppression was the primary DLT. Using the FDA's expanded definition for DLT, 1 additional patient (129933) experienced DLT (grade 3 SGPT) at Dose Level 4. Per the FDA's definition, no patients should have been treated at Dose Level 4 and additional patients should have been treated at Dose Level 2.

Table 14: DLTs for Stratum 1 (Heavily pre-treated patients)

1	91716	30	-	-	-
	120154	30	-	-	-
	126751	30	-	G3 Bilirubin G4 Creatinine	Removed from study after C1 due to PD

	127534	30	-	-	-
	122726	30	-	-	-
2	127990	39	G4 ANC (<7 days)	-	Removed from study after C1 due to PD
	123123	39	-	-	-
	124498	39	-	-	-
	126006	39	-	-	-
3	128436	50	-	-	-
	126423	50	G4 ANC	-	Removed from study after C1 due to PD
	126099	50	G4 ANC	-	Dose reduced to 39 mg/m^2 at C2
	561278	50	-	G3 Bilirubin	Removed from study after C1 due to PD and death
	128934	50	-	-	-

Table 15: DLTs for Stratum 2 patients (Less heavily pre-treated patients)

3	128544	50	G4 ANC	-	Removed from study after C1 due to PD
	128733	50	-	-	-
	128080	50	-	-	-
	124463	50	-	-	-
	561687	50	-	-	-
	562504	50	-	-	-
4	129933	65	-	G3 SGPT	Withdrew after C13 for liver transplant
	130019	65	-	-	-
	130329	65	-	-	-
	130499	65	G4 ANC	G3 Diarrhea G3 Bilirubin G4 Creatinine	Withdrew after C20 Consent withdrawn
	350572	65	G4 Thrombocytopenia	G3 Diarrhea G3 Infection	Removed from study after C1 due to PD

	207606	65	G4 ANC	-	Removed from study after C1 due to PD

Table 16: DLTs for Stratum 3 patients (Children < 6 years old)

2	350057	39	-	-	-
	128116	39	-	-	-
	129939	39	G4 ANC	-	-
	124134	39	-	G3 Diarrhea G3 Infection	-
3	130844	50	G4 ANC G4 thrombocytopenia G4 Infection G4 Erythema	G3 Diarrhea	Removed from study after C1 due to AE
	130294	50	-	-	-
	131148	50	-	-	-

In the <6 years old stratum, the MTD was established by POG at 39 mg/m^2. Myelosuppression was the primary DLT in this group. However, per protocol, 3 additional patients should have been treated at this dose level. Using the FDA's expanded definition for DLT, 1 additional patient at Dose Level 2 experienced DLTs (grade 3 diarrhea and grade 3 infection). Using this definition, grade 3 diarrhea was also a DLT for the patient at Dose Level 3. Escalation to Dose Level 3 should not have occurred and additional patients should have been treated at the 30 mg/m^2 dose level.

Using the expanded DLT definition recommended by the FDA, the Sponsor concurs that the MTD in the heavily pretreated and less heavily pretreated patients are appropriate (i.e. 39 mg/m2 and 50 mg/m2). Two additional heavily pretreated patients should have been treated at the 39 mg/m^2 dose. For the <6 years old cohort, the MTD was exceeded at 39 mg/m^2 and additional patients should have been treated at 30 mg/m^2.

Adverse events:
AEs were not routinely captured on the CRFs beyond cycle 1. A total of 13 patients (39.4%) had at least 1 AE. The nonhematological AEs most commonly reported were gastrointestinal disorders (nausea, vomiting, diarrhea) with 10 patients (30.3%) experienced at least one of them. Hematological toxicity was experienced by 6% (2/33 patients) of the patients overall. Grade 3-4 toxicities were reported by 21.2% of the patients; the most frequent grade 3-4 AE was diarrhea.

Stratum 1 AEs:

Five patients were treated in Stratum 1 at Dose Level 1 (30 mg/m^2). Most of the AEs were grade ≤2. One patient experienced a grade 4 neutropenia (assumed to be <7 days).

Four patients were treated in Stratum 1 at Dose Level 2 (39 mg/m^2). No AEs were reported on the CRFs for this cohort. One patient experienced a grade 4 neutropenia at Cycle 1. All other laboratory toxicities were grade ≤2.

Five patients were treated in Stratum 1 at Dose Level 3 (50 mg/m^2). Most of the AEs were grade ≤2. One patient experienced a grade 4 convulsion related to their primary disease. Two patients experienced grade 4 neutropenia and 1 patient experienced grade 3 bilirubin during Cycle 1.

Stratum 2 AEs

Six patients were treated in Stratum 2 at Dose Level 3 (50 mg/m^2). Only grade 1 clinical toxicities were reported. Two patients experienced grade 4 neutropenia (1 patient during Cycle 1) and 2 patients experienced grade 3 thrombocytopenia. One patient experienced a grade 3 liver dysfunction.

Six patients were treated in Stratum 2 at Dose Level 4 (65 mg/m^2). Three patients experienced grade 3 diarrhea and 1 patient experienced grade 3 vomiting. One patient had a grade 3 infection. Grade 3 neutropenia was experienced by 2 patients. Three patients experienced a grade 4 neutropenia (2 patients during Cycle 1). Two patients experienced grade 3 liver dysfunction and grade 4 bilirubin, respectively, both during Cycle 1. .

Stratum 3 AEs

Four patients were treated in Stratum 3 Dose Level 2 (39 mg/m^2). One patient experience grade 3 diarrhea and grade 3 infection during Cycle 1. Two patients experienced grade 4 neutropenia (1 patient during Cycle 1.

Three patients were treated in Stratum 3 Dose Level 3 (50 mg/m^2). One patient experienced grade 3 diarrhea, grade 4 infection, and grade 4 erythema multiforme during Cycle 1. The same patient experienced grade 4 thrombocytopenia.

Table 17: Serious Adverse Events

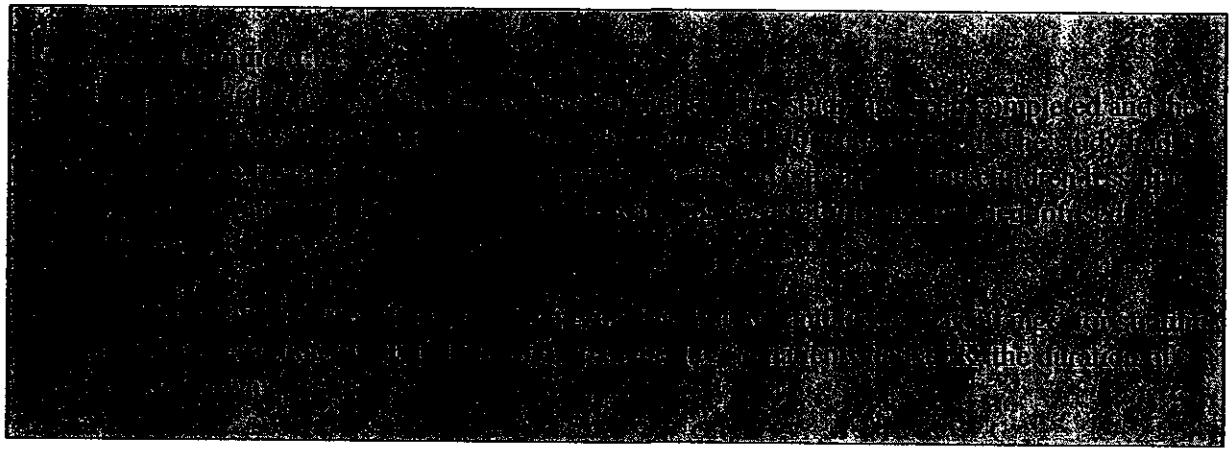
[illegible]	[illegible]	[illegible]	[illegible]	AE	[illegible]	[illegible]
122726 (1)	30	7	Neuroblastoma	G4 ANC	Yes	Yes
124134 (3)	39	1	Ependymoma	G3 Infection	Yes	Yes
126099 (1)	50	1	Pinealoblastoma	G4 Convulsions	No	No

Patient # (Stratum)	Starting Dose (mg/m²)	# of Cycle	Diagnosis	SAE	Investigator's Opinion Related to CPT-11?	Sponsor's Opinion Related to CPT-11?
130844 (3)	50	1	Brain Stem Glioma	G4 Erythema multiforme	UNK	UNK
				G4 ANC G4 thrombocytopenia	Yes	Yes
350572 (2)	65	1	Wilm's Tumor	G4 thrombocytopenia G3 Infection	Yes	Yes

Efficacy Results:

One patient (130844) was not evaluable for response. Four partial responses and 6 children with stable disease were observed [Blaney 2001] in patients in Stratum 1 and 2. No child in Stratum 3 responded. The PRs received 2-20 cycles of treatment and the SD received 4-15 cycles of treatment. The remaining patients had PD as their best response to irinotecan.

	Tumor Type	Stratum	Dose Level (mg/m²)	Cycles	Best Overall Response
128436	Hodgkin's Lymphoma	1	50	2	PR
122726	Neuroblastoma	1	30	15	PR
130499	Hepatocarcinoma	2	65	20	PR
124463	Glioblastoma	2	50	20	PR



5.4 St Jude Study

Title:

"A Phase I Study of Irinotecan (CPT-11) in pediatric patients with refractory solid tumors"

Date First Patient Enrolled: 14 October 1996
Date Last Patient Completed: 09 November 1997
No. of Patients enrolled: 23

Study Design:

The study was an open- label, uncontrolled, dose- escalation, phase I trial conducted in 1 center in the US enrolling patients with recurrent solid tumor unresponsive to conventional therapy. Prior to Amendment # 1, patients with prior craniospinal irradiation (XRT) and/ or = 30 Gy to > 50% of the pelvis were to be enrolled into Stratum 2.

Sequential cohorts of 3 patients were enrolled to receive progressively higher starting dose levels of irinotecan as a **60- min IV infusion on Cycle Days 1- 5 and 8- 12. Cycles were repeated every 21 days**. If 1 of 3 patients at a dose level developed a Cycle 1 DLT, an additional 3 patients were to be treated at that dose level. Dose escalations could continue unless 2/ 6 or 2/ 3 patients in a dose level experienced a DLT. Overall 6 patients were to be treated at the MTD. Toxicities were graded by the investigators according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 1.

Throughout therapy, patients were evaluated for clinical and laboratory adverse events. Blood samples for PK sample analysis were collected on Days 1 and 10 of Cycle 1 only. Tumor measurements were obtained prior to dosing and every 6 weeks thereafter to assess response to therapy. Patients were treated until progression of disease (PD), unacceptable toxicity or a decision by the physician or patient to discontinue therapy.

Results

DLT Determination

Due to possible hematologic toxicity, patients with previous craniospinal irradiation and/ or = 30 Gy to > 50% of the pelvis were to be enrolled in a separate strata). However, after a number of patients were enrolled and assessed for toxicity it was noted that the myelosuppression observed in these patients was not different from that observed in patients with lower intensity or no prior irradiation. Therefore, the protocol was amended and this stratification was removed. For purpose of this report, the DLTs and MTD data are reported without reference to a separate strata for prior irradiation.

"A total of 73 cycles of irinotecan treatment were administered. The median duration of treatment was 2.5 cycles with a range of 1- 7 cycles. The median cycle duration was 21 days (range 20- 34 days)."

Table 18: Cycle 1 DLTs

Applicant table 7

13322	20	-
14099	20	G3 Diarrhea
13468	20	Neutropenic fever, G3 Hypotension
13893	20	-
14884	20	-
13707	20	G3 Vomiting
13804	20	G3 Diarrhea
14520	20	-
14880	20	G4 Diarrhea, G3 Vomiting, G3 Nausea
13450	24	G3 Diarrhea
13829	24	-
13956	24	-
13440	24	-
13453	24	-
11669	24	Neutropenic fever, G4 Diarrhea, G3 Hypotension
14451	24	*NE for DLT; pt only received 5 doses of Cycle 1*
13906	24	G4 Fever, G3 SGPT/SGOT
14461	24	-
13272	24	G4 Diarrhea
14980	24	G4 Fever, G4 Diarrhea, G3 Infection, G4 Hypotension
13404	29	G4 Diarrhea
14113	29	G4 Neutropenia

"Nine patients were treated at the starting dose of 20 mg/ m2. Of the 9 patients, 5 experienced a DLT. Only 1 patient (13468) experienced a hematological toxicity during Cycle 1 (febrile neutropenia with grade 3 hypotension). The remaining 4 patients with DLTs experienced grade 3- 4 diarrhea and grade 3 nausea and vomiting."

"The dose was escalated to 24 mg/ m^2 and 11 patients were treated at this level. Six of the patients enrolled experienced grade 2- 4 events: however, 1 patient (14451) did not complete Cycle 1 and was not considered evaluable for DLT by the investigator. One patient experienced febrile neutropenia (11669); the other patients experienced nonhematological toxicities (grade 3-4 diarrhea, grade 4 fever, grade 3 infection and grade 3 SGPT/ SGOT."

"An attempt was made to escalate the dose to 29 mg/ m^2 and 2 patients were treated at this dose level but both experienced grade 4 toxicities (diarrhea and neutropenia)."

"Due to the number of patients experiencing a DLT at 24 mg/ m^2, the investigator established the MTD at 20 mg/ m^2. However, as the final data are presented without reference to the original

stratification, the statistical properties of the original dose escalation algorithm no longer apply. Based on this data, as both the 24 mg/m^2 and 20 mg/m^2 dose levels show similar rates of DLT, the Sponsor concurs that the lower dose of 20 mg/ m^2 daily x 5, for 2 consecutive weeks every 3 week schedule is a possible starting dose."

"None of the patients in the 20 mg/ m^2 dose group (MTD) required a dose reduction. Most of the dose reductions that were required in the 24 and 29 mg/ m^2 dose groups occurred in Cycle 2. Over all dose groups, 11 patients had a cycle delay > 24 days and 18 of 73 (25%) cycles were delayed."

Adverse Events:

Frequencies of clinically important AEs reported for all patients are summarized below. All 22 patients (100%) had at least 1 AE. The most common nonhematologic AEs were gastrointestinal disorders (diarrhea, vomiting, nausea) and hyponatremia. Hematologic toxicity was the second most frequent AE, experienced by 19 (86%) patients overall. Eighteen (82%) patients experienced AEs that were = grade 3 severity. The most frequent of these were hematologic and gastrointestinal AEs experienced by 15 (68%) and 10 (44%) patients, respectively.

Nine patients were treated at the 20 mg/ m^2 dose level (MTD). The most frequent grade 3 or 4 AEs were anemia and neutropenia (6 patients each), leukopenia (5 patients), and diarrhea (3 patients). Other grade 4 AEs were neutropenic fever, infection, blood phosphorous, blood potassium, hypocalcemia, and hypercalcemia (1 patient each). One patient (14880) experienced a fatal cardiac arrest.

Table 19: Selected Adverse Events for the St. Judes Study- All patients, All Cycles

Applicant table 11

MedDRA Term						
Any	22 (100)	-	4 (18.2)	4 (18.2)	12 (54.5)	2 (9.1)
Blood/Lymphatic (Any)	19 (86.4)	1 (4.5)	3 (13.6)	8 (36.4)	7 (31.8)	-
Leukopenia	17 (77.3)	2 (9.1)	5 (22.7)	6 (27.3)	4 (18.2)	-
Anemia	16 (72.7)	2 (9.1)	5 (22.7)	9 (40.9)	-	-
Neutropenia	16 (72.7)	1 (4.5)	2 (9.1)	7 (31.8)	6 (27.3)	-
Thrombocytopenia	10 (45.5)	4 (18.2)	3 (13.6)	2 (9.1)	1 (4.5)	
Cardiac (Any)	2 (9.1)	1 (4.5)	-	-	-	1 (4.5)
Arrhythmia	1 (4.5)	1 (4.5)	-	-	-	-
Cardiac arrest	1 (4.5)	-	-	-	-	1 (4.5)
Gastrointestinal (Any)	22 (100)	-	11 (50.0)	4 (18.2)	6 (27.3)	-
Diarrhea	22 (100)	2 (9.1)	10 (45.5)	3 (13.6)	6 (27.3)	-
Vomiting	12 (54.5)	2 (9.1)	6 (27.3)	2 (9.1)	1 (4.5)	-
Nausea	11 (50.0)	3 (13.6)	6 (27.3)	1 (4.5)	1 (4.5)	
Abdominal pain	4 (18.2)	-	3 (13.6)	-	1 (4.5)	-

Stomatitis	2 (9.1)		1 (4.5)	1 (4.5)	-	-
Constipation	2 (9.1)	1 (4.5)	1 (4.5)			
General (Any)	11 (50.0)	-	6 (27.3)	-	4 (18.2)	1 (4.5)
Pyrexia	10 (45.5)	-	5 (22.7)	-	5 (22.7)	-
Rigors	2 (9.1)	1 (4.5)	-	-	1 (4.5)	-
Condition aggravated	1 (4.5)	-	-	-	-	1 (4.5)
Fatigue	1 (4.5)	-	1 (4.5)	-	-	-
Infections (Any)	7 (31.8)	2 (9.1)	1 (4.5)	2 (9.1)	2 (9.1)	-
Infection	6 (27.3)	1 (4.5)	1 (4.5)	2 (9.1)	2 (9.1)	-
Herpes zoster	1 (4.5)	1 (4.5)				
Investigations (Any)	15 (68.2)	5 (22.7)	5 (22.7)	4 (18.2)	1 (4.5)	-
Blood phosphorus	9 (40.9)	4 (18.2)	4 (18.2)	-	1 (4.5)	-
Blood potassium	8 (36.4)	4 (18.2)	2 (9.1)	1 (4.5)	1 (4.5)	-
Weight decreased	10 (45.5)	5 (22.7)	5 (22.7)	-	-	-
Blood magnesium decreased	5 (22.7)	2 (9.1)	1 (4.5)	2 (9.1)	-	-
Blood chloride	4 (18.2)	4 (18.2)	-	-	-	-
Blood albumin	3 (13.6)	2 (9.1)	1 (4.5)	-	-	-
Blood creatinine	3 (13.6)	3 (13.6)	-	-	-	-
Blood urea	3 (13.6)	2 (9.1)	1 (4.5)	-	-	-
Blood bicarbonate	2 (9.1)	1 (4.5)	1 (4.5)	-	-	-
Blood Bilirubin	2 (9.1)	1 (4.5)	1 (4.5)	-	-	-
ALT increased	4 (18.2)	1 (4.5)	1 (4.5)	2 (9.1)		
AST increased	4 (18.2)	1 (4.5)	1 (4.5)	2 (9.1)		
Blood uric acid increased	2 (9.1)	1 (4.5)	1 (4.5)			
Metabolism/Nutrition (Any)	16 (72.7)	7 (31.8)	3 (13.6)	3 (13.6)	3 (13.6)	-
Hyponatremia	13 (59.1)	7 (31.8)	4 (18.2)	1 (4.5)	1 (4.5)	-
Hypocalcemia	9 (40.9)	7 (31.8)	-	1 (4.5)	1 (4.5)	-
Anorexia	5 (22.7)	1 (4.5)	4 (18.2)	-	-	-
Hyperglycemia	3 (13.6)	1 (4.5)	1 (4.5)	1 (4.5)	-	-
Hypercalcemia	2 (9.1)	1 (4.5)	-	-	1 (4.5)	-
CNS (Any)	4 (18.2)	4 (18.2)	-	-	-	-
Headache	3 (13.6)	3 (13.6)	-	-	-	-
Somnolence	1 (4.5)	1 (4.5)				
Respiratory (Any)	1 (4.5)	1 (4.5)	-	-	-	-
Cough	1 (4.5)	1 (4.5)	-	-	-	-
Skin (Any)	1 (4.5)	1 (4.5)				
Rash maculopapular	1 (4.5)	1 (4.5)				
Vascular (Any)	5 (22.7)	-	1 (4.5)	3 (13.6)	1 (4.5)	-
Hypotension	4 (18.2)	-	1 (4.5)	2 (9.1)	1 (4.5)	-
Hypertension	1 (4.5)	-	-	1 (4.5)	-	-

Discontinuations:

Due to Adverse Events One patient withdrew from this study due to an AE that was considered serious at the dose level of 24 mg/m2. This patient experienced neutropenic fever, grade 4 diarrhea, grade 3 hypotension.

On-Study Deaths:

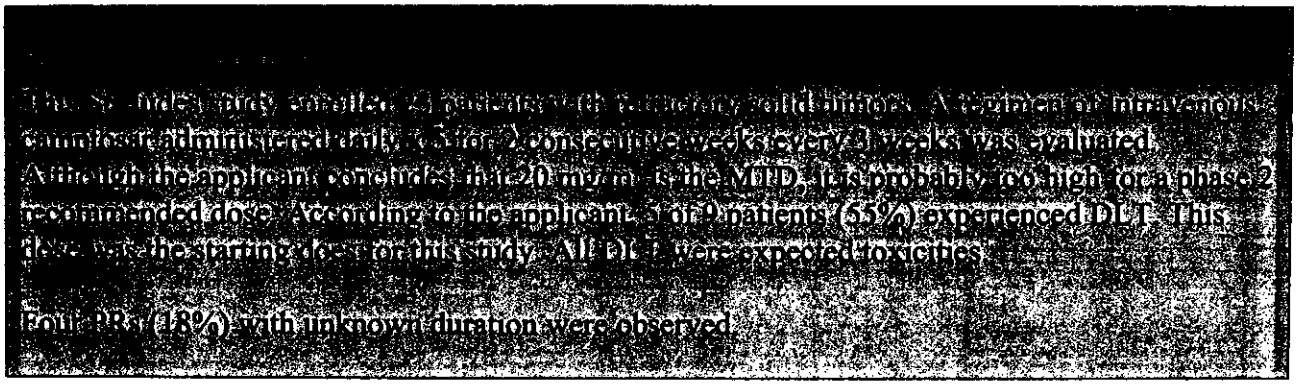
Patients were considered to have died on- study if their death occurred = 30 days of the last dose of irinotecan. Four patients (18.2%) died on-study and all deaths were due to PD.

Efficacy Results:

The best overall tumor response observed for each patient is shown in the table below. All 22 patients were evaluated for response. There were 4 PRs (18.2%) overall, 1 each at 20 and 29 mg/m^2 and 2 at 24 mg/m^2. The patients with PR were on treatment from 2-6 cycles. All but 1 patient (13322) had their PR confirmed with a follow- up assessment. At the MTD, (20 mg/m^2) the PR rate was 11%.

Overall there were 15 (68.2%) patients with SD, 8 patients at 20 mg/ m^2, 6 patients at 24 mg/ m^2 and 1 patient at 29 mg/m^2. The patients with SD were on treatment from 2-7 cycles. Three (13.6%) patients in the 24 mg/ m^2 dose group had PD as their best overall tumor response.

	[illegible]	[illegible]	[illegible]	[illegible] Response
13322	Rhabdomyosarcoma	20	5	PR
13468	PNET	20	4	SD
13707	Osteosarcoma	20	2	SD
13804	Neuroblastoma	20	3	SD
13893	Neuroblastoma	20	7	SD
14099	Osteosarcoma	20	2	SD
14520	Osteosarcoma	20	2	SD
14880	Hepatoblastoma	20	3	SD
14884	Osteosarcoma	20	2	SD
11669	Carcinoma of Larynx	24	2	PR
13956	Rhabdomyosarcoma	24	5	PR
13272	Oligodendroglioma	24	3	SD
13450	Anaplastic astrocytoma	24	2	SD
13829	PNET	24	5	SD
13906	Neuroblastoma	24	2	SD
14461	Rhabdomyosarcoma	24	2	SD
14980	Osteosarcoma	24	4	SD
14451	Medulloblastoma	24	1	PD
13440	PNET	24	2	PD
13453	Astrocytoma	24	2	PD
14113	Neuroblastoma	29	6	PR
13404	Neuroblastoma	29	7	SD



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St. Judes Study
Phase I study 4

Phase 2 Studies

5.5 Study P9761

A Phase II Trial of Irinotecan in Children with Refractory Solid Tumors: A Children's Oncology Group (COG) Study.

Note: A preliminary report has been submitted for this study. 3 strata were still open for stage 3 after the cut-off date, and approximately 10 patients were enrolled after cut off date.

Date of First Patient Enrolled: 17 November 1999
Date of Last Patient Completed: 16 September 2002

Study Design

Primary Objectives:
To determine the efficacy of irinotecan in the treatment of children with refractory neuroblastoma, sarcomas of soft tissue or bone, other solid tumors, or brain.

Secondary Objectives:
- To further evaluate the toxicity of irinotecan when given daily for 5 days, repeated every 21 days.
- To further evaluate the PK/PD of irinotecan and its metabolites SN-38, SN-38G, and APC using a limited sampling strategy.
- To determine patient UGT1A1 genotype, and correlate genotype with toxicity and PK (SN-38, SN-38G AUC) parameters

Entry Criteria:
Diagnosis:
a. Solid Tumors Patients with histologically or cytologically documented solid tumors which are recurrent or refractory, including:
1) neuroblastoma
2) Ewing's Sarcoma/peripheral primitive neuroectodermal tumor
3) osteosarcoma
4) rhabdomyosarcoma
5) other extracranial solid tumors, that are refractory to conventional therapeutic modalities

b. CNS Tumors Patients with histologically documented brain tumors who exhibit recurrent or refractory tumor growth will be eligible. Patients will be stratified based on tumor histology into the following groups:
1) medulloblastoma/PNET
2) ependymoma
3) brain stem glioma
4) other CNS tumor

For patients with intrinsic brain stem tumors or classic optic glioma, the requirement for histologic verification may be waived. However, for patients with brain stem tumors treated with

hyperfractionated radiotherapy, biopsy is strongly recommended prior to study entry to rule out radionecrosis as a possible cause of MRI changes. Biopsy is required for patients treated with radiosurgery.
Measurable Disease:.
Age: Patient must be >1 at the time of study enrollment, and <21.99 years of age at the time of original diagnosis.
Life Expectancy: of 8 weeks and have no severe uncontrolled infection.
Performance status: Karnofsky > 50% for patients > 10 years of age or Lansky > 50% for children < 10 years of age.
Adequate Hematologic Status, organ function, recovered from prior therapy

Exclusion Criteria
Patients who have received more than two prior chemotherapy regimens are not eligible for this study. Patients who have received prior irinotecan.
Patients who have had prior total body irradiation are excluded from this study.
Patients who are taking anticonvulsants. Such patients may be eligible for the Phase I trial of irinotecan in patients on anticonvulsants.
Patients with uncontrolled infections.
Women of childbearing age must not be pregnant or lactating. This group is excluded because of the teratogentic potential of this agent demonstrated in rat and rabbit models.

Treatment Schema

Week	1					2	3	4					5	6	7
Day	1	2	3	4	5			1	2	3	4	5			E
	↑	↑	↑	↑	↑			↑	↑	↑	↑	↑			V
															A
															L

T = Irinotecan I.V. over 60 minutes
*EVAL = Additional imaging studies as needed for tumor evaluation, obtain every other cycle (CR and PR). All responding patients must have their response confirmed 3-6 weeks after the first documentation of response. Following response confirmation, disease can be reassessed every 12 weeks (sooner if clinically indicated).

Dosage and schedule:
Irinotecan was administered at a dose of 50 mg/m^2/ day for 5 consecutive days. Cycles were repeated every 3 weeks. The drug was given as a 60- minute IV infusion.

The dose of Irinotecan will be 50mg/m^2.

Participation in Pharmacokinetic Studies:
Pharmacokinetic studies will be obtained on day 1 during the first course. The first 12 patients enrolled will have complete pharmacokinetic sampling obtained for validation of the limited sampling strategy. Subsequent patients will have limited samples drawn on day one.

Dose modification
Any Grade 3 or 4 non-hematologic toxicity should be reported immediately to the Study Coordinator. The Study Coordinator should also be notified of any dosage modification secondary to toxicity.

a. Myelosuppression: Patients with greater than 25 days between treatment courses secondary to thrombocytopenia will have the dose for subsequent courses reduced to 39 mg/m^2.

Patients with more than 25 days between treatment courses secondary to neutropenia may receive the same dose of irinotecan in the next course with G- CSF (Filgrastim) support. If the treatment course with G-CSF (Filgrastim) support is greater than 25 days secondary to myelosuppression, then a reduction in the irinotecan dose, as outlined above, should be made for subsequent courses. If G-CSF (Filgrastim) support is not utilized, the irinotecan dose should be reduced as outlined above.

b. Organ system toxicity: Irinotecan related irreversible (within 4 weeks of drug administration) grade 3 or 4 renal, hepatic, central nervous system toxicity will result in discontinuation of irinotecan in the patient experiencing the toxicity.

c. Diarrhea: In patients who experience irinotecan related grade 4 diarrhea despite maximum therapy with loperamide, the dose of irinotecan in the next cycle will be reduced to 39 mg/m^2/day. Subsequent cycles should not begin until the diarrhea is grade 1 or less. Notify the study coordinator of all dose reductions due to diarrhea.

Results
No CRFs or electronic datasets were included. The results reported are submitted in the study report.

A total of 170 patients were accrued. All 170 patients received ≥1 dose of irinotecan and received a total of 633 cycles of treatment. The median number of cycles was 2.0 [range: 1- 30]. The distribution by tumor type is given in the "disposition" table below.

Table 20 : Disposition

Applicant table 2

	BSG	ES	OSA	RMS	Other Solid	MBL	NBL	PNET	Other CNS
N = 170	18	18	12	19	43	21	9	10	20
%	10.6	10.6	7.1	11.2	25.3	12.4	5.3	5.9	11.8

Abbreviations: BSG= Brain stem glioma, EPM= Ependymoma, ES= Ewing's sarcoma, MBL= Medulloblastoma, NBL= Neuroblastoma, OSA= Osteosarcoma, PNET= Primitive neuroectodermal tumor, RMS= Rhabdomyosarcoma

The majority of the patients (76.5%) received 2 cycles of treatment. Seventeen percent patients received = 6 cycles and a few patients (11.2%) received 8 cycles. Over the duration of the study, 53 (31.2%) of the patients experienced a cycle delay > 24 days and 137 (21.6%) out of 633 total cycles were delayed.

Most patients (72%) discontinued treatment because of disease progression. Only 1.8 % discontinued treatment because of AE.

Table 21: Reasons for discontinuation

N (%)	18	18	12	19	43	21	9	10	20	170 (100%)
PD	12 (66.7)	14 (77.8)	9 (75.0)	16 (84.2)	32 (74.4)	12 (57.1)	8 (88.9)	7 (70.0)	13 (65.0)	123 (72.4)
Other	2 (11.1)	3 (16.7)	1 (8.3)	2 (10.5)	2 (4.7)	3 (14.3)	-	-	1 (5.0)	14 (8.2)
Consent Withdrawn	2 (11.1)	1 (5.6)	1 (8.3)	-	2 (4.7)	1 (4.8)	1 (11.1)	-	3 (15.0)	11 (6.5)
Death	-	-	1 (8.3)	-	2 (4.7)	1 (4.8)	-	-	2 (10.0)	6 (3.5)
Completed Txt	-	-	-	1 (5.3)	3 (7.0)	-	-	-	-	4 (2.4)
AE	1 (5.6)	-	-	-	-	1 (4.8)	-	1 (10.0)	-	3 (1.8)
Protocol Deviation	1 (5.6)	-	-	-	1 (2.3)	1 (4.8)	-	-	-	3 (1.8)
On Txt	-	-	-	-	1 (2.3)	2 (9.5)	-	2 (20.0)	1 (5.0)	6 (3.5)

NBL = Neuroblastoma, OSA = Osteosarcoma, PNET = Primitive neuroectodermal tumor, RMS = Rhabdomyosarcoma, Txt = Treatment

There were proportionally more males (60%) than females (40%). Most (88.2%) patients had a good ECOG PS (0 - 1) and a few patients (10.6%) had PS of 2. All age categories were represented but the majority of the patients (58.2%) were in the age group 2 - < 12 years. Only 4 (2.4%) patients were enrolled in the 1 mo - < 2 years category. The median age was 9.9 years [range 1.2 - 23.5 years]. All except 5 patients had received prior therapy.

Table 22: Prior Therapy

Applicant table 7

N (%)	18 (100%)	18 (100%)	12 (100%)	19 (100%)	43 (100%)	21 (100%)	9 (100%)	10 (100%)	20 (100%)	170 (100%)
Chemo Txt	2 (11.1)	1 (5.6)	-	1 (5.3)	6 (14.0)	1 (4.8)	-	-	1 (5.0)	12 (7.1)
Surgery + Chemo Txt	1 (5.6)	2 (11.1)	10 (83.3)	-	12 (27.9)	1 (4.8)	-	-	1 (5.0)	27 (15.9)
Chemo Txt + XRT	6 (33.3)	1 (5.6)	1 (8.3)	3 (15.8)	4 (9.3)	1 (4.8)	7 (77.8)		2 (10.0)	25 (14.7)
Surgery + XRT	-	-	-	1 (5.3)	-	-	-	4 (40.0)	-	5 (2.9)
Surgery + XRT+ Chemo Txt	8 (44.4)	12 (66.7)	1 (8.3)	14 (73.7)	19 (44.2)	18 (85.7)	2 (22.2)	6 (60.0)	16 (80.0)	96 (56.5)

No Data	1 (5.6)	2 (11.1)	-	-	2 (4.7)	-	-	-	-	5 (2.9)

Abbreviations: BSG = Brain stem glioma, Chemo = Chemotherapy, EPM = Ependymoma, ES = Ewing's sarcoma, MBL = Medulloblastoma, NBL = Neuroblastoma, OSA = Osteosarcoma, PNET = Primitive neuroectodermal tumor, RMS =

Efficacy:

The total response rate was about 5%. The TTP is summarized in Table 16 of the study report. The median TTP for all substrata was 6.6 weeks [95% CI 6.0 - 7.6]. The median overall survival for all substrata was 28.7 weeks, with a range of 19.7 – 54.1 weeks [95% CI 21.6 – 32.7].

Table 23: Best overall response

Applicant table 12

N (%)	18 (100%)	18 (100%)	12 (100%)	19 (100%)	43 (100%)	21 (100%)	9 (100%)	10 (100%)	20 (100%)	170 (100%)
CR+PR	-	1 (5.6)	-	3 (15.8)	1 (2.3)	3 (14.3)	-	-	1 (5.0)	9 (5.3)
CR	-	-	-	1 (5.3)	1 (2.3)	-	-	-	-	2 (1.2)
PR	-	1 (5.6)	-	2 (10.5)	-	3 (14.3)	-	-	1 (5.0)	7 (4.1)

Table 24: Patients who responded to Irinotecan

Applicant table 13

214404	6/M	Rhabdomyosarcoma Other Solid Tumors	4	50	CR
140862	3/F	(Hepatoblastoma)	22	50	CR
131228	3/M	Neuroblastoma	7	50	PR
214038	10/M	Rhabdomyosarcoma	7	50	PR
573449	5/F	Rhabdomyosarcoma	3	50	PR
568076	20/M	Medulloblastoma	21	50	PR
707059	12/F	Medulloblastoma	16	50	PR
140451	11/M	Medulloblastoma	6	50	PR
565790	17/F	Other CNS Tumors (Germinoma)	8	50	PR

Safety:

170 patients received a total of 633 cycles. The median number of cycles was 2 [range 1- 30 cycles].Of the 170 patients, 134 (78.8%) experienced at least 1 irinotecan-related AE. The most

common (64.7%) drug- related AEs were gastrointestinal. The second most common (52.4%) drug- related AEs were hematologic. The incidence rate of drug- related AEs of grade 3 or higher was 52.4% (89 patients, including 1 grade 5 AE).

Diarrhea occurred in 104 (61.2%) patients with only 35 (20.6%) patients experiencing grade 3- 4 diarrhea. Vomiting was experienced by 46 (27.1%) patients and was severe (grade 3- 4) in 13 (7.6%) patients.

The most frequent hematologic AE was neutropenia experienced by 66 (38.8%) patients. Grade 3- 4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Anemia was experienced by 46 (27.1%) patients. Out of these patients 17 (10.0%) had grade 3- 4 anemia. Thrombocytopenia was experienced by 25 (14.7%) patients. Only 9 (5.3%) of these patients had grade 3- 4 thrombocytopenia.

Table 25: CPT- 11- Related Adverse Events – All Substrata, All Cycles

Applicant table

		Maximum CTC Grade					
		All	1	2	3	4	5
System Organ Class	MedDRA Term	134	13	32	49	39	1
Blood/ Lymphatic	Any	89	10	12	35	31	1
	Febrile Neutropenia	15	-	1	12	1	1
	Neutropenia	66	6	6	24	30	-
	Anemia	46	13	16	13	4	-
	Lymphopenia	11	-	5	4	2	-
	Hemolysis	1	-	1	-	-	-
	Leucopenia	57	7	13	19	18	-
	Thrombocytopenia	25	7	9	8	1	-
Cardiac	Any	1	-	1	-	-	-
	Edema	1	-	1	-	-	-
Eye	Any	1	1	-	-	-	-
	Eye irritation	1	1	-	-	-	-
Gastrointestinal	Any	110	24	41	38	5	-
	Diarrhea	104	33	34	32	3	-
	Vomiting	46	14	19	12	1	-
	Nausea	26	12	6	8	-	-
	Abdominal pain	21	9	5	7	-	-
	Stomatitis	5	1	2	1	1	-
	Constipation	3	3	-	-	-	-
	Rectal bleeding	3	2	1	-	-	-
	Bowel sounds	1	1	-	-	-	-
	Caecitis	1	-	-	1	-	-
	Dyspepsia	1	1	-	-	-	-
	Dysphagia	1	-	1	-	-	-
	Flatulence	2	-	2	-	-	-
	Salivary gland disorder	1	1	-	-	-	-
	Hematemesis	1	-	-	1	-	-
	Hiccups	1	1	-	-	-	-
	Ileus	1	-	-	1	-	-
General	Any	21	8	10	3	-	-
	Fatigue	12	5	5	2	-	-
	Pyrexia	9	4	5	-	-	-
	Rigors	2	1	1	-	-	-
	Chest pain	1	-	1	-	-	-
	Pain	1	-	-	1	-	-
Hepatobiliary	Any	13	7	3	3	-	-
	Hypoproteinemia	13	7	3	3	-	-
Infections	Any	13	1	6	5	1	-
	Infection	13	1	6	5	1	-
	Implant infection	1	-	-	1	-	-
	Wound infection	1	1	-	-	-	-
Investigations	Any	38	14	15	7	2	-
	ALT increase	19	9	7	3		-

		Maximum CTC Grade					
		All	1	2	3	4	5
System Organ Class	MedDRA Term	134	13	32	49	39	1
	AST increase	13	8	2	2	1	-
	Bilirubin	9	2	3	3	1	-
	Creatinine	6	5	1	-	-	-
	Weight decreased	6	1	4	1	-	-
	Magnesium	5	4	1	-	-	-
	GGT	4	1	1	1	1	-
	Alkaline Phosphatase	3	2	1	-	-	-
	aPTT	2	2	-	-	-	-
	Lipase increase	1	-	1	-	-	-
	MRI abnormal	1	-	1	-	-	-
Metabolism/ Nutrition	Any	35	9	10	7	9	-
	Hypokalemia	19	8	3	4	4	-
	Dehydration	13	-	6	6	1	-
	Anorexia	8	1	3	1	3	-
	Hypophosphatemia	7	5	-	2		-
	Hyponatremia	6	1	-	3	2	-
	Hypocalcemia	5	1	3	1	-	-
	Hypercalcemia	2	1	1	-	-	-
	Hyperglycemia	2	1	1	-	-	-
	Hypernatremia	1	1	-	-	-	-
	Vit B1 deficiency	1	-	1	-	-	-
Musculoskeletal	Any	4	3	-	1	-	-
	Arthralgia	2	1	-	1	-	-
	Joint stiffness	1	1	-	-	-	-
	Muscle cramp	1	1	-	-	-	-
	Muscle weakness	1	-	-	1	-	-
	Pain in limb	1	1	-	-	-	-
CNS	Any	9	5	1	2	1	-
	Dizziness	5	3	1	1	-	-
	Headache	2	2	-	-	-	-
	Convulsion	1	-	-	1	-	-
	Hemorrhagic stroke	1	-	-	-	1	-
	Insomnia	1	1	-	-	-	-
	Peripheral neuropathy	1	1	-	-	-	-
Renal/Urinary	Any	1	-	1	-	-	-
	Urinary frequency	1	-	1	-	-	-
Respiratory	Any	4	1	1	2	-	-
	Pneumonitis	2	1		1	-	-
	Dyspnea	1	-	1	-	-	-
	Epistaxis	1	-	-	1	-	-
	Hemoptysis	1	-	-	1	-	-
	Hypoxia	1	-	-	1	-	-
	Rhinitis	1	1	-	-	-	-
	Tachypnea	1	-	-	1	-	-

		Maximum CTC Grade					
		All	1	2	3	4	5
System Organ Class	MedDRA Term	134	13	32	49	39	1
Skin	Any	10	3	7	-	-	-
	Alopecia	5	1	4	-	-	-
	Dermatitis	2	1	1	-	-	-
	Dermatitis exfoliative	2	1	1	-	-	-
	Pigmentation disorder	1	1	-	-	-	-
	Pruritis	1	-	1	-	-	-
	Sweating increase	1	1	-	-	-	-
Procedures	Any	14	-	2	11	1	-
	RBC transfusion	12	-	1	11	-	-
	Platelet transfusion	7	-	1	5	1	-
Vascular	Any	4	2	2	-	-	-
	Flushing	4	3	1	-	-	-
	Hypotension	1	-	1	-	-	

[redacted]

[redacted] phase 2 study that enrolled 70 patients with refractory solid tumors in children [redacted] aged from 1.2-23.3 years. Irinotecan was infused at 50mg/m² x 5 days q 3 weeks. [redacted] patients had received some prior treatment. No data was available for 5 patients. Three [redacted] of the patients received 2 cycles of treatment. The RR was 5% (2 CRs and 2 PRs). The [redacted] was 6.6 weeks and median OS was 28.7 weeks (range 21.6 – 32.7 weeks). The [redacted] events were as expected.

The trial was a reasonably large, phase 2 trial. The RR was low, although 2 CR were observed. Median TTP and OS had a relatively short duration.

5.6 D9802

A Phase II "Up- Front Window Study" Of Irinotecan (CPT-11) Followed By Multimodal, Multiagent Therapy For Selected Children And Adolescents With Newly Diagnosed Stage 4/ Clinical Group IV Rhabdomyosarcoma: An IRS- V Study A Preliminary Report on the Up-Front Window Single- Agent Irinotecan (SAI) Treatment

Studied Period: 09 September 1999 - 11 September 2001
Patients enrolled: 21
Principal Investigator:
Alberto Pappo M.D.
St Jude Children's Research Hospital
Memphis, TN 38105- 2794
# of Study Sites: 20

Objectives:

• To estimate the objective tumor response rate (RR) associated with 2 cycles SAI when administered as up-front window therapy, using a low-dose, protracted, intravenous (IV) schedule in high- risk, previously untreated children with metastatic RMS

• To describe the toxicities associated with irinotecan when administered as described above

• To study the pharmacokinetics (PK) of irinotecan (SAI and VCPT) in previously untreated children with RMS who are treated on a low dose, protracted course and who also receive vincristine.

Study design:

The study was a multi- center, open- label, uncontrolled, single arm, phase II trial in children and adolescents with newly diagnosed, stage 4/ clinical group IV metastatic RMS.

The study aimed at assessing whether the RR associated with 2 cycles of SAI (single-agent irinotecan) deserved clinical interest. In patients who achieved objective response, the **SAI was to be followed by multimodal therapy of alternating cycles of VAC or VCPT. Radiotherapy was to be delivered between Weeks 15 and 22 of the induction phase.**

Irinotecan was to be administered at a dose of 20 mg/m^2/day for 5 consecutive days, as a 60 minute IV infusion. Patients were to receive irinotecan: Weeks 0 and 1, rest 1 week then repeat at Weeks 3 and 4. Antiemetics (ondansetron and granisetron) in appropriate dosage were recommended in the protocol. Early diarrhea was treated with atropine prophylaxis and late diarrhea was treated with loperamide and other supportive care as appropriate.

Accepted clinical and radiographic response criteria were used to evaluate tumor response. The assessment of the efficacy of the multimodal therapy following the SAI window was an additional goal of the study. Safety was monitored throughout the study: the standard NCI

definitions of toxicity (NCI Common Toxicity Criteria [CTC] Version 2.0) were used by the investigators consistent with the usual cooperative group practice in the phase II evaluation of cytotoxic agents.

PK studies were included to look for associations between drug exposure parameters and toxicity or efficacy. The time- course of plasma concentrations of irinotecan and its active metabolite SN- 38 as well as SN- 38G, the glucuronide metabolite of SN- 38, and APC were measured. Plasma concentrations of both the lactone and carboxylate species of the parent drug and metabolites were measured. PK assessments were carried out after the first irinotecan dose in Week 0 (SAI window), Week 9 (VCPT induction phase), and Week 26 (VCPT continuation phase). Only the PK data from Week 0 are presented in the sponsor's report.

Study Regimen:
Single- agent irinotecan (SAI) was administered at a dose of 20 mg/m^2 x5 days (Weeks 0 and 3), rest for 2 days, resume daily x5 (Weeks 1 and 4), followed by tumor assessment. Then depending on their response to SAI, patients went onto multiagent, multimodal therapy.

Patients completing the 2 irinotecan cycles were to continue as medically recommended to either of the 2 treatment schema based on the tumor response achieved within the previous period.

Treatment assignment A: patients responding to irinotecan (CR or PR) were to receive multimodal, multiagent therapy as follows:

- Induction treatment (Weeks 6- 14) VCPT alternating with V and VAC schema
- Radiotherapy (Weeks 15- 22)
- Continuation (Weeks 26- 44) VCPT alternating with V and VAC schema

Treatment assignment B: patients rated as NR/ SD/ PD were to receive multimodal, multiagent therapy as follows:
- Induction treatment (Weeks 6- 14) VAC alternating with V schema
- Radiotherapy (Weeks 15- 22)
- Continuation (Weeks 26- 44) VAC alternating with V schema

Patients not eligible for the SAI upfront window, with parameningeal primary tumors and evidence of base of skull erosion, cranial nerve palsy, or intracranial extension or spinal cord compression, or any other patient requiring emergency radiotherapy, or patients who declined window therapy, or patients assigned by study chair were to receive:

- Induction treatment (Weeks 0- 6) VAC alternating with V schema
- Radiotherapy (Weeks 0- 6)
- Continuation (Weeks 6- 25) VAC alternating with V schema
- Radiotherapy (Weeks 15- 22).

Results:

A total of 21 patients were enrolled in this study. Most patients (66%) completed the planned 2 cycles of irinotecan. Five patients (24%) patients changed therapy because of disease progression (4 patients) and stable disease (1 patient). Only 3 (14.3%) patients were enrolled in the 1 month-2 year category, 4 (19.0%) patients were enrolled in the 2-<12 year category and no patients were enrolled in the <1-month category. The median age was 12.8 years [range 0.8-19.2 years].

Table 26: Reason for discontinuation for study 9802

	SAI Window	
	N	(%)
Total	**21**	**100.0**
Disease Progression	1	4.8
Death	1	4.8
Changed Treatment Regimen	5	23.8
Completed 2 Cycles	14	66.7

All patients had metastatic disease; bone and lymph nodes were equally the most frequently involved (66.7%) metastatic sites, followed by skin (38.1%). Five (23.8%) patients had lung metastases. Twenty of 21 patients had previously had surgery for their disease.

Table 27: Disease diagnosis at baseline for Study D8902

		SAI Window	
		N	%
Initial Diagnosis	Alveolar RMS	16	76.2
	Embryonal RMS	2	9.5
	RMS NEC	2	9.5
	Undiff Sarcoma	1	4.8
Primary Site	Abdominal	1	4.8
	Bone	5	23.8
	Buttocks	2	9.5
	Gonads	2	9.5
	Head & Neck	1	4.8
	Muscle	3	14.3
	Orbit	1	4.8
	Pelvis	5	23.8
	Unknown	1	4.8
Metastatic Site*	Bone	14	66.7
	Cutaneous	8	38.1
	Head & Neck	1	4.8
	Liver	1	4.8
	Lung	5	23.8
	Lymph Nodes	14	66.7
	Muscle	1	4.8
	Pelvis	2	9.5
	Spine	1	4.8
	Thorax	2	9.5
	Unknown	1	4.8
	Other	1	4.8

SAI= Single- agent irinotecan,
RMS= Rhabdomyosarcoma,
NEC= Not elsewhere classified

Extent of Exposure

All 21 patients received = 1 dose of irinotecan and a total of 35 cycles of SAI treatment. The majority (66.7%) of patients received 2 cycles of SAI. The median cycle duration was 21.0 days [range: 7- 30].

Irinotecan Dose Modifications

Over the duration of the window treatment with irinotecan, 4 (19.0%) patients had 5 cycles (14.3 %) delayed more than 24 days. As per protocol, irinotecan dose was not to be reduced. No patient had a dose reduction during the window period. The information is presented in

Efficacy Results:

Nine of 21 patients (43%) had a PR as the best response to irinotecan. However, the irinotecan window was closed to accrual due to 14% early deaths associated with PD.

Table 28: Best response during SAI Window for Study 9802

Total	21	100.0
CR	0	0
PR	9	42.9
SD	6	28.6
PD	6	28.6

Table 29: Serious Adverse Events:

System Organ Class	**MedDRA Term**	**All**	**3**	**4**	**All**	**3**	**4**
Any	**N = 21**	**5**	**1**	**4**	**6**	**2**	**4**
	Any	1	-	1	1	-	1
Blood/Lymph							
	Neutropenia	1	-	1	1	-	1
General	Any	1	1	-	1	1	-
	Pyrexia	1	1	-	1	1	-
Infection	Any	4	3	1	5	4	1
	Infection	4	3	1	5	4	1
Metabolism/	Any	2	-	2	2	-	2
Nutrition							
	Hyperuricemia	1	-	1	1	-	1
	Hyponatremia	1	-	1	1	-	1
CNS	Any	1	-	1	1	-	1
	Hemorrhagic stroke	1	-	1	1	-	1
Respiratory	Any	3	2	1	3	2	1
	Dyspnea	2	1	1	2	1	1
	Epistaxis	1	1	-	1	1	-
	Hypoxia	1	1	-	1	1	-
	Pleural effusion	1	-	1	1	-	1
	Pneumonitis	1	-	1	1	-	1
Vascular	Any	1	-	1	1	-	1
	Hypotension	1	-	1	1	-	1

Although not reported in he Sponsor's table for SAE, the study report had a 9.5 % incidence of G3 diarrhea, 19% incidence of G3 vomiting and a 9.5 % G3 abdominal pain. There were no treatment discontinuations in the SAI period due to AE. Treatment was discontinued in one patient because of death.

D9802 was a phase 2 study in which SAI (single agent irinotecan) was administered sequentially with multi-agent therapy. Twenty one patients with previously untreated rhabdomyosarcoma were enrolled. Twenty mg/m²/day of irinotecan was infused for 5 consecutive days on weeks 0 and 1, then 1 week then repeat at Weeks 3 and 4. In patients who achieved objective response, this was to be followed by multimodal therapy of alternating cycles of VAC or VCPT. Although a PR rate of 33% was observed, the SAI part of the study was closed by the DSMB because of early deaths (14%) and PD (29%).

The AE profile was different from that observed in adults. Across all courses of therapy and irrespective of causal relationship, the most significant grade 3 or 4 AEs were dehydration (28.6%) associated with severe hypokalaemia (23.8%) and hyponatremia (14.3%). Severe infection was reported in 5 patients (23.8%). Of note only 4 patients (19%) had grade 3 vomiting and no grade 4 was reported. Grade 3 diarrhea was reported in only 2 patients (9.5%) and no grade 4 diarrhea was reported. Laboratory abnormalities were used for monitoring tolerability, but were not reported on the CRFs. No patient withdrew from the SAI window because of AEs.

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Amna Ibrahim
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John Johnson
6/14/04 01:36:04 PM
MEDICAL OFFICER

Medical Officer's Review of 120-Day Safety Report

NDA:	20,571
Drug:	Camptosar (Irinotecan, CPT-11)
Serial no. of NDA:	SE8- 021-PM
Serial # of Safety Report:	018
Sponsor:	Pfizer Pharmaceuticals
Medical Reviewer:	Amna Ibrahim MD
Team Leader:	John Johnson MD
Letter date of supplement:	December 22, 2003
Letter date of 120-Day Safety Report:	June 8, 2004

In this supplemental NDA, four Phase 1 and two Phase 2 trial study reports were submitted. No efficacy was established. These study reports have already been reviewed and entered in DFS. Brief description of the phase 2 studies, doses involved and major toxicities will be added to the label.

A submission dated June 8th, 2004 for the 120-day safety report has been submitted by the applicant for patients 22 years old or younger from September 1st, 2003 – March 31st, 2004. The safety reports were generated by the applicant from one of the following sources that included at least one related adverse event:
1- Spontaneous reports of SAE
2- Study reports
3- SAE reported in literature

A total of 74 cases were entered in the applicant database. Fifty-five of these were from "blood and Lymphatic System Disorders", "Gastrointestinal Disorders" and Infections and infestations. Five reports were in the "General Body Disorders" and "Administrative Site Conditions". Except for 6 cases, all of the 74 cases included events considered already listed in the irinotecan Core Data Sheet (CDS). The Sponsor's Core Data Sheet has all information collected from clinical trials in adult patients and postmarketing experience in adult patients, and was used as a reference. This Core data Sheet was updated in November 2002.

These 6 cases were summarized by the applicant. In 4 cases, the etiology of the AE could be reasonably assigned to concomitant condition/therapy. One patient (#2003192247US) developed pulmonary fibrosis. This patient had previously received cyclophosphamide as well as radiation, but the fields of radiation were unknown at the time of the report. Another patient (#2002118047FR) had an AE included in the "Nervous System Disorder". According to the applicant, this AE had been reported previously and follow-up information did not change the previous information. This 8.5 year old French patient experienced vomiting, cough, hiccups, increased sweating and confusion, which the investigator listed as Neurocortical syndrome. Neurocortical syndrome is unlisted in the CDS. The individual AE are either known to be related to irinotecan or other concomitant therapy or condition.

Recommendation:
Information on adverse events from the Core Data Sheet should be used to update the label, if there are differences. The AE from Core Data Sheet should be submitted for FDA review and included in the upcoming labeling changes discussions. The sponsor should inform the Division of a date by which this data can be submitted to this Division.

Amna Ibrahim M.D.
Medical Reviewer

John Johnson M.D.
Clinical Team Leader

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

/s/

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6/23/04 03:05:40 PM
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