CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-571 SE8-021

Drug name:	CAMPTOSAR
Generic name:	Irinotecan
Formulation:	20 mg/ml solution for intravenous injection
Adult Indication:	Metastatic carcinoma of the colon or rectum
Pediatric Indication:	None
Current Submission:	Pediatric Supplement
Applicant:	Pfizer (agent for Pharmacia and Upjohn) 235 East 42nd Street New York NY 10017
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	22-Dec-2003, 13-Feb-2004, 21-Jan-2004, 31-Mar- 2004
Primary Reviewer:	Roshni Ramchandani, Ph.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.
Team Leader:	Brian Booth, Ph.D.
Type of Submission:	NDA-Supplemental

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I. Executive Summary

Irinotecan hydrochloride (CPT-11, CAMPTOSAR) is a prodrug derivative of camptothecin, an alkaloid obtained from plants such as the *Camptotheca acuminata* tree. Camptothecins are inhibitors of topoisomerase I.

In June 1996, the Food and Drug Administration (FDA) first approved irinotecan, under subpart H regulations for accelerated approval for the second-line treatment of patients with recurrent or progressive metastatic carcinoma of the colon or rectum. Subsequently, full approval was granted for the second-line treatment of metastatic colorectal cancer in October 1998. In April 2000, the FDA approved the use of irinotecan in combination with 5-FU and leucovorin, for first-line therapy for metastatic colorectal cancer.

The current submission includes phase 1 and phase 2 studies evaluating the safety, effectiveness and pharmacokinetics of irinotecan in pediatric patients with a range of malignancies. Six clinical studies (four phase 1 studies and two phase 2 studies) form the basis for full compliance with the CAMPTOSAR Written Request for Pediatric Studies, issued by the FDA on October 30, 2000. These trials provide information regarding the safety and pharmacokinetics (PK) of irinotecan using 3 different schedules of administration and document the activity of irinotecan in a range of pediatric malignancies. Two of the phase I studies evaluated daily x 5, q 3 weeks schedule (POG 9571 and P9871). Another study evaluated a [daily x 5] x 2, q 3 weeks (St. Judes Study). Schedule. A fourth study evaluated a schedule similar to the adult schedule of weekly x 4, q 6 weeks (H6957). For the two phase 2 trial the daily x 5, q 3 weeks schedule and [daily x 5] x 2, q 3 weeks were studied. The applicant met the requirements of the written request and Pediatric exclusivity was granted to the applicant on March 11, 2004.

Results of the pharmacokinetic analyses of irinotecan and its metabolites showed considerable variability in peak concentrations (Cmax) and area under the concentration curve (AUC) following single IV infusions of irinotecan at doses ranging from 50 mg/m^2 to 125 mg/m^2. As in adults, irinotecan appears to be metabolized to an active metabolite, SN38 (300 to 1000 fold more active than the parent), via carboxylesterase and to inactive metabolites, APC and NPC, via CYP 3A4. The mean ($\pm$ SD) clearance of irinotecan from 2 studies were 16.2 ($\pm$ 6.7) L/h/m^2 and 17.3 ($\pm$ 4.6) L/h/m^2. Concomitant use of enzyme-inducing anticonvulsants (EIACs) resulted in a significantly lower exposure to SN38, where there was a 67-70% reduction in dose-adjusted Cmax and AUC in patients receiving EIACs (n=5) compared to patients who were not receiving any anticonvulsants (n=13), although the data are limited.

Exploratory analysis conducted by the applicant did not show any correlations between irinotecan or SN38 exposure and measures of effectiveness (response rates) or toxicity (incidence of severe diarrhea or neutropenia). Exposure-response analysis of the data across all 6 studies conducted by the reviewer showed a trend for increased incidence of

severe (grade 3 or 4) diarrhea and severe (grade 3 or 4) neutropenia with an increase in exposure (AUC) of SN38 in pediatric solid tumor patients. However, this was not statistically significant. These trends were consistent with data in adult patients. A comprehensive characterization of the

exposure-toxicity relationship would be critical in targeting of optimal exposures in future studies.

The phase 2 studies included in this supplemental application did not show effectiveness following irinotecan treatment in children with CNS and non-CNS solid tumors. The applicant is not recommending the use of irinotecan in children, however they would like to include information about the pharmacokinetics and safety of irinotecan in the label. The Office of Clinical Pharmacology and Biopharmaceutics recommends that information on the pharmacokinetics in the pediatric population should be included in the label.

A. Recommendations

1. There appears to be a correlation between the incidence of severe (grade 3 or 4) diarrhea and SN38 AUC as well as severe (grade 3 or 4) neutropenia and SN38 AUC. However, this relationship was not statistically significant. Pharmacokinetic data was not collected in the majority of the patients. Knowledge of the exposure-toxicity relationship for irinotecan and SN38 would be critical in targeting optimal exposures in future studies. We recommend collection of pharmacokinetic (PK) data to adequately characterize the disposition of irinotecan and SN38 in ongoing as well as future trials when given in combination with other drugs or as a single agent. An optimal sparse sampling approach spanning an appropriate duration post-infusion in all patients should be used.

2. Genotypic differences in UGT1A1, a phase 2 enzyme involved in the glucuronidation of SN38, can result in a decreased rate of elimination of SN38 leading to elevation of SN38 levels and an increased risk of severe toxicity in patients with the less-efficient isoform. Thus, we recommend that you evaluate the relationship between UGT1A1 genotypes on the exposure of SN38 as well as on toxicity:

    - In existing data collected from the phase 2 trial already conducted and/or
    - In future trials to be conducted.

3. Labeling Changes for Irinotecan (#1)

Current Applicant Label

PRECAUTIONS

Pediatric Use

~~The safety and effectiveness of CAMPOTSAR in pediatric patients have not been established.~~

(b) (4)

[redacted]

FDA Proposed Labeling:

The following text should be included under the 'PRECAUTIONS' section under the 'Pediatric Use' subsection.

The effectiveness of Irinotecan in pediatric patients has not been established Results from two studies were submitted. One hundred and seventy children with refractory solid tumors were enrolled in one phase II trial in which 50 mg/m^2 of irinotecan was infused for 5 consecutive days every 3 weeks. Grade 3- 4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3- 4 diarrhea was observed in 35 (20.6%) patients. In the second phase II trial children with untreated rhabdomyosarcoma, 20 mg/m2 of irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent therapy was followed by multimodal therapy. Accrual to was halted

Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric solid-tumor trials at dose levels of 50 mg/m2 (60-min infusion, n=48) and 125 mg/m2 (90-min infusion, n=6). Irinotecan clearance (mean ± S.E.) was 17.3 ± 6.7 L/hr/m2 for the (b) (4) dose and 16.2 ± 4.6 L/hr/m2 for the (b) (4) dose, which is comparable to that in adults. Dose-normalized SN-38 AUC values were comparable between adults and children. Minimal accumulation of irinotecan and SN-38 was observed in children on daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x 2 weeks every 3 weeks].

4. Labeling Changes for Irinotecan (#2)

Current Applicant Label

CLINICAL PHARMACOLOGY
Pharmacokinetics in Special Populations
Pediatric

~~*Pediatric:* Information regarding the pharmacokinetics of irinotecan is not available.~~

(b) (4)

FDA Proposed Labeling:

The applicant proposed text under the 'CLINICAL PHARMACOLOGY' section in the 'Pharmacokinetics in Special Populations' subsection under 'Pediatric' from lines 117 to 129 in the annotated proposed label, should be deleted.

B. Phase IV Commitments

None (not applicable).

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The pharmacokinetics of irinotecan and its metabolites were examined in six studies (four phase 1 and two phase 2 studies) conducted in pediatric solid tumor (including CNS tumors) patients. Results of the PK analyses show considerable variability in peak concentrations and AUC following single IV infusions of irinotecan at doses ranging from 50 mg/m^2 to 125 mg/m^2. The PK of irinotecan and SN38 showed substantial inter-patient and intra-patient variability as observed in adults. As in adults, irinotecan appears to be metabolized to an active metabolite, SN38, via carboxylesterase and to inactive metabolites, APC and NPC, via CYP 3A4.

The mean (± SD) clearance of irinotecan from 2 studies (phase 1 study H6957 and phase 2 study P9761) were 16.2 (± 6.7) L/h/m^2 and 17.3 (± 4.6) L/h/m^2, and mean elimination half-life was 3.9 and 4.7 hours, respectively. The clearance of irinotecan was correlated with body size metrics (body weight and body surface area) in pediatric patients, and did not appear to differ between male and female patients or between patients who had been heavily pretreated vs. those who had been less-heavily pretreated prior to irinotecan treatment. Concomitant use of enzyme-inducing anticonvulsants (EIACs) resulted in a significantly lower exposure to SN38, where there was a 67-70% reduction in dose-adjusted Cmax and AUC in patients receiving EIACs (n=5) compared to patients who were not receiving any anticonvulsants (n=13). (b) (4)

Exploratory analysis conducted by the applicant did not show any correlations between irinotecan or SN38 exposure and measures of effectiveness (response rates) or toxicity (incidence of severe diarrhea or neutropenia). Exposure-response analysis of the data across all 6 studies conducted by the reviewer also does not indicate a significant correlation between incidence of severe (grade 3 or 4) diarrhea or severe (grade 3 or 4) neutropenia and exposure (AUC) of SN38 in the pediatric solid tumor patients. However, the proportion of pediatric patients with grade 3 and 4 diarrhea as well as grade 3 and 4 neutropenia appears to increase with an increase in SN38 AUC. This is in accordance with data in adult patients. A comprehensive characterization of the exposure-toxicity relationship would be critical in targeting of optimal exposures in future studies. The Agency recommends that the applicant collect PK data, using optimal sparse sampling for an appropriate duration post-dose, to ensure reliable estimation of

SN38 AUC in all future studies. The collected data should be analyzed to examine the exposure-response relationship for measures of toxicity of irinotecan.

OCPB Briefing was held on June 9, 2004

Attendees: Drs. A. Bhattaram, B. Booth, J. Collins, F. Freuh, J. Gobburu, P. Hinderling, J. Hunt, P. Jadhav, P. Lee, L. Lesko, M. Mehta, A. Men, R. Powell, R. Ramchandani, A. Selen, Y. Wang, G. Williams.

II. Question Based Review

A. General Attributes of the Drug

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

Irinotecan hydrochloride (CPT-11, CAMPTOSAR) is a prodrug derivative of camptothecin, an alkaloid obtained from plants such as the *Camptotheca acuminata* tree. Camptothecins are inhibitors of topoisomerase I.

In June 1996, the Food and Drug Administration (FDA) first approved irinotecan for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease had recurred or progressed following 5-fluorouracil (5-FU)-based therapy (second-line therapy). The initial approval of irinotecan was based on data from phase 2 studies and was obtained under subpart H regulations covering accelerated approval of new drugs for serious or life-threatening diseases. Subsequently, full approval for the second-line treatment of metastatic colorectal cancer was granted in October 1998 based on the results from 2 phase III studies. In April 2000, the FDA approved the use of irinotecan as a component of first-line therapy for metastatic colorectal cancer when given in combination with 5-FU and leucovorin; approval was based on the results of 2 phase III studies.

Rationale for development of irinotecan for use in pediatric patients:
Despite an increasing cure rate for many pediatric solid tumors, metastatic disease and certain histologies continue to carry a poor prognosis and require new therapies. The 5-year progression-free survival of children with metastatic rhabdomyosarcoma (RMS), the most common soft-tissue sarcoma, has not changed significantly over the past 10-15 years. Similarly, long-term progression-free survival is rarely attained in children who present with disseminated neuroblastoma (NBL), Ewing's sarcoma or locally advanced glioblastoma, the second-leading cancer-related cause of death in children younger than 15 years of age. Thus, there is a pressing medical need to develop new and more effective treatment options for the management of solid tumors in the pediatric population.

Currently, the use of new cytotoxic agents in children is primarily based on preclinical data from xenograft models of childhood tumors and evaluation in adults. Irinotecan has been found to show activity in several preclinical xenograft models of childhood tumors in mice bearing human neuroblastoma, rhabdomyosarcoma, medulloblastoma, ependymoma, and glioblastoma. Irinotecan was also efficacious in mice bearing rhabdomyosarcoma xenografts selected in vivo for resistance to vincristine, melphalan, and topotecan. Finally, irinotecan treatment resulted in a high frequency of complete regression in xenografts from 6 neuroblastoma cell lines over 12 weeks.

The current submission includes phase 1 and phase 2 studies evaluating the safety, effectiveness and pharmacokinetics of irinotecan in pediatric patients with a range of malignancies. Six clinical studies (four phase 1 studies and two phase 2 studies) form the basis for full compliance

with the CAMPTOSAR Written Request for Pediatric Studies, issued by the FDA on January 22, 2001. These trials provide information regarding the safety and pharmacokinetics (PK) of irinotecan using 3 schedules of administration and document the activity of irinotecan in a range of pediatric malignancies.

Phase I studies:

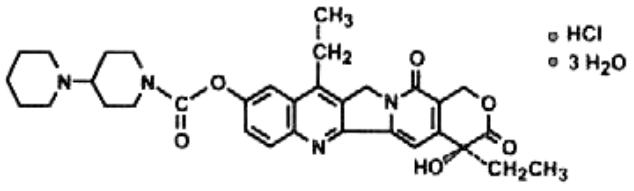
- P9571: A trial of irinotecan in children with solid tumors: A Pediatric Oncology Group (POG) phase I cooperative agreement study.
- P9871: A phase I study of irinotecan in patients with refractory solid tumors who are concomitantly receiving anticonvulsants: A COG study.
- H6957: A pediatric phase I and pharmacokinetic study of irinotecan (CPT-11): A preliminary report.
- St Jude Children's Research Hospital: A phase I study of irinotecan (CPT-11) in pediatric patients with refractory solid tumors.

Phase 2 studies:

- P9761: A phase II trial of irinotecan in children with refractory solid tumors: A Children's Oncology Group (COG) study - A preliminary report.
- D9802: A phase II "up-front window study" of irinotecan (CPT-11) followed by multi-modal, multi-agent 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.

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

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminat*a. The chemical name is ***(S***)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-***1***H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'-bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate.



Irinotecan Hydrochloride

Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6 \bullet HCl \bullet 3H_2O$ and a molecular weight of 677.19. It is slightly soluble in water and organic solvents.

CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 ml-fill vials contain 40 mg irinotecan hydrochloride and 5 ml-fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

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

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan. The precise contribution of SN-38 to the activity of irinotecan is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form. Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

Indications:
CAMPTOSAR Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. CAMPTOSAR is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

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

The supplemental NDA submitted does not show effectiveness of irinotecan in pediatric populations and dosing regimens are not recommended in pediatrics.

Two regimens of irinotecan are approved for use as a single agent, 125 mg/m^2 weekly and 350 mg/m^2 once every 3 weeks.

Two regimens are approved for its use in combination with leucovorin and 5-fluorouracil, i.e., 125 mg/m^2 in weeks 1 through 4 of a 6-week regimen (Saltz) and 180 mg/m^2 once every 2 weeks in a 6-week regimen (Douillard). Details of regimens are provided in the label.

B: Pediatric Study Decision Tree

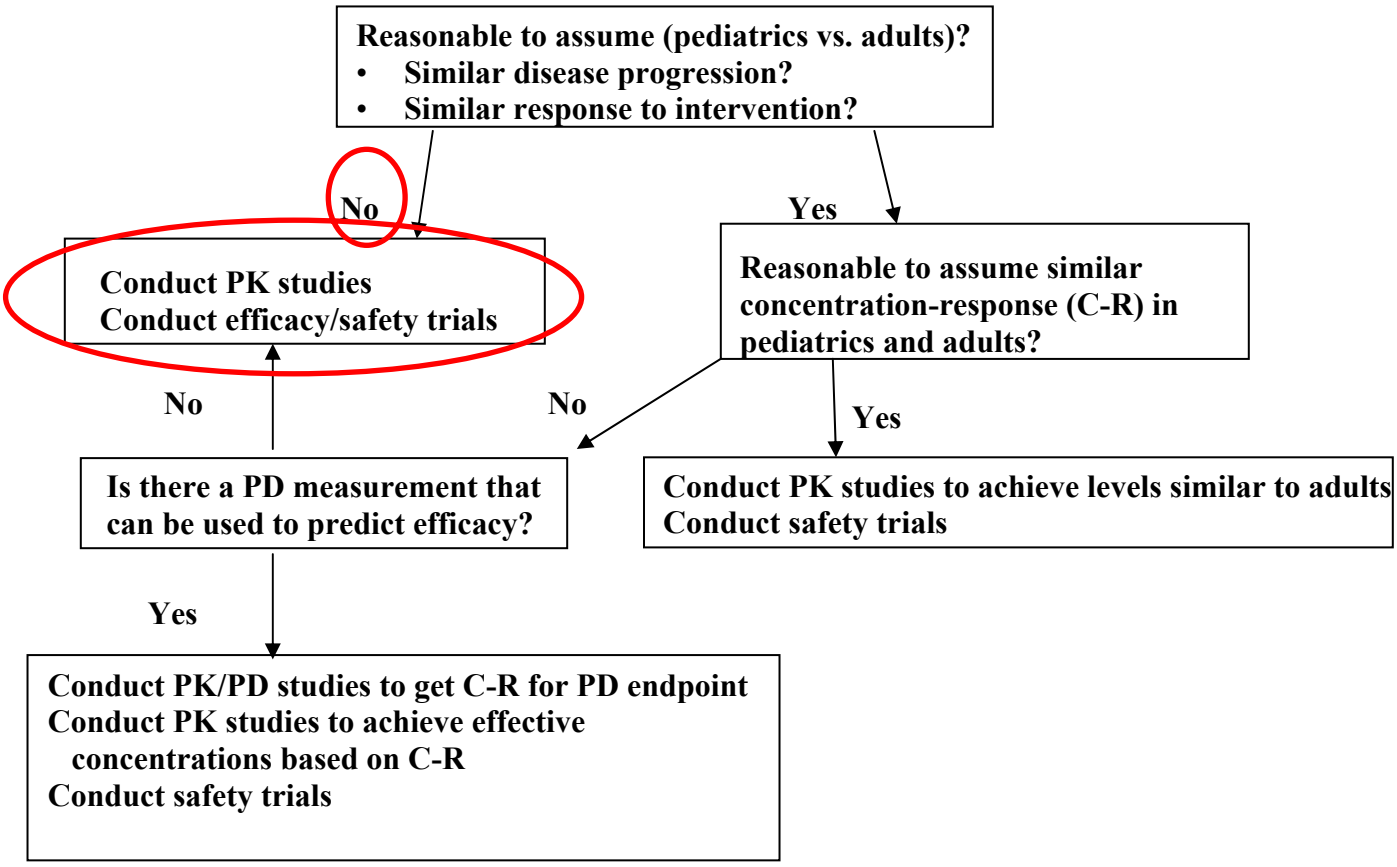
Irinotecan was evaluated in pediatric cancer patients for treatment of solid tumors, including CNS tumors and well as rhabdomyosarcoma, in this submission. The drug has been approved for use in adults as a single agent and in combination with 5-fluorouracil (and leucovorin) for the treatment of colorectal cancers.

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

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

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

The overall pharmacological effect of the drug, i.e., topoisomerase inhibition leading to cytotoxic effects on tumor cells would be expected to be similar in pediatrics vs. adults. However, the sensitivity and dose-response characteristics of pediatric tumors to intervention may be different from that in adults.



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

C: Clinical Pharmacology

General attributes

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

Six clinical studies form the basis for full compliance with the CAMPTOSAR Written Request for Pediatric Studies, issued by the FDA on January 22, 2001. These trials provide information

regarding the safety and pharmacokinetics (PK) of irinotecan using 3 schedules of administration and document the activity of irinotecan in a range of pediatric malignancies.

Phase I studies:

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The table on the following page provides a summary of the PK studies.

TABLE I: Summary of studies in which pharmacokinetic evaluations were performed.

Protocol #	**Schedule**	**PK Dose Levels (# PK Datasets Analyzed at Each Dose)**	**Analytes**	**# PK Samples (excl pre-dose)**
Inst: H6957 PHA: 98-6475-178	Weekly x 4 every-6-weeks	125 (6), 160 (4), 200 (2) [Total=12]	Total: CPT-11, SN-38, SN-38G, APC	13 over 25 h
Inst: P9571 PHA: M 6475 056	Daily x 5 every-3-weeks	30(2), 39 (8), 50 (10), 65 (5) [Day 1 total=26] Day 4: 30 (2), 39 (4), 50 (7), 65 (5) [Day 4 total=18]	Total: CPT-11, SN-38, SN-38G, APC	10 over 13 h
Inst: P9871 PHA: CPTAIV-0020-452	Daily x 5 every-3-weeks	30 (1), 50 (1), 100 (4), 130 (2) [Total=8] By stratum: 6 EIAC, 2 non-EIAC, 1 valproate	Total: CPT-11, SN-38, SN-38G, APC	10 over 13 h
Inst: St Jude PHA: CPTAIV-020-453	Daily x 5, x 2 every-3-weeks	20 (9), 24 (10), 29 (2) [Day 1 Total=21] [Day 10 Total=19]	Lactone: CPT-11, SN-38	7 over 7 h
Inst: P9761 PHA: 440E-ONC-0020-222	Daily x 5 every-3-weeks	50 (13 "Full sampling"; 48 "Limited sampling")	Total: CPT-11, SN-38, SN-38G, APC	"Full sampling": 10 over 13 h. "Limited sampling": 5 over 25 h.
Inst: D9802 PHA: 440E-ONC-0020-207	Daily x 5, x 2 every-3-weeks	20 (4)	Lactone & Total: CPT-11, SN-38, SN-38G, APC	6 over 7 h

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

The primary measure in the phase 1 studies was safety and the incidence of all adverse events, including serious adverse events (grade 3 or 4) were recorded based on the NCI common toxicity criteria.

In the phase 2 studies, the primary endpoint was the response rate, i.e., the percent of patients in a particular stratum that showed a response to the drug. The response could include complete responses (CR), partial responses (PR) or stable disease (SD).

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

Multiple dose PK was evaluated in one of the phase 1 studies (P9571) where concentration-time profiles were obtained on days 1 and 4 of a 5-day repeat-dose administration, given every 3 weeks (see section 2.2.5.9).

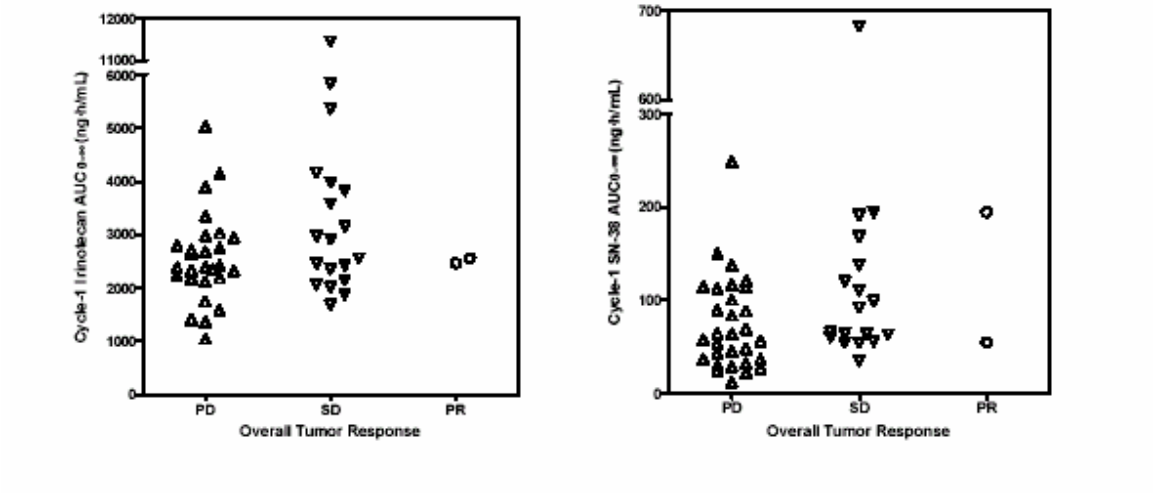
In five of the six studies submitted, the parent drug (irinotecan) and three metabolites, SN38, SN38G and APC were measured in plasma using validated methods. Please see the Analytical Section for details.

Exposure-response

C4. Is there a relationship between irinotecan and/or SN38 exposure/SN38G and effectiveness (response rates) in pediatric patients?

Treatment with irinotecan did not result in overall effectiveness for solid tumors including CNS tumors in pediatric cancer patients. Therefore, the applicant did not examine exposure-response relationships in this submission. The applicant did plot the exposure (AUC) of irinotecan as well as its active metabolite SN38 for patients who showed a partial response (PR), stable disease (SD) and disease progression (PD), and saw no overall differences (see figure below). However, the number of patients showing PR was very small and definitive conclusions cannot be drawn from these data.

Figure 1: Plots of AUC of irinotecan (left panel) and SN38 (right panel) vs. overall tumor response in the phase 2 study P9761.



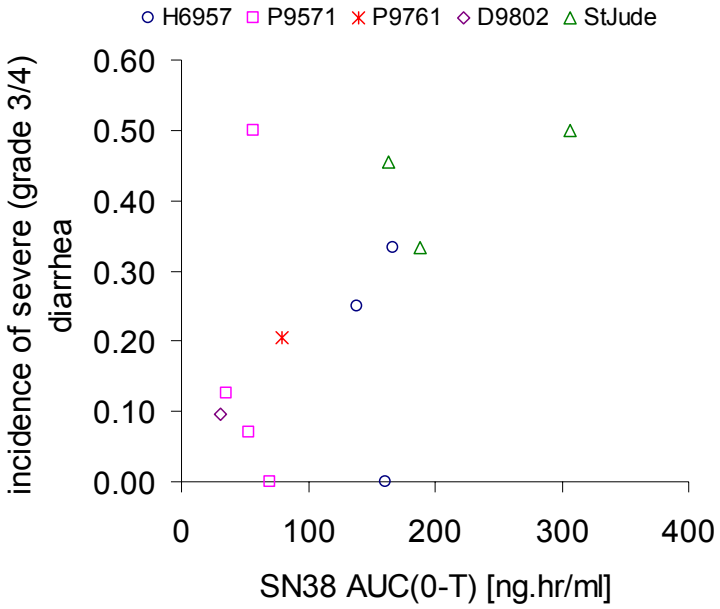
C5. Is there a relationship between irinotecan and/or SN38 and/or SN38G exposure and incidence of adverse events including diarrhea and neutropenia in pediatric patients?

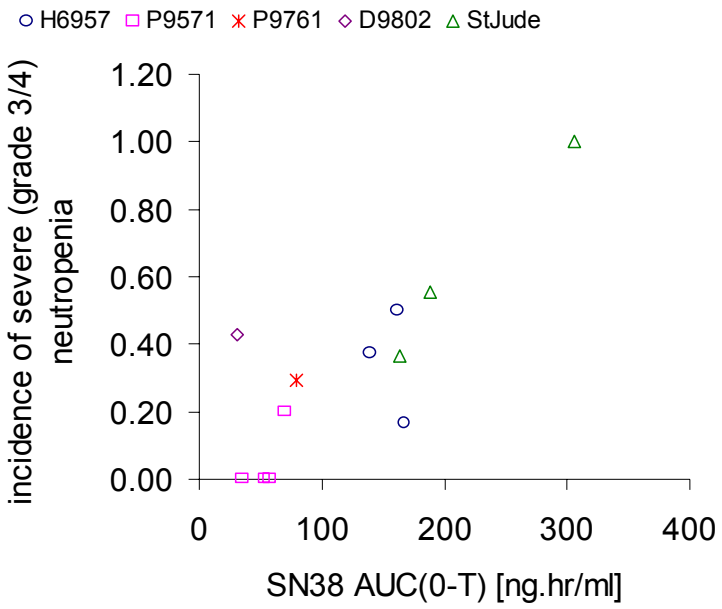
Results of attempts to correlate pharmacokinetics with pharmacodynamics (PK/PD), particularly for measures of toxicity have been mixed. Some studies have shown significant associations between irinotecan and/or SN-38 exposure and the severity of diarrhea or neutropenia.

The relationship between irinotecan (and metabolite) exposure and incidence of toxicity was explored by the applicant by plotting the AUC of irinotecan and of SN38 vs. severity of diarrhea (CTC grade), and vs. severity of neutropenia. The data for this exploratory analysis was from the phase 2 study in solid tumor patients (P9761), and included only those subjects for whom PK data was available. The applicant did not find an association between irinotecan exposure and toxicity.

The reviewer has also examined the relationship between irinotecan and SN38 exposure and incidence of severe diarrhea and neutropenia. The data from all the studies were combined and the association between incidence of severe (grade 3 or 4) diarrhea and exposure to irinotecan and SN38, as well as the association between incidence of severe (grade 3 or 4) neutropenia and exposure to irinotecan and SN38 were examined. The following figures show the scatter-plots of incidence of diarrhea or neutropenia vs. AUC of SN38 and suggest a trend toward higher incidence of toxicity with increasing exposure.

Figure 2: Incidence of severe diarrhea vs. mean AUC of SN38 (upper panel) and severe neutropenia vs. mean AUC of SN38 (lower panel).





The association between SN38 AUC and incidence of toxicity was not statistically significant probably because the analysis could only include those patients in whom PK evaluations were made, since we were unable to impute AUCs for the other patients (who did not have PK evaluations). This was due to the large variability in SN38 clearance and the lack of significant covariates in parameter models for clearance of SN38. The above plots do however suggest a trend toward a higher incidence of toxicity with increased exposure to SN38 and should be examined further in future studies.

C5b. What is the putative mechanism for irinotecan toxicity?

Diarrhea is the major dose-limiting non-hematologic toxicity of irinotecan. Following irinotecan treatment, diarrhea can be acute, occurring early and accompanied by cholinergic symptoms such as cramps, diaphoresis, salivation etc. It is short lasting and rapidly suppressed by atropine. Late onset diarrhea can also occur, usually after the third day following irinotecan treatment, and tends to be unpredictable and severe. Thus there is a need to understand the pathophysiologiy of this late-onset diarrhea and its relationship to exposure to irinotecan and/or its metabolites. There are several mechanisms postulated for the occurrence of late-onset diarrhea (Saliba et al., J Clin Oncol 16:2745-51, 1998). Secretory diarrhea occurs when there is abnormal ion transport in the intestinal epithelial cells resulting in increased excretion of electrolytes (including Na+) and fluids. Exudative diarrhea occurs when there is disruption of the integrity of the intestinal mucosa, leading to protein loss, mucus and blood in stools. Another type of late-onset diarrhea occurs when there are abnormalities in GI motility (deranged motility diarrhea). In the case of irinotecan, diarrhea is thought to be secretory with an exudative component, due to the presence of watery stools accompanied with loss of alpha-1-antitrypsin, and also because irinotecan-induced diarrhea is treatable with loperamide, which has anti-secretory properties.

Studies examining the relationship between exposure to irinotecan or SN38 and diarrhea have yielded inconsistent findings, with some studies showing a significant relationship between irinotecan AUC and/or SN38 exposure and incidence of severe diarrhea, and other studies failing to determine a significant relationship. Some of the reasons for this inconsistency include 1) the large variability in the elimination kinetics of SN38, 2) variability in the ratio of AUCs of SN38 to SN38G (the biliary index) which reflects the SN38 concentrations in the bile. High ratios have been correlated with a higher incidence of severe diarrhea in some, but not all studies. 3) Interindividual differences in local GI β-glucuronidase activity, which would in turn, reflect the degree of breakdown of SN38G in the GI tract back to the more active (and presumably toxic) metabolite SN38.

The other major toxicity is hematologic, with myelosuppression resulting in neutropenia, leukopenia and anemia. Neutropenia has been seen in 13% to 66% of patients in clinical trials of irinotecan as a single agent or in combination in adults and pediatric cancer patients. Neutropenia is associated with infection and fever. Studies examining the relationship between exposure to irinotecan or SN38 and neutropenia have also yielded inconsistent findings, with some studies showing a significant relationship between irinotecan AUC and/or SN38 exposure and incidence of severe neutropenia, and other studies failing to determine a significant relationship. One of the reasons for this inconsistency may be the substantial variability in the pharmacokinetics of SN38.

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

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

C7. Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Three different dosing regimens were examined in the phase 1 studies for irinotecan, once-weekly, daily x5 every 3 weeks, and daily x5 for 2 weeks every 3 weeks. The once-weekly regimen was similar to weekly regimens that have been used in adult patients. The other two regimens were derived from preclinical studies in xenograft models. The optimal schedule for irinotecan administration is not yet known, and some anti-tumor activity has been observed on all schedules in all the studies evaluated. Given the preliminary analysis showing a trend for a high correlation between SN38 AUC and incidence of severe diarrhea and incidence of neutropenia, further studies should be done to better understand this relationship and its impact on dose selection.

Pharmacokinetics

C8. What are the PK characteristics of the drug and its major metabolite?

The PK of irinotecan and its metabolites in adult patient populations have been evaluated in previous applications as well as published in the literature. This review will summarize the PK characteristics in adults and the address the questions specifically in the context of pediatric populations.

Summary of Pharmacokinetics in adults:
After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

C9. What are the single dose and multiple dose PK parameters?

The following table summarizes the PK parameters following single doses of irinotecan in pediatric cancer patients. These data were obtained from the phase 1and phase 2 studies submitted in this application.

Multiple dose PK were evaluated in study P9571, wherein subjects received daily (60-min) infusions of irinotecan for 5 days, once every 3 weeks. Blood samples were collected on days 1 and 4 to evaluate the effect of repeated dosing on the PK of irinotecan and its metabolites. This is discussed further below.

Table II: Pharmacokinetic parameters for irinotecan in pediatric solid tumor patients.

Dose	Irinotecan					SN-38		
	Cmax	AUC	T1/2	Vz	CL	Cmax	AUC	t1/2
(mg/m^2)	(ng/mL)	(ng·h/mL)	(h)	(L/m^2)	($L/h/m^2$)	(ng/mL)	(ng·h/mL)	(h)
50[b] (N=48[c])	685 ± 264	AUC(0-24) 2899 ± 1571 AUC(0-∞) 2963 ± 1611	4.71 ± 0.66	118 ± 49.8	17.3 ± 6.72	14.2± 12.6	AUC(0-24) 79.4 ± 95.2 AUC(0-∞) 95.0 ± 100	8.93 ±6.29
125[d,e] (N=6)	1815 ± 575	AUC(0-24) 7044±2437 AUC(0-∞) 7263±2626	3.86 ± 1.87	121 ± 57	16.2 ± 4.56	23.6 ± 18.2	AUC(0-24) 166.8 ± 140.6 AUC(0-∞) 215 ± 208	6.85 ±6.40

Cmax - maximum plasma concentration; AUC - area under the plasma concentration-time curve from time 0-24 h after the end of the infusion or extrapolated to infinite time t½ - terminal elimination half-life; Vz - volume of distribution of terminal elimination phase; CL - total systemic clearance from plasma.
a Plasma specimens collected for 24 h following the end of the Cycle 1, Day 1 infusion.
b 60-min infusion.
c N=53 for irinotecan Cmax; N=52 for SN-38 Cmax.
d 90-min infusion.
e One patient was sampled through only 8 h and this patient's data were excluded from the AUC mean±SD.

C10. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK of irinotecan has not been studied in healthy adults or children, therefore comparison between the PK in healthy volunteers and patients is not known.

C11. What are the characteristics of drug absorption?

Irinotecan is administered as an IV infusion, thus drug absorption is not applicable.

C12. What are the characteristics of drug distribution?

The volume of distribution of irinotecan in pediatric solid tumor patients is approximately 120 L/m^2, suggesting extensive tissue distribution. Irinotecan and SN38 exist in a pH-dependent equilibrium between its carboxylate and lactone forms. The ratio of lactone:total concentrations of irinotecan appears to be similar to that in adults, based on limited information (AUCs for 7 hours in 4 patients) in study D9802.

Plasma protein binding for irinotecan is <50%, while SN38 shows ~95% plasma protein binding, similar to adults.

C13. Does the mass balance study suggest renal or hepatic as the major route of elimination?

The following table (from a review paper by Mathijsen et al., 2001) summarizes the cumulative urinary and fecal excretion of irinotecan (CPT-11) and metabolites. Approximately 55% of an administered dose of irinotecan is excreted unchanged in urine and in feces. The metabolites are predominantly excreted in the feces, except for SN38G, which is mostly excreted by the renal route.

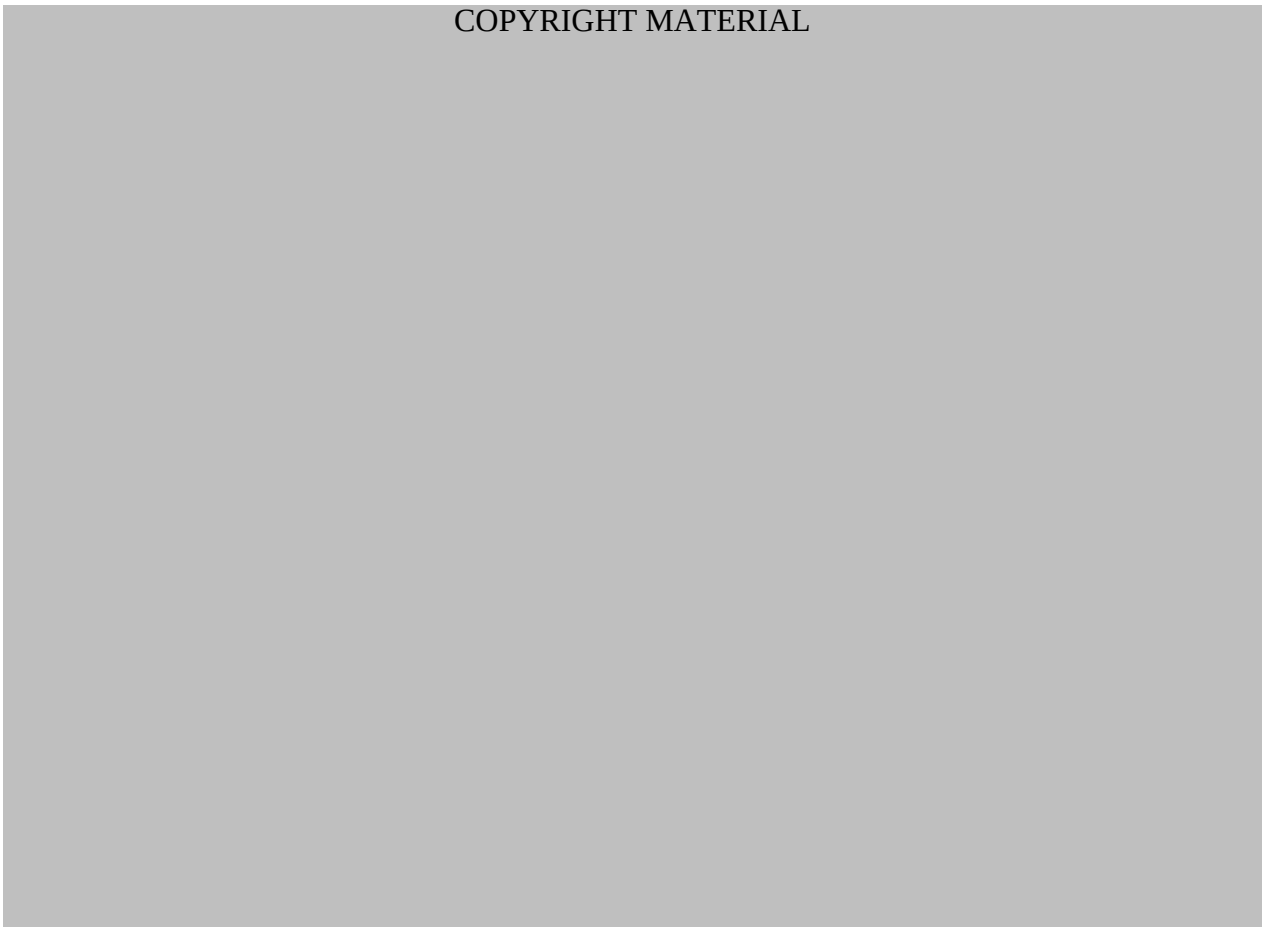
Table III: Cumulative urinary and fecal excretion of irinotecan and metabolites (From Mathijsen et al., 2001).

Compound	Urine	Feces	Total
CPT-11	22.4 ± *5.50*	32.3 ± 4.47	54.7
SN-38G	3.02 ± 0.77	0.27 ± 0.17	3.29
SN-38	0.43 ± 0.12	8.24 ± 2.51	8.67
APC	2.23 ± 1.5.3	8.29 ± 2.95	10.5
NPC	0.14 ± 0.08	1.36 ± 0.94	1.50
Total compounds	30.2 ± 6.60	62.0 ± 7.60	92.2
Not extracted	1.25 ± *1.55*	9.86 ± 3.77	11.1

C14. What are the characteristics of drug metabolism?

The following figure, also from Mathijsen et al., 2001, shows the metabolic scheme for irinotecan and its metabolites in adults. Irinotecan is metabolized by several enzymes, primarily in the liver. Metabolism by caroboxylesterase-2 (CE) results in the formation of the active species SN38. Oxidative metabolism by CYP 3A4 results in formation of the aminopantanecarboxylic acid metabolite, APC, and the primary amine metabolite, NPC. SN38 is converted via glururonidation by UGT1A1 to SN38-gluronide (SN38G). Concentration vs. time profiles in pediatric patients as well as the ratios of AUCs of the various metabolites to the parent suggest that the disposition of irinotecan in the pediatric population is similar to that in adults.

Figure 3: Metabolic pathways of irinotecan. The schematic shows CE-mediated formation of the active metabolite SN-38 and its subsequent conversion to a glucuronide derivative (SN-38G) by UGTIAI and IA7 isoforms (UGTIA7), with de-glucuronidation by intestinal β-glucuronidase (β-Glu). CPT-11 can also undergo CYP3A4-mediated oxidative metabolism to form APC and NPC, of which the latter can be hydrolyzed by CE to release SN-38.



C15. What are the characteristics of drug excretion?

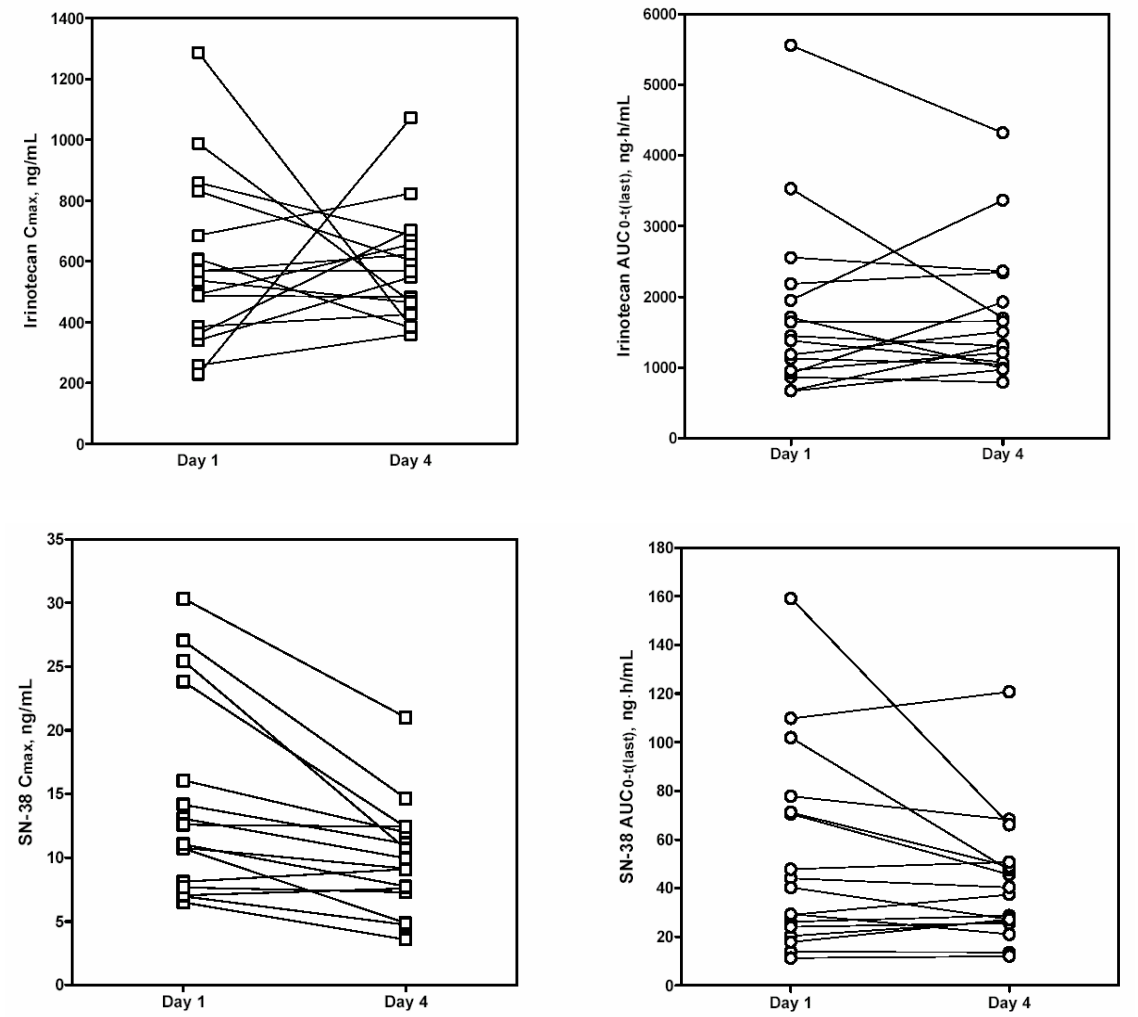
Based on the C^{14} study in adult cancer patients (Slatter et al., 2000), about 54% of a dose of irinotecan is excreted unchanged, with 22% being excreted in urine and about 32% excreted in feces. SN38, APC and NPC appear to be excreted in feces, while SN38G is primarily excreted in urine.

C16. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose proportionality of irinotecan was examined in the individual phase 1 studies submitted in the current application. One study, in which doses of 125, 160 and 200 mg/m^2 were administered, did not show evidence of dose proportionality, probably due to the narrow range of doses used. In study P9571, doses ranging from 30 to 65 mg/m^2 were administered, and the resulting Cmax and AUC for irinotecan and SN38 were plotted as a function of the dose. The plots show large variability in exposure following irinotecan administration, and Cmax values show a clear trend for dose-proportional increases. However, the trend for AUC(0-last) was less clear and may be due to the short duration of sampling in this study (13 hrs). The applicant did

not conduct any formal statistical analysis to examine dose proportionality in this or any other study.

Figure 4: Scatter plots of irinotecan dose vs. irinotecan and SN38 Cmax (upper panels) on day 1 and day 4, and irinotecan and SN38 AUC (lower panels) on day1 and day 4.



C17. How do the PK parameters change with time following chronic dosing?

Study P9571 in pediatric solid tumor patients consisted of a 3-week cycle of daily irinotecan administration for 5 continuous days followed by a 16 day rest period. Concentration vs. time profiles for irinotecan and SN38 were obtained on day 1 and day 4 in this study. Cmax and AUCs were compared to determine the accumulation of drug following repeated dosing. Results showed no difference in Cmax or AUC for irinotecan between day 1 and day 4. Cmax for SN38 was 35% lower on day 4 compared to day 1 (p=0.002), however this was not considered to be clinically significant as there was no difference in AUCs for SN38.

C18. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

There was substantial inter-individual variability in PK parameters in the pediatric patients. The following table shows the mean +/- SD of the PK parameters for irinotecan and its metabolites in 3 studies that employed different regimens: once-weekly (study H6957), daily x5 every 3 weeks (P9761), and daily x5 for 2 weeks every 3 weeks (D9802).

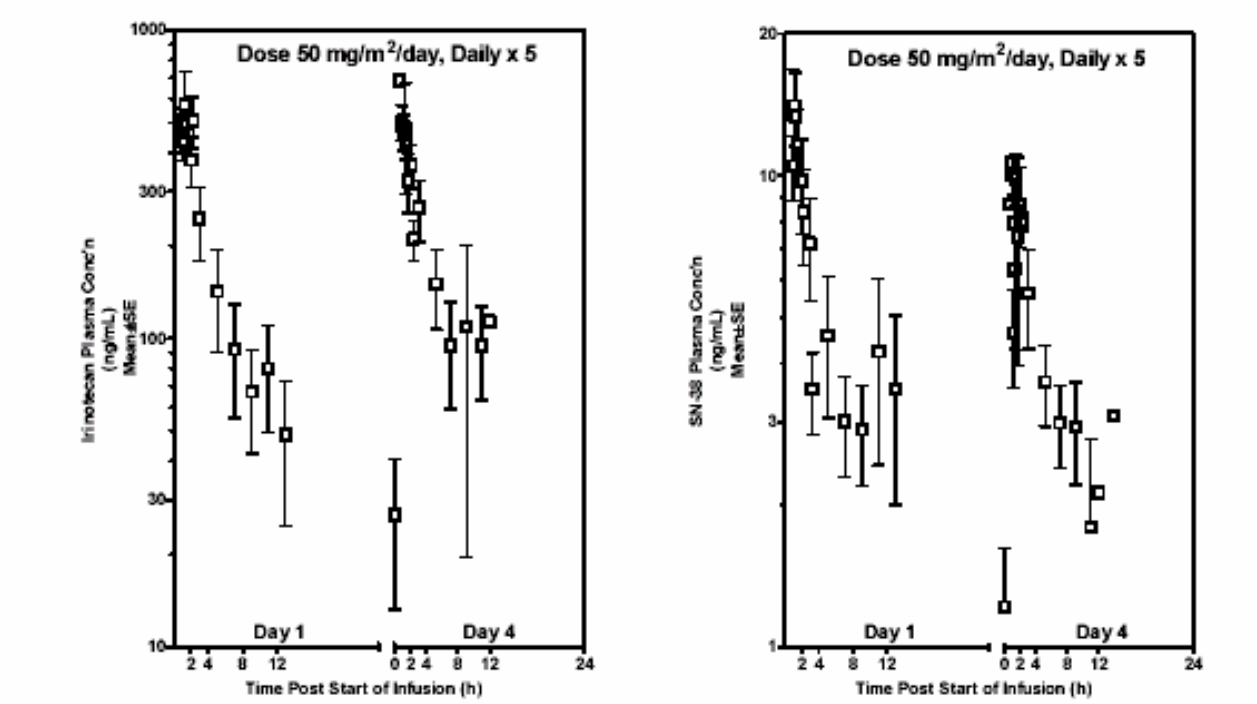
Table 4: PK parameters(mean ± SD) in 3 pediatric trials.

	H6957	P9761	D9802	
Schedule	**Wkly x4 every-6-weeks**	**Daily x5 every-3-weeks**	**(Daily x5) x2 every-3-weeks**	
Dose, mg/m^2	**125**	**50**	**20**	
N	**6**	**48[e]**	**7**	
Forms Assayed	**Total**	**Total**	**Total**	**Lactone**
Irinotecan				
tmax, h	1.42±0.30	1.11±0.304	1.60±0.636	1.26±0.019
Cmax, ng/mL	1815±575	685±264	237±63.0	132±69.9
AUC0-t(last)[c], ng·h/mL	7044±2437	2899±1571	879±386	327±134
AUC0-∞, ng·h/mL	7263±2626	2963±1611	NC[b]	NC
CL, L/h/m^2	16.2±4.6	17.3±6.72	NC	NC
V_Z, L/m^2	121±57	118±49.8	NC	NC
$t_{1/2,Z}$, h	3.86±1.87	4.71±0.66	NC	NC
SN38				
tmax, h	1.79±0.397	1.26±0.564	1.45±0.401	1.48±0.392
Cmax, ng/mL	23.6±18.2	14.2±12.6	13.7±8.68	9.88±6.87
AUC0-t(last)[c], ng·h/mL	167±141	79.4±95.2	44.1±25.1	28.2±18.2
AUC0-∞, ng·h/mL	215±208	95.0±100	NC	NC
$t_{1/2,Z}$, h	6.85±6.40	8.93±6.29	NC	NC
SN38G				
tmax, h	2.38±0.705	1.98±0.884	1.68±0.314	1.57±0.314
Cmax, ng/mL	71.3±55.9	27.8±16.4	30.7±18.6	24.5±15.4
AUC0-t(last)[c], ng·h/mL	660±712	223±186	106±56.8	89.8±54.3
AUC0-∞, ng·h/mL	841±1019	264±216	NC	NC
$t_{1/2,Z}$, h	7.37±5.22	7.91±3.85	NC	NC
APC				
tmax, h	2.79±0.623	2.55±0.712	2.12±0.453	1.79±0.385
Cmax, ng/mL	202±95.7	60.9±54.8	33.6±27.0	23.8±16.3
AUC0-t(last)[c], ng·h/mL	1809±1224	563±578	145±128	90.9±61.5
AUC0-∞, ng·h/mL	1964±1411	593±595	NC	NC
$t_{1/2,Z}$, h	4.41±1.99	5.15±1.34	NC	NC
AUC ratios				
REC (SN-38/CPT-11)	0.027±0.014	0.035±0.047	0.062±0.042	0.112±0.0086
REG (SN-38G/SN-38)	3.60±1.12	3.68±2.82	2.86±1.64	4.03±2.78
REO (APC/CPT-11)	0.270±0.148	0.203±0.154	0.179±0.178	0.317±0.261

[a] All times are from the start of the infusion. Infusion durations: H6957, 1.5 h; P9761, 1 h; D9802, 1 h.
[b] NC, Not computed because of the short duration of PK sampling.
[c] t(last)=25 h in H6957 and P9761 and 7 h in D9802. [d] Computed using AUC0-∞ for H6957 and P9761 and AUC0-7 for 9802. [e] N=53 for irinotecan, SN-38G, and APC tmax and Cmax values. N=51 for SN-38 tmax and Cmax.

In study P9571, PK parameters were determined on day 1 and 4 of a 5-day daily dosing regimen. Since there is minimal accumulation of irinotecan or SN38 during these daily dosing regimens, the comparison of PK parameters on day 1 and 4 could provide some information about intra-patient variability. As figure 4 (above) and figure 5 (below) show, there is some indication of fairly high intra-patient variability. The applicant conducted paired t-tests to compare the Cmax and AUC for irinotecan andSN38 between days 1 and 4, and found no significant differences, except in the Cmax for SN38, which was 35% lower on day 4 compared to day 1 (p=0.002). The applicants indicated that this was probably not clinically significant since the AUCs for the 2 doses were similar.

Figure 5: Cycle 1 day 1 and day 4 irinotecan (left panel) and SN38 (right panel) plasma concentration-time profiles in patients treated with 50 mg/m^2 daily x5 (n=10).



D. Intrinsic Factors

D1. What is the influence of age, gender and body size (weight, BSA) on PK in pediatric patients?

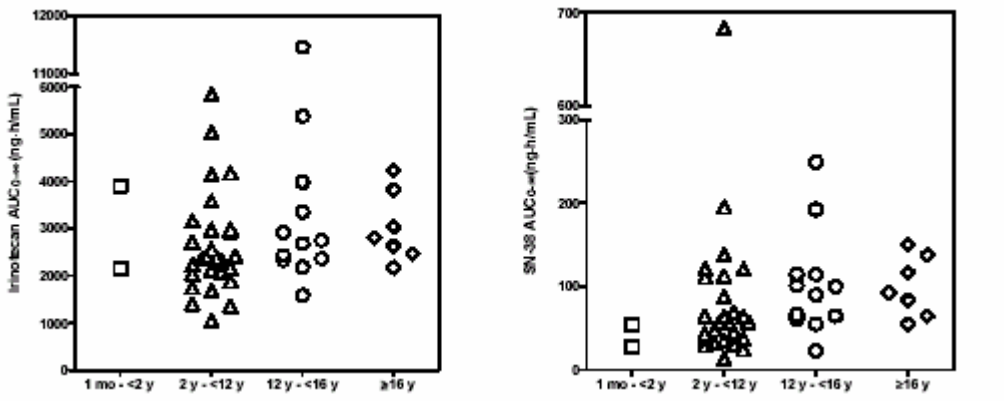
The applicant has evaluated the influence of gender, age (within the pediatric population) and measures of body size on the PK of irinotecan and its metabolites. The data for these analyses were obtained from only 1 study, i.e., the phase 2 study P9761.

a) Effect of age:

The pediatric sample was divided into 4 age groups: 1 month to <2 yrs, 2 to <12 yrs, 12 to < 16 yrs, and > 16 yrs. The following figure shows the irinotecan AUC (left panel) and SN38 AUC

(right panel) for subjects in each of the age groups. There appeared to be only 2 patients in the youngest age group. The AUC of irinotecan and SN38 does not appear to differ among the age groups. The applicant also examined the Cmax for irinotecan and SN38, and reports that the Cmax also does not appear to differ across the age groups, however those data are not shown.

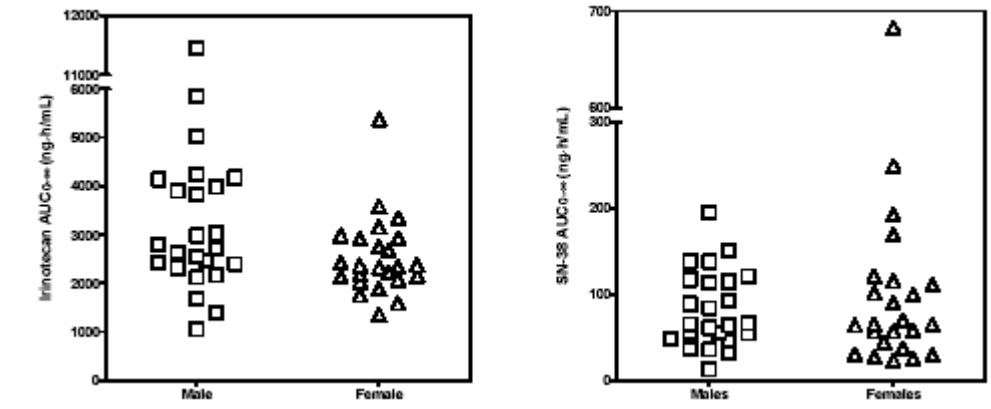
Figure 6: Scatter plots of irinotecan (left panel) and SN-38 (right panel) AUC0-∞ values versus age group (dose=50 mg/m^2, study P9761).



b) Effect of gender:

The following figure shows the irinotecan AUC (left panel) and SN38 AUC (right panel) for male and female patients. The AUC of irinotecan and SN38 do not appear to differ between the male and female patients. The applicant also compared Cmax for irinotecan and SN38 between male and female patients, and found no differences, however those data are not shown.

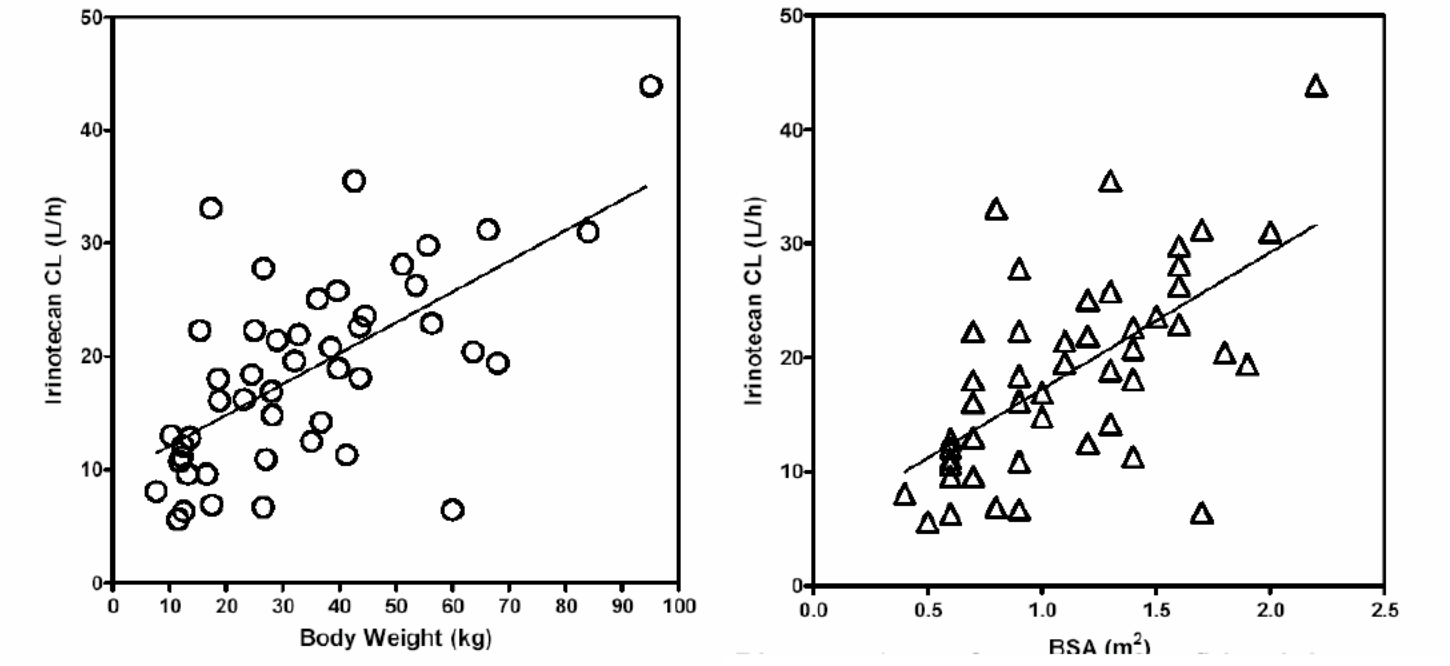
Figure 7: Scatter plots of irinotecan (left panel) and SN-38 (right panel) AUC0-∞ values for male and female subjects (dose=50 mg/m^2, study P9761).



c) Effect of body size:

To examine the influence of body size, the CL of irinotecan (in L/hr) was plotted against the weight (kg), height (cm) and body surface area (BSA, m^2) for the subjects in the phase 2 study P9761.

Figure 8: Irinotecan CL vs. body weight and body surface area.



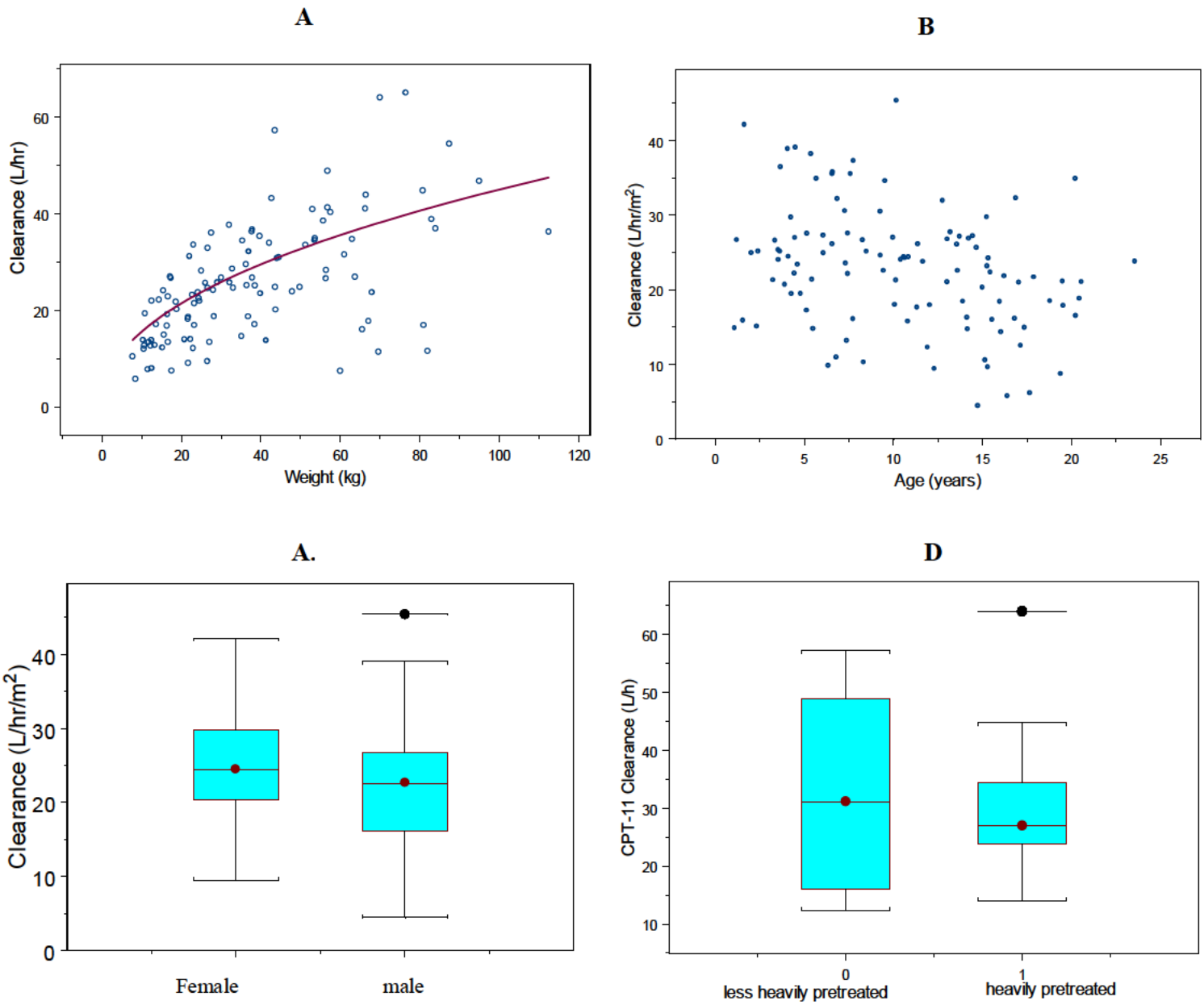
Linear regression analyses showed a significant association between irinotecan CL and each of the body metrics, with r2 = 0.433 for weight, r2 = 0.403 for height, and r2 = 0.383 for BSA. This finding suggests that the dosing of children based on BSA is warranted, although BSA only accounts for a part of the variance in CL of irinotecan, and other intrinsic and extrinsic factors probably also contribute to the overall variance in CL or irinotecan.

Reviewer's Analysis

As part of the population PK analysis, the influence of gender, age (within the pediatric population), pretreatment and measures of body size on irinotecan clearance was examined.

Figure 9 shows scatter plots of irinotecan clearance as a function of body weight, gender, age and pretreatment. Body weight was a significant predictor of irinotecan clearance. Addition of other covariates to the model for clearance, including age, gender and pre-treatment did not result in significant changes in objective function value and indicate that these covariates were not significant predictors of CL of irinotecan, after the inclusion of weight in the model.

Figure 9: Irinotecan clearance (model-predicted) vs. body weight (panel A), age (panel B), gender (panel C) and pre-treatment (panel D).



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

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

Table V: Upper table - Irinotecan and SN38 PK parameters in pediatric solid tumor patients. Lower table – Irinotecan and SN38 PK parameters in adult solid tumor patients

Children:

Dose	**Irinotecan**					**SN-38**		
	Cmax	**AUC**	**T1/2**	**Vz**	**CL**	**Cmax**	**AUC**	**t1/2**
(mg/m^2)	**(ng/mL)**	**(ng·h/mL)**	**(h)**	**(L/m^2)**	**(L/h/m^2)**	**(ng/mL)**	**(ng·h/mL)**	**(h)**
50[b] (N=48[c])	685 ± 264	AUC(0-24) 2899 ± 1571 AUC(0-∞) 2963 ± 1611	4.71 ± 0.66	118 ± 49.8	17.3 ± 6.72	14.2± 12.6	AUC(0-24) 79.4 ± 95.2 AUC(0-∞) 95.0 ± 100	8.93 ±6.29
125[d,e] (N=6)	1815 ± 575	AUC(0-24) 7044±2437 AUC(0-∞) 7263±2626	3.86 ± 1.87	121 ± 57	16.2 ± 4.56	23.6 ± 18.2	AUC(0-24) 166.8 ± 140.6 AUC(0-∞) 215 ± 208	6.85 ±6.40

Adults:

Dose	**Irinotecan**					**SN-38**		
	Cmax	**AUC**	**T1/2**	**Vz**	**CL**	**Cmax**	**AUC**	**t1/2**
(mg/m^2)	**(ng/mL)**	**(ng·h/mL)**	**(h)**	**(L/m^2)**	**(L/h/m^2)**	**(ng/mL)**	**(ng·h/mL)**	**(h)**
125[a] (N=64)	1660 ± 797	AUC0-24: 10200 ± 3270 AUC0-∞: 10667 ± 3491	5.8 ± 0.7	110 ± 48.5	13.3 ± 6.01	26.3 ± 11.9	AUC0-24: 229 ± 108 AUC0-∞: 282.6 ± 144.8	10.4 ± 3.1
340[b] (N=6)	3392 ± 874	AUC0-24: 20604 ± 6027 AUC0-∞: 22897 ± 7157	11.7 ± 1.0	234 ± 69.6	13.9 ± 4.0	56.0 ± 28.2	AUC0-24: 474 ± 245 AUC0-∞: 687 ± 366	21.0 ± 4.3

Data for pediatrics is from study P9761 (50 mg/m^2) and H6957 (125 mg/m^2). Data for adults is from 2 studies, one of 125 mg/m^2 irinotecan given weekly and one of 340 mg/m^2 irinotecan given every 3 weeks.

Comparison of parameters between pediatrics and adults show the following:

- There is substantial variability in exposure measures and PK parameters for irinotecan and SN38 in pediatric patients, as was previously seen in the adult patients.
- Exposure to irinotecan, following comparable doses (125 mg/m^2) appears to be similar between pediatrics and adults (Cmax (ng/ml): 1815 ± 575 in pediatrics, 1660 ± 797 in adults; AUCINF (ng.hr/ml): 7263 ± 2626 in pediatrics, 10667 ± 3491 in adults).
- The applicant suggests that the CL (L/hr/m^2) in pediatrics is higher than in adults and that the half-life (hr) in pediatrics is shorter than in adults. Comparison of values reported in the above tables does show higher mean CL values and lower mean t1/2 values for pediatrics, however, given the variability, it is unlikely that this difference will be statistically significant. It does not appear that the applicant has conducted a formal statistical analysis comparing the parameters between pediatric and adult patients.
- Exposure to SN38 (Cmax and AUC) does not appear to be different between pediatric and adult patients.

Results of the population PK analysis conducted by the reviewer showed that the PK parameters for irinotecan in pediatric patients are close to PK parameter estimates obtained from population analysis in adult patients (Xie et al., 2002), indicating that there do not appear to be major differences in PK between pediatrics and adults. For details, please see pharmacometrics review.

E. Extrinsic Factors

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

The interaction between irinotecan and enzyme-inducing anticonvulsants (EIACs) was the objective of two of the phase 1 studies, H6957 and P9871. No patients on EIACs were enrolled into study H6957 therefore the evaluation of the effect of anticonvulsants was done for patients in P9871.

The effect of concomitant anticonvulsants on irinotecan PK was evaluated in study P9871. The study included 3 groups of patients:

- Stratum 1: Patients receiving enzyme-inducing anticonvulsants (EIAC) including phenytoin (n=3), carbamezapine (n=2), oxcarbazepine (n=1)
- Stratum 2: Patients receiving valproic acid (VAL) (n=1). This arm was included to examine the potential inhibitory effect of valproic acid on SN38 glucuronidation.
- Stratum 3: Patients receiving other anticonvulsants (Other AC) including clobazam (n=1). One additional patient was placed in this stratum even though the patient was receiving carbamezapine, which is an EIAC.

Due to the small number of patients in this trial who received non-EIAC, PK parameters in P9871 patients receiving EIACs were compared to parameters determined in study P9761, which was a concurrently run phase 2 trial of single-agent irinotecan in children with various solid tumors; patients receiving AC were excluded from P9761. A cohort of 13 patients in P9761

underwent PK sampling on the identical schedule to P9871. PK parameters derived from P9761 (no AC) and P9871 (EIACs) were compared statistically using unpaired, 2-sided t-tests.

PK parameters for irinotecan and 3 metabolites are summarized in the following table. To facilitate comparison, systemic exposure parameters such as AUC and Cmax have been normalized to a 100mg/m^2 dose. The degree of interpatient variability in the P9871 trial (EIAC and non-EIAC groups) is considerable but appears to be comparable to that observed in other pediatric trials and in the adult population. Comparison of PK parameters for the P9871 EIAC group with the P9761 no-AC cohort clearly shows that concomitant treatment with EIACs had a major impact on the SN-38 exposure. Dose-adjusted mean SN-38 AUC0-t(last) in EIAC patients was ~70% lower compared to that in non-AC patients. Similarly, dose-adjusted mean SN-38 Cmax in EIAC patients was 67% lower than that in non-AC patients. SN-38 exposure in the 2 non-EIAC patients in this study was intermediate with considerable variability. Mean irinotecan AUC0-t(last) in the EIAC group was 30% lower than that in the no-AC group. While statistically significant (p=0.04), the magnitude of the EIAC effect on irinotecan was less than on SN-38 (Table VI). While mean APC AUC0-t(last) values differed substantially, the interpatient variability was so great that the difference was not statistically significant.

Table VI: PK parameters for subjects in study P9761 (no ACs) and study P9871 (non-EIACs and EIACs).

PK Parameters	P9761 (mean±SD; N=13) No ACs	Non-EIACs (range; N=2)	P9871 EIACs (mean±SD; N=5)	EIAC vs. P9761 No AC p-value[c]
Irinotecan				
tmaxa (h)	1.06±0.053	1.00-1.07	1.03±0.075	NS
Cmax (ng/mL)	1255±305	803-1198	1264±902	NS
AUC0-t(last) (ng·h/mL)	3596±1464	2434-3412	2520±560	0.040
SN38				
tmax (h)	1.12±0.13	1.42-1.67	1.10±0.109	NS
Cmax (ng/mL)	30.0±10.2	25.8-76.3	9.99±1.59	0.0006
AUC0-t(last) (ng·h/mL)	106.6±42.6	99.0-138	32.9±9.72	0.0001
SN38G				
tmax (h)	1.63±0.511	1.42-2.00	1.23±0.18	NS
Cmax (ng/mL)	72.6±34.9	29.1-79.2	54.2±36.1	NS
AUC0-t(last) (ng·h/mL)	354±220	141-376	234±244	NS
APC				
Tmax (h)	2.06±0.588	1.57-2.00	1.93±0.78	NS
Cmax (ng/mL)	86.4±31.9	55.3-318	272±261	0.0178
AUC0-t(last) (ng·h/mL)	506±208	341-1954	1516±1638	NS
AUC Ratios				
SN-38/irinotecan	0.031±0.011	0.041-0.041	0.013±0.005 (5)	0.0003
SN-38G/SN-38	3.64±2.18	1.42-2.70	6.83±5.85 (5)	NS
APC/irinotecan	0.155±0.071	0.140-0.573	0.556±0.487 (5)	0.0079

a tmax values for irinotecan and all metabolites are relative to the start of the infusion.
b Ratio of metabolite AUC0-t(last) to irinotecan AUC0-t(last). Also known as relative extent of conversion (SN-38/irinotecan; REC); relative extent of glucuronidation (SN-8G/SN-38; REG); and relative extent of oxidation (APC/irinotecan; REO).
c p-value from unpaired, 2-sided t-test (with Welch's correction for significantly different variances) of P9871 EIAC data versus P9761 no-AC data; NS=not significant. **Abbreviations:** AC= Anticonvulsant, EIAC= Enzyme-inducing AC

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

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

(b) (4)

[redacted]

Other

E3. Are there any additional unresolved issues or omissions with regard to the evaluation of the PK and PD of irinotecan and its metabolites in pediatric patients?

Polymorphisms in UGT1A1 enzymes:

UGT-Uridine diphosphate glucuronosyl transferase is a phase 2 microsomal enzyme predominantly found in the liver. There are many different isoforms (UGT1A1, UGT1A3, UGT1A4 etc.). UGT1A1 is involved in the conversion of SN38 to SN38G. The gene for UGT1A1 shows polymorphism in the promoter region. The normal allele has a (TA)6TAA sequence (TATATATATATATAA) whereas a variant allele has a (TA)7TAA sequence. This results in the following genotypes: 6/6, 6/7 and 7/7 with frequencies of 43%, 48% and 9%. The presence of the 7-allelle (UGT1A1*28) makes the isoform less able to glucuronidate (i.e., the 7-allelle is less efficient). Thus patients with the polymorphism have a decreased ability to glucuronidate SN38 to SN38G (Iyer et al., 1999). This could result in elevation in SN38 levels and increase the risk for severe toxicity including neutropenia and diarrhea.

A recent study by Innocenti et al. (2004) in 66 patients showed that 3 of the 6 patients (50%) with the 7/7 genotype showed severe grade 4 neutropenia compared with 3 of 24 patients (12.5%) with 6/7 genotype and 0 of 29 patients (0%) with 6/6 genotype. The relative risk of developing grade 4 neutropenia for the 7/7 patients was 9-fold higher than the risk for the other 2 groups combined: 50% risk (3 of 6 patients) for 7/7 patients vs. 5.6% risk (3 of 53 patients) for 6/6 and 6/7 patients.

These findings, along with other studies (Ando et al., 2000, Iyer et al., 2002) point to the need for further evaluation of the influence of UGT1A1 genotypes on the pharmacokinetics of irinotecan and SN38 as well as on the risk for severe toxicity, both in pediatric and adult cancer patients.

F: Analytical Section

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

Plasma samples were assayed for concentrations of irinotecan and its metabolites using validated, sensitive, specific, isocratic, high performance liquid chromatographic methods with

fluorescence detection (HPLC-FL). The following table lists the analytes measured for each study.

Table VII: Analytes measured, by protocol.

Protocol #	Analytes	Assays conducted by:
H6957	Total forms: Irinotecan, SN38, SN38G, APC	Pharmacia
P9571	Total forms: Irinotecan, SN38, SN38G, APC	(b) (4)
P9871	Total forms: Irinotecan, SN38, SN38G, APC	Pharmacia
St. Jude	Lactone forms: Irinotecan, SN38	(b) (4)
P9761	Total forms: Irinotecan, SN38, SN38G, APC	(b) (4)
D9802	Lactone and Total forms: Irinotecan, SN38, SN38G, APC	(b) (4)

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

For 5 of the 6 studies, the active metabolite SN38 and its glucuronide metabolite SN38G were assayed. In addition, the major CYP450 metabolite formed via CYP 3A4, APC was also measured. Measurement of metabolites is important for complete characterization of the disposition of irinotecan. Additionally, measurement of active metabolites are important for correlating with measures of response (and toxicity) of drugs as part of exposure-response analysis.

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

For all moieties, the total form is measured. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form. Studies have shown that the ratio of lactone to total concentration of irinotecan is fairly constant (0.34 to 0.44), and concentration-time curves for the lactone form and total concentration are highly correlated. Thus PK parameters computed from analysis of total (lactone+carboxylate) concentrations accurately reflect the PK of the bioactive lactone species. Since lactone-specific assays require rapid chemical processing and analysis of plasma samples to minimize post-sampling changes in lactone levels, many PK studies of irinotecan (including most of those reported herein), have been based on assays for total rather than lactone concentrations.

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

The method, in general, is similar for all the studies. In brief, the procedure involves the precipitation of plasma proteins using an acidified acetonitrile solution of internal standard (IS) camptothecin, followed by a 15-min incubation at 40°C. After the subsequent addition of the buffer, the sample is centrifuged and the supernatent is analyzed by HPLC with fluorescence detection.

In order to determine the concentrations of SN-38G, a separate portion of each plasma sample was subjected to an enzymatic hydrolysis procedure via the addition of β-glucuronidase solution. The conversion reaction was terminated by precipitating proteins using an acidified acetonitrile solution of the IS. The remainder of the analysis was carried out as described above. Table VIII lists the chromatographic conditions for each method.

Table VIII: Chromatographic conditions for each method.

	Pharmacia method	(b) (4) method [Rivory, 1994]	(b) (4) method [Owens, 2003]
Studies	H6957 P9871	P9571 P9761 St.Jude	D9802 (irinotecan+SN38+SN38G+APC total and lactone)
Column	Zorbax SB C8 column	NovaPak C18 column	Symmetry C8 column
Mobile phase	25% acetonitrile: 75% 25mM TEA buffer (pH 4.2)	22% acetonitrile: 78% 0.075M NH4 acetate buffer (pH 6.4)	A (100% from 0-15min) :- - 14% acetonitrile - 86% 0.75 M ammonium acetate + 5 mM tetrabutylammonium phosphate B (40% from 15-28 min) :- - 50% acetonitrile: - 50% 0.75 M ammonium acetate + 5 mM tetrabutylammonium phosphate
Detector wavelength - Excitation - Emission	372 nm 425 nm (0-15min) 535 nm (15-24min)	355 nm 515 nm	380 nm 460 nm (0-9.95min) 520 nm (9.95-13.4min) 460 nm (13.4-17.3min) 530 nm (17.3-35min)

F5. What are the figures of merit and performance characteristics for the methods used to assess concentrations of irinotecan and its metabolites?

The following table shows the figures of merit and performance characteristics for the methods used in the 6 studies. In all cases, the calibration curves were linear and had very high

coefficients of determination. The LLOQs were acceptable. Precision and accuracy of controls for all analytes were also within acceptable ranges (+/- 15%).

Specificity of the method was shown for 6 independent lots of plasma. Irinotecan, SN-38, APC, and SN-38G in plasma were shown to be stable through 3 freeze/thaw cycles. Stability of the analytes in extracted samples (in the autosampler and at room temperature) for 24 h was also demonstrated. The analytical method was shown to be specific in the presence of a series of potential coadministered medications. Long-term stability of irinotecan and SN-38 in plasma has been documented to 2 y when samples are stored at -20°C. The long-term stability of SN-38G in plasma has been documented to 1 y when samples are stored at 20°C.

Table IX: Figures of merit for each analyte, by method.

	Irinotecan	**SN38**	**APC**	**SN38G**
Pharmacia Method – Study H6957				
Linear range (ng/ml)	1.28-3840	0.48-640	0.96-1280	0.37-889
LLOQ (ng/ml)	1.28	0.48	0.96	0.37
QC samples:				
Mean Accuracy (%)	97.2-98.4%	90.0-100.0%	95.0-98.6%	100.0-103.5%
Precision (CV%)	3.1-7.9%	3.7-9.1%	6.1-11.8%	3.3-6.6%
Pharmacia Method – Study P9871				
Linear range (ng/ml)	1.28-3840	0.48-640	0.96-1280	0.37-889
LLOQ (ng/ml)	1.28	0.48	0.96	0.37
QC samples:				
Mean Accuracy (%)	92.2-97.5%	97.5-99.2%	105.0-112.5%	97.5-101.7%
Precision (CV%)	2.5-3.5%	2.2-4.7%	3.1-5.1%	3.5-5.0%
(b) (4) **Method: P9571, P9761, ST JUDE**				
Linear range (ng/ml)	10-1700	1.0-200	1.0-200	-
LLOQ (ng/ml)	2.0	1.0	1.0	-
QC samples:				
Mean Accuracy (%) (low control)	103%	106%	94%	-
Precision (CV%)	1.1-1.9%	1.4-3.3%	0.8-9.1%	-
(b) (4) **Method: D9802 (Lactone and Carboxylate)**				
Linear range (ng/ml)	5-300	0.5-25	2-25	2-25
LLOQ (ng/ml)	5.0	0.5	2.0	2.0
QC samples:				
Mean Accuracy (%)	90.3-114.4%	93.7-102.3%	92.9-102.3%	90.2-99.2%
Precision (CV%)	5.0-12.9%	7.1-18.6%	5.3-11.5%	4.1-9.5%

G. References

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III. Detailed Labeling Recommendations

1. Labeling Changes for Irinotecan (#1)

Current Applicant Label

PRECAUTIONS
Pediatric Use

~~The safety and effectiveness of CAMPOTSAR in pediatric patients have not been established.~~

(b) (4)

[redacted]

(b) (4)

FDA Proposed Labeling:

The following text should be included under the 'PRECAUTIONS' section under the 'Pediatric Use' subsection.

The effectiveness of Irinotecan in pediatric patients has not been established Results from two (b) (4) studies were submitted. One hundred and seventy children with refractory solid tumors were enrolled in one phase II trial in which 50 mg/m^2 of irinotecan was infused for 5 consecutive days every 3 weeks. (b) (4) Grade 3- 4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3- 4 diarrhea was observed in 35 (20.6%) patients. In the second phase II trial (b) (4) children with untreated rhabdomyosarcoma, 20 mg/m2 of irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent therapy was followed by multimodal therapy. Accrual to (b) (4) was halted (b) (4).

Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric solid-tumor trials at dose levels of 50 mg/m2 (60-min infusion, n=48) and 125 mg/m2 (90-min infusion, n=6). Irinotecan clearance (mean ± S.E.) was 17.3 ± 6.7 L/hr/m2 for the (b) (4) dose and 16.2 ± 4.6 L/hr/m2 for the (b) (4) dose, which is comparable to that in adults. Dose-normalized SN-38 AUC values were comparable between adults and children. Minimal accumulation of irinotecan and SN-38 was observed in children on daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x 2 weeks every 3 weeks].

2. Labeling Changes for Irinotecan (#2)

Current Applicant Label

CLINICAL PHARMACOLOGY
Pharmacokinetics in Special Populations
Pediatric

~~*Pediatric:* Information regarding the pharmacokinetics of irinotecan is not available.~~

(b) (4)

FDA Proposed Labeling:

The applicant proposed text under the 'CLINICAL PHARMACOLOGY' section in the 'Pharmacokinetics in Special Populations' subsection under 'Pediatric' from lines 117 to 129 in the annotated proposed label, should be deleted.

IV. Appendices

B. A. Proposed Package Insert (Annotated)

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

F. B. Individual Study Reviews

Study #:	**H9657**
Title:	A Pediatric Phase 1 and Pharmacokinetic Summary of Irinotecan (CPT-11): A Preliminary Report
Principal Investigator:	Susan M. Blaney, MD Texas Children's Cancer Center, Houston TX 77030
Study Centers:	Texas Children's Cancer Center (TCCC) 6621 Fannin Street, MC 3-3320 Houston, TX 77030 MD Anderson Cancer Center (MDACC) 1515 Holcombe Boulevard Houston, TX 77030

Primary Objectives:

- To estimate the maximum tolerated dose (MTD) and dose-limiting toxicity (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 (enzyme-inducing anticonvulsants).

Secondary Objective:

- To gain preliminary information on the clinical benefit of irinotecan for pediatric patients with refractory or progressive solid tumors.

Study Design:

The study was an open-label, 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 as a 90 min IV infusion, weekly x 4 weeks. Cycles were repeated every 6 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 according to the NCI CTC. 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 EIACs.

Drug administration:
Successive cohorts of patients were enrolled to progressively higher doses of irinotecan. The planned starting doses of irinotecan (by stratum) are shown below. Subsequent dose levels (>200 mg/m^2/week) were 260, 335 and 435 mg/m^2/week. If the MTD was exceeded at 125 mg/m^2, subsequent patients could be enrolled at a dose of 100 mg/m^2.

Table S-I: Starting Dose Levels.

Starting Dose Level (mg/m^2/week)	Stratum 1	Stratum 2	Stratum 3	Total Patients
125	6	0	0	6
160	3	5	0	8
200	0	2	0	2
Total	9	7	0	16

Irinotecan was supplied by Pharmacia in amber vials as a 20mg/ml sterile solution in 2 sizes:
1) 2 ml vial containing 40 mg of irinotecan hydrochloride trihydrate
2) 5 ml vial containing 100 mg of irinotecan hydrochloride trihydrate.

Irinotecan was administered IV in 5% dextrose solution over 90 min. The appropriate volume of the 20 mg/ml solution was mixed with 5% dextrose to final concentration of irinotecan of 0.12 mg/ml to 1.1 mg/ml irinotecan.

Dose escalation proceeded in cohorts of 3 to 6 patients until >1 of 3 or ≥ 2 of 6 patients experienced a DLT. 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.

Safety Evaluations and Procedures:
Please see following table for schedule of study evaluations and PK assessments.
Efficacy was assessed using standard bidimensional solid tumor response criteria.
Concomitant medications included atropine for early-onset diarrhea, loperamide for treatment of late-onset diarrhea, antiemetics including dexamethasone, ondansetron, and growth factors at the discretion of the individual investigator (but not during cycle 1).

Pharmacokinetic Assessments: PK samples for all patients were obtained on Day 1 of Cycle 1. Blood samples (3-5 mL) were collected in green-top, heparin-containing tubes at a site contralateral to the drug infusion site. The exact time of each draw and the exact time of drug administration were recorded. Blood samples were immediately centrifuged and the plasma was pipetted into a separate tube which was then stored at -20^{0}C. Sample times were prior to the start

of the irinotecan infusion, at 30 and 60 min during the infusion, at the end of the infusion, and at 5, 15, and 30 min and 1, 2, 4, 6, 8, between 10 to 12 h, and 24 h following the completion of the infusion.

Table S-II: Schedule of study evaluations.

Evaluation	Prestudy	Cycle 1	Cycle 2	Subsequent Cycles	Off-Study
Med/Onc History	x	x	x	x	x
Physical examination	x	weekly	x	x	x
PS	x	x	x	x	x
CBC diff, platelets	x	twice weekly	weekly	weekly	x
Electrolytes incl. Ca^{+2}, PO_4, Mg^{+2}	x	weekly	x	x	x
Total protein/albumin	x	-	x	x	x
Urinalysis	x	-	-	-	-
Tumor evaluation	x	End of cycle	End of cycle	Every other cycle	x
PK sample collection	-	x	-	-	-

Analytical Methods: Plasma samples were assayed for total (lactone + carboxylate species) concentrations of irinotecan, SN-38, APC, and SN-38G using validated, sensitive, specific, isocratic, high performance liquid chromatographic methods with fluorescence detection (HPLC-FL).

Data Analysis: Irinotecan, SN-38, SN-38G, and APC plasma-concentration data were analyzed by noncompartmental methods using Kinetica 2000, version 3.1 (InnaPhase Corp). Cmax,Tmax, lambda, $t_{1/2}$, AUC(0-last), AUC(inf), CL and Vz were measured or determined. Metabolic ratio, defined as the ratio of SN-38 $AUC_{0\text{-}inf}$ to irinotecan $AUC_{0\text{-}inf}$, was used as a measure of the relative extent of conversion of irinotecan to SN-38. The relative extent of SN-38 metabolism to SN-38G was defined as the ratio of SN-38G $AUC_{0\text{-}inf}$ to SN-38 $AUC_{0\text{-}inf}$. The relative extent of conversion to APC was defined as the ratio of APC $AUC_{0\text{-}inf}$ to irinotecan $AUC_{0\text{-}inf}$.

Results and Discussion:

Subject disposition:

A total of 16 patients completed the study. No subjects were entered into stratum 3 (enzyme-inducing anticonvulsants). Table S-I lists the number of patients enrolled in strata 1 and 2, by starting dose level.

Baseline characteristics:

Table S-III: Patient demographics and baseline characteristics.

Characteristics	Categories	Stratum 1	Stratum 2	N	(%)
Age	2-<12y	5	5	10	(62.5)
	12-<16y	1	1	2	(12.5)
	□16y	3	1	4	(25.0)
Gender	Male	6	1	7	(43.8)
	Female	3	6	9	(56.3)
Ethnic Origin	White	6	1	7	(43.8)
	African American	-	3	3	(18.8)
	Other	3	3	6	(37.5)
PS	ECOG 0	7	5	12	(75.0)
	ECOG 1	2	2	4	(25.0)
	ECOG 2	-	-	-	
Tumor Type	Rhabdomyosarcoma	1	1	2	(12.5)
	Hepatic Sarcoma	1	-	1	(6.3)
	Leiomyosarcoma	1	-	1	(6.3)
	Ewing's Sarcoma	2	-	2	(12.5)
	Neuroblastoma	1	-	1	(6.3)
	Glioma	-	3	3	(18.8)
	Ependymoma	1	1	2	(12.5)
	Optic Glioma	-	1	1	(6.3)
	Hepatoblastoma	1	-	1	(6.3)
	Synovial Sarcoma	1	-	1	(6.3)
	Breast Carcinoma	-	1	1	(6.3)
Sites of Disease	Brain/Brain Stem/Post fossa	1	3	4	(25.0)
	Pelvis	2	-	2	(12.5)
	Liver	2	-	2	(12.5)
	Pineal	-	1	1	(6.3)
	Lung	1	-	1	(6.3)
	Retroperitoneum	1	-	1	(6.3)
	Mandible	1	-	1	(6.3)
	Chest Wall	-	1	1	(6.3)
	Optic Nerve	-	1	1	(6.3)
	Paraspinal	1	-	1	(6.3)
	Breast	-	1	1	(6.3)
Prior ChemoTxt	0 Regimen	-	2	2	(12.5)
	1 Regimen	1	1	2	(12.5)
	>2 Regimens	8	4	12	(75.0)
Prior Therapy	XRT only	-	1	1	(6.3)
	ChemoTxt + Surgery	2	1	3	(18.8)
	ChemoTxt + XRT	-	2	2	(12.5)
	XRT + Surgery	-	1	1	(6.3)
	ChemoTxt + XRT + Surgery	7	2	9	(56.3)

Pharmacokinetics**:**

Figure S1 shows the mean concentration time profiles for irinotecan and its metabolites. The PK parameters of irinotecan and its metabolites for each dose group are summarized in the table below. There is considerable inter-and intra-dose group variability associated with the PK parameters for irinotecan and metabolites. In all dose groups, tmax values are in the order of APC>SN-38G>SN-38, indicating that the formation of APC was the slowest among the 3

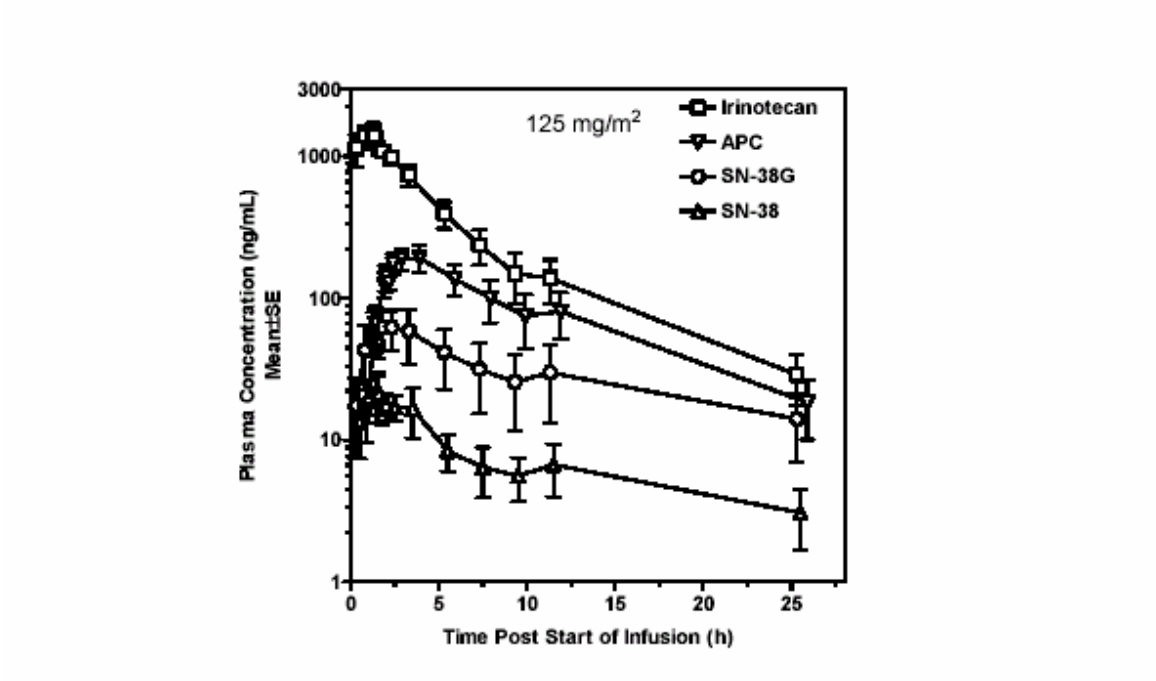
metabolites. The $t_{1/2}$ values of SN-38 and its metabolite SN-38G were similar, indicating that the elimination of the latter may be formation rate-limited. In this pediatric patient population, irinotecan has a mean CL of 21.56 ± 7.79 L/h/m^2 and a mean $t_{1/2}$ ranging from 1.4 to 6.9 h.

Table S-IV. Summary of PK parameters for irinotecan, SN38, SN38G and APC.

Dose, mg/m^2 (N)	**125 (6[b])**	**160 (4[c])**	**200 (2)**
Irinotecan			
tmax (h)[d]	1.42±0.30	0.514±0.034	1.00-1.50
Cmax (ng/mL)	1815±575	2102±658	1950-2000
AUC0-24 (ng·h/mL)	7044±2437	4722±3097	5542-7037
AUC0-∞ (ng·h/mL)	7263±2626	5659±2271	5594-7315
CL (L/h/m^2)	16.2±4.6	26.7±8.0	23.7-31.0
Mean±SD of CL in all patients (all dose levels) =21.56±7.79 L/h/m^2.			
Vz (L/m^2)	121±57	244±89	79.7-227
t1/2,z (h)	3.86±1.87	6.10±0.80	2.33-5.08
SN38			
tmax (h)	1.79±0.40	1.72±0.75	1.00
Cmax (ng/mL)	23.6±18.2	26.8±15.3	19.2-44.6
AUC0-24 (ng·h/mL)	167±141	139±72.4	103-219
AUC0-∞ (ng·h/mL)	215±208	243±200	119-268
t1/2,z (h)	6.85±6.40	13.5±24.0	4.47-10.0
SN38G			
tmax (h)	2.38±0.70	1.64±0.44	1.50-2.50
Cmax (ng/mL)	71.3±55.9	58.7±16.0	44.3-57.2
AUC0-24 (ng·h/mL)	660±712	316±132	296-334
AUC0-∞ (ng·h/mL)	841±1019	404±146	358-584
t1/2,z (h)	7.37±5.22	13.9±3.5	8.74-12.4
APC			
tmax (h)	2.79±0.62	1.92±0.40	2.08-3.50
Cmax (ng/mL)	202 ± 96	214±127	175-309
AUC0-24 (ng·h/mL)	1809±1224	899±248	975-1715
AUC0-∞ (ng·h/mL)	1964±1411	931±246	994-2134
t1/2,z (h)	4.41±1.99	5.75±0.94	4.39-4.65
AUC ratios			
SN-38/irinotecan	0.027±0.014	0.045±0.042	0.021-0.037
SN-38G/SN-38	3.60±1.12	2.38±1.18	2.18-3.00
APC/irinotecan	0.270±0.148	0.181±0.078	0.178-0.292

[a]Mean±SD for 125 and 160 mg/m^2 cohorts. Range for 200 mg/m^2 cohort.
[b]One patient was sampled through only 8 h.[c]N=6 for Cmax and tmax values for all analytes in the 160 mg/m^2 patient cohort. [d]Time relative to the start of the infusion.
[e]Harmonic mean. [f]Ratio of metabolite AUC0-∞ to irinotecan AUC0-∞
Also known as relative extent of conversion (SN-38/irinotecan; REC); relative extent of glucuronidation (SN-38G/SN-38; REG); and relative extent of oxidation (APC/irinotecan; REO).
Abbreviations: APC= Aminopentanecarboxylic acid metabolite of irinotecan, SN-38=Bioactive metabolite of irinotecan, SN-38G= SN-38 glucuronide

Figure S1: Irinotecan and metabolite plasma concentration-time profiles (mean +/- SE) following a 90-min infusion at 125 mg/m2. (Data have been offset slightly in the x-direction to prevent overlapping points and error bars.



The PK profiles of irinotecan and its metabolites (SN-38, SN-38G and APC) following the administration of irinotecan IV were characterized by substantial interpatient variability, as has been reported for adults.

Pharmacokinetic evaluations indicated that the 125 mg/m^2 dose in children achieved irinotecan and SN-38 exposures (Cmax and AUC) comparable to those associated with clinical efficacy in adults administered the same dose and schedule. For example, the administration of 125 mg/m^2 led to Cmax of 1815 $\pm$ 575 and 23.6 $\pm$ 18.2 ng/mL for irinotecan and SN-38 respectively. These values compare favorably with Cmax in adults receiving the same dose; eg, Cmax of 1660$\pm$797 and 26.3$\pm$11.9 for irinotecan and SN-38, respectively [CAMPTOSAR Package Insert].
AUC values were also comparable with those reported in adults administered the dose of 125 mg/m^2.

Adverse Events:

Across all cycles of therapy, the most common grade 3-4 non-hematologic AEs were gastrointestinal grade 3-4 diarrhea (25%) and grade 4 abdominal pain (6.3%) Clinically important hematological toxicities were grade 3-4 neutropenia (43.8%), grade 3-4 leukopenia (37.5%) and grade 4 anemia (6.3%).
These types of AEs are entirely consistent with what has been reported with single-agent irinotecan in adults. Of note, despite neutropenia being the most frequent hematologic toxicity, it was complicated by neutropenic fever in only 2 (12.5%) patients. No patient discontinued study due to toxicity and no toxic deaths were reported. The 60-day all cause mortality was 6.25%.

The following table shows the serious adverse events, by subject.

Table S-V: Serious adverse events, by subject.

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

There was no apparent association between toxicity and plasma exposures of irinotecan or SN-38 in this pediatric trial. However, this conclusion should be taken with caution due to the small number of patients with grade 3-4 toxicity for whom PK samples were available.

Efficacy measures:

No objective tumor responses were reported. Four (28.6%) of the 14 patients evaluable for response had SD as a best response and received treatment for 1-4 cycles. Three out of the 4 patients with SD were heavily pretreated patients. Stabilization of the disease was reported in all 3 age groups represented in the study. Of the patients with SD, the primary tumor type was Ewing's sarcoma (1 patient), ependymoma (1 patient), rhabdomyosarcoma (1 patient) and breast carcinoma (1 patient).

Conclusions:

- The maximum tolerated dose of irinotecan in pediatric solid tumor patients was 125 mg/m^2/week. DLTs were grade 4 neutropenia and grade 4 diarrhea .

- The PK of irinotecan and its metabolites (SN-38, SN-38G and APC) following the administration of irinotecan IV were characterized by substantial interpatient variability, as has been reported for adults.

- The 125 mg/m^2 dose in children achieved irinotecan and SN-38 exposures (Cmax and AUC) comparable to those associated with clinical effectiveness in adults administered the same dose and schedule.

- There was no apparent association between toxicity and plasma exposures of irinotecan or SN-38 in this pediatric trial. However, this conclusion should be taken with caution due to the small number of patients with grade 3-4 toxicity for whom PK samples were available.

Study #:	**P9871**
Title:	A Phase 1 study of Irinotecan in patients with refractory solid tumors who are concomitantly receiving anticonvulsants: A COG study.
Principal Investigator:	A. Moghrabi, M.D. St Justine Hospital, Montreal, Canada
Study Centers:	8 centers in US and Canada

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 Objective:
• 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).
Within each stratum, sequential cohorts of 3 patients were enrolled to receive progressively higher starting dose levels of irinotecan as a 60 min IV infusion daily x 5 repeated 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.

Based on the estimated number of dose levels and prior experience with irinotecan, it was projected that up to 25 patients might be enrolled in Stratum 1 (patients on EIAC), which was the stratum to be used to determine study closure.

Drug Administration:
The test product was commercial supplies of CAMPTOSAR Injection. Irinotecan was administered as a 60 min IV infusion. The appropriate volume of 20 mg/mL solution was mixed with 5% dextrose to a final concentration of 0.12 mg/mL to 1.1 mg/mL irinotecan.

Starting dose levels for each stratum is shown in the following table. Higher doses were used in the EIAC group in anticipation of the increased metabolism of irinotecan in these patients.

Table S-VI: Starting dose levels by stratum.

	Stratum 1 (EIAC)	Stratum 2 (VAL	Stratum 3 (Other AC)
Dose Levels	**Starting Dose (mg/m^2/day)**	**Starting Dose (mg/m^2/day)**	**Starting Dose (mg/m^2/day)**
1	100	30	50
2	130	39	65
3	170	50	85
4	220	65	110
5	285	85	140

Safety Evaluations and Procedures:
Please see following table for schedule of study evaluations and PK assessments.

Table S-VII: Study evaluations and PK assessments

Evaluation	**Pre-Study**	**Cycle 1**	**Cycle 2**	**Subsequent Cycles**	**Off-Study**
Med/Onc History	X	X	X	X	X
Physical examination	X	Weekly	X	X	X
PS	X	X	X	X	X
CBC, differential, platelets	X	2x Weekly	Weekly	Weekly	X
PK	-	X	-	-	-
Urinalysis	X	-	-	-	-
Electrolytes: Ca^{+2}, PO_4, Mg^{+2}	X	Weekly	Weekly	Q cycle[a]	X
BUN, creatinine, ALT, bilirubin, GGT, alk phos	X	Weekly	Weekly	Q cycle[a]	X
AC Drug Level	X	X	X	Every other cycle	
Total protein/albumin	X	-	X	X	X
Tumor evaluation	X	End of cycle	End of cycle	Every other cycle	X
Pregnancy Test[b]	X	-	-	-	-

[a] If no problems in the first 2 courses
[b] Pts of child bearing potential required a negative pregnancy test prior to starting treatment
Abbreviations: AC= anticonvulsant, Alk phos= alkaline phoshatase, ALT= alanine aminotransferase, BUN= Blood urea nitrogen, CBC= complete blood count, GGT= gamma glutamyl transferase, PK= pharmacokinetics, PS= performance status

Efficacy was assessed using standard bidimensional solid tumor response criteria.
Concomitant medications included atropine for early-onset diarrhea, loperamide for treatment of late-onset diarrhea, antiemetics including dexamethasone, ondansetron, and growth factors at the discretion of the individual investigator (but not during cycle 1). Medications that could interfere with CYP P450 metabolism (inhibitors, inducers, substrates) were avoided.
Pharmacokinetics (PK):

Enrolled patients who consented to the PK correlative study had blood draws performed on Day 1 of Cycle 1. Blood samples (3-5 mL) were collected in heparinized, green-top tubes from a vein contralateral from the infusion site. Samples were centrifuged immediately and the decanted plasma was immediately stored at -20^0 C. Blood draw times were: prior to the irinotecan infusion, at the end of the 60 min infusion, and at 5, 15, and 30 min and 1, 2, 4, 6, 8, and between 10 to 12 h following the completion of the infusion.

Analytical Methods:
Plasma samples were assayed for total (lactone + carboxylate species) concentrations of irinotecan, SN-38, APC, and SN-38G using validated, sensitive, specific, isocratic, high-performance, liquid chromatographic methods with fluorescence detection (HPLC-FL). Assays were conducted (b) (4)

Data Analysis:
Irinotecan, SN-38, SN-38G, and APC plasma-concentration data were analyzed by noncompartmental methods using Kinetica 2000, version 3.1 (InnaPhase Corp). Cmax,Tmax, lambda, t1/2, AUC(0-last), AUC(inf), CL and Vz were measured or estimated. Metabolic ratio, defined as the ratio of SN-38 $AUC_{0\text{-}inf}$ to irinotecan AUC0-inf, was used as a measure of the relative extent of conversion of irinotecan to SN-38. The relative extent of SN-38 metabolism to SN-38G was defined as the ratio of SN-38G $AUC_{0\text{-}inf}$ to SN-38 $AUC_{0\text{-}inf}$. The relative extent of conversion to APC was defined as the ratio of APC $AUC_{0\text{-}inf}$ to irinotecan $AUC_{0\text{-}inf}$.

Due to the small number of patients in this trial who received non-EIAC, PK parameters in P9871 patients receiving EIACs were compared to parameters determined in a concurrent phase II trial (P9761) of single-agent irinotecan in children with various solid tumors; patients receiving AC were excluded from P9761. A cohort of 13 patients in P9761 underwent PK sampling on the identical schedule to P9871. PK parameters derived from P9761 (no AC) and P9871 (EIACs) were compared statistically using unpaired, 2-sided t tests.

Results

Subject Disposition:
A total of 9 patients were enrolled in the study. The following table shows the number of patients per stratum and reasons for discontinuation of treatment.

Patients excluded from analysis:
Patient 705024, who was taking carbamazepine, was assigned in error to the "other anticonvulsant" cohort and received a starting dose of 50 mg/m^2.

Table S-VIII: Subject disposition, by stratum.

	EIAC			VAL		Other AC		
	100 mg/m^2	**130 mg/m^2**	**All Dose Levels**	**30 mg/m^2**	**All Dose Levels**	**50 mg/m^2**	**All Dose Levels**	**All Strata**
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
Abbreviations: AC= Anticonvulsant, EIAC= Enzyme-inducing AC, PD= Progressive disease, VAL= Valproic acid								

The following table shows the demographics and baseline characteristics of the patients.

Table S-IX: Subject demographics.

		EIAC			VAL		Other ACs		
		100 mg/m^2	**130 mg/m^2**	**All Dose Levels**	**30 mg/m^2**	**All Dose Levels**	**50 mg/m^2**	**All Dose Levels**	**All Strata**
	N %	4	2	6	1	1	2	2	9
Age Group	**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
Gender	**Male**	3 75.0	2 100.0	5 83.3	1 100.0	1 100.0	1 50.0	1 50.0	7 77.8
	Female	1 25.0	-	1 16.7	-	-	1 50.0	1 50.0	2 22.2
Ethnic Origin	**White**	2 50.0	2 100.0	4 66.7	1 100.0	1 100.0	-	-	5 55.6
	Black	2 50.0	-	2 33.3	-	-	1 50.0	1 50.0	3 33.3
	Other	-	-	-	-	-	1 50.0	1 50.0	1 11.1
ECOG PS	**0**	2 50.0	-	2 33.3			2 100.0	2 100.0	4 44.4
	1	2 50.0	1 50.0	3 50.0	-	-	-	-	3 33.3
	2	-	1 50.0	1 16.7	1 100.0	1 100.0			2 22.2

Safety evaluation:
Using the DLT definitions in the protocol or by the FDA, the MTD has not been established for any of the strata. Additional patients are needed in all strata to define the DLTs and MTDs for patients receiving ACs concurrently with irinotecan. However, this trial was closed by COG in October 2002 due to slow accrual.

The overall safety profile was similar to that observed with irinotecan treatment in adults and most adverse experiences were predictable and manageable. Seven of 9 patients had AES : The most common AEs were gastrointestinal disorders diarrhea (6 patients) and vomiting (3 patients). Grade 3 toxicities were observed in one third of the patients, there were no reported grade 4 or grade 5 AEs. The only grade 3 hematological toxicity was reported for patient 700986 who experienced Cycle 1 grade 3 neutropenia and febrile neutropenia. However, this patient received at least 14 additional cycles of treatment at a lower dosage.

Pharmacokinetics:

PK parameters for irinotecan and 3 metabolites are summarized in Table S-X below. To facilitate comparison, systemic exposure parameters such as AUC and Cmax have been normalized to a 100 mg/m 2 dose. In addition, since there were only 2 patients receiving non-enzyme inducing anticonvulsants in P9871, data from the concurrent COG protocol P9761, in which no children were taking anticonvulsants, have been included. The degree of interpatient variability in the P9871 trial (EIAC and non-EIAC groups) is considerable but appears to be comparable to that observed in other pediatric trials and in the adult population.

Comparison of PK parameters for the P9871 EIAC group with the P9761 no-AC cohort (Table S-X) clearly shows that concomitant treatment with EIACs had a major impact on the SN-38 exposure. Dose-adjusted mean SN-38 AUC0-t(last) in EIAC patients was ~70% lower compared to that in no AC patients. Similarly, dose-adjusted mean SN-38 Cmax in EIAC patients was 67% lower than that in no-AC patients. SN-38 exposure in the 2 non-EIAC patients in this study was intermediate with considerable variability.

Mean irinotecan AUC0-t(last) in the EIAC group was 30% lower than that in the no-AC group. While statistically significant (p=0.04), the magnitude of the EIAC effect on irinotecan was less than on SN-38 (Table S-X). While mean APC AUC0-t(last) values differed substantially, the interpatient variability was so great that the difference was not statistically significant.

Substantial differences were also noted in the REC (SN-38/irinotecan AUC0-t(last)) and REO (APC/irinotecan AUC0-t(last)) ratios (Figure 4). The REC ratio is significantly higher in the no-AC patients compared to that in the EIAC patients. However, the REO ratio is significantly lower in the no-AC group. These findings are consistent with the fact that the concomitant treatment with EIACs results in the induction of irinotecan oxidative metabolism to APC and therefore directly increases the APC exposure and decreases irinotecan exposure to some extent. The latter also results in the decrease in the SN-38 exposure. In contrast, no significant difference in REG (SN-38G/SN-38 AUC0-t(last)) ratio was observed suggesting that EIAC treatment does not effect formation of SN-38G from SN-38.
It is important to note that enzyme-inducing agents like the anticonvulsants are known to induce multiple drug metabolizing enzymes as well as drug transport proteins, making it very difficult to assign a specific mechanism to EIAC effects on a drug that has such a complex disposition as irinotecan.

Table S-X: Comparison of irinotecan and metabolite PK parameters from studies P9761 (no AC) and P9871 (patients on AC) [Systemic exposure parameters (Cmax and AUC) normalized to 100 mg/m^2 dose]

PK Parameters	P9761 (mean±SD; N=13) No ACs	P9871 Non-EIACs (range; N=2)	P9871 EIACs (mean±SD; N=5)	P9871 EIAC vs P9761 No AC p-value[c]
Irinotecan				
tmax[a] (h)	1.06±0.053	1.00-1.07	1.03±0.075	NS
Cmax (ng/mL)	1255±305	803-1198	1264±902	NS
$AUC_{0\text{-}t(last)}$ (ng·h/mL)	3596±1464	2434-3412	2520±560	0.040
SN-38				
tmax (h)	1.12±0.13	1.42-1.67	1.10±0.109	NS
Cmax (ng/mL)	30.0±10.2	25.8-76.3	9.99±1.59	0.0006
$AUC_{0\text{-}t(last)}$ (ng·h/mL)	106.6±42.6	99.0-138	32.9±9.72	0.0001
SN-38G				
tmax (h)	1.63±0.511	1.42-2.00	1.23±0.18	NS
Cmax (ng/mL)	72.6±34.9	29.1-79.2	54.2±36.1	NS
$AUC_{0\text{-}t(last)}$ (ng·h/mL)	354±220	141-376	234±244	NS
APC				
tmax (h)	2.06±0.588	1.57-2.00	1.93±0.78	NS
Cmax (ng/mL)	86.4±31.9	55.3-318	272±261	0.0178
$AUC_{0\text{-}t(last)}$ (ng·h/mL)	506±208	341-1954	1516±1638	NS
$AUC_{0\text{-}t(last)}$ Ratios[b]				
SN-38/irinotecan	0.031±0.011	0.041-0.041	0.013±0.005 (5)	0.0003
SN-38G/SN-38	3.64±2.18	1.42-2.70	6.83±5.85 (5)	NS
APC/irinotecan	0.155±0.071	0.140-0.573	0.556±0.487 (5)	0.0079

[a] tmax values for irinotecan and all metabolites are relative to the start of the infusion.
[b] Ratio of metabolite $AUC_{0\text{-}t(last)}$ to irinotecan $AUC_{0\text{-}t(last)}$. Also known as relative extent of conversion (SN-38/irinotecan; REC); relative extent of glucuronidation (SN-38G/SN-38; REG); and relative extent of oxidation (APC/irinotecan; REO).
[c] p-value from unpaired, 2-sided t-test (with Welch's correction for significantly different variances) of P9871 EIAC data versus P9761 no-AC data; NS=not significant.
Abbreviations: AC= Anticonvulsant, EIAC= Enzyme-inducing AC

Figure S2: Mean dose-normalized plasma concentration-time profiles of irinotecan and SN38 for patients in studies P9871 and P9761.

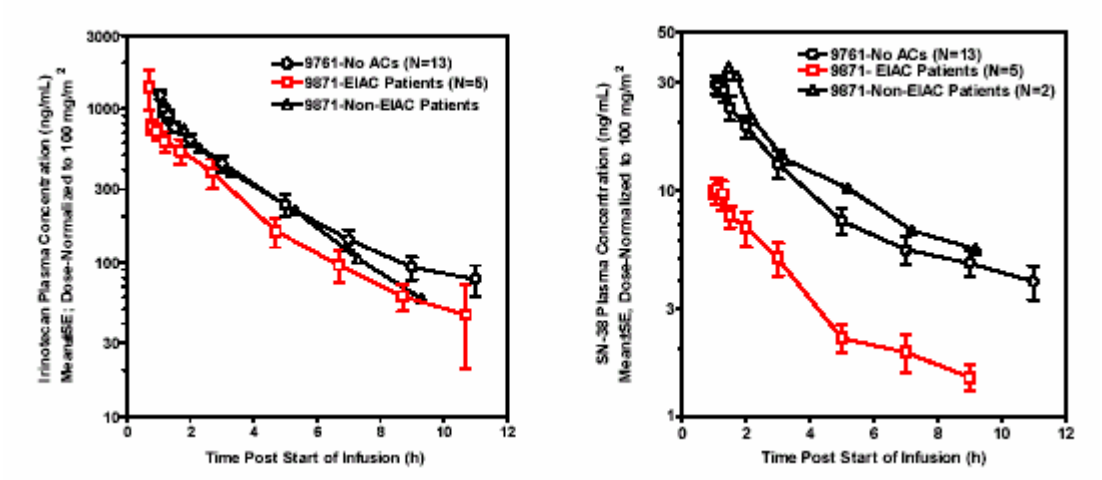
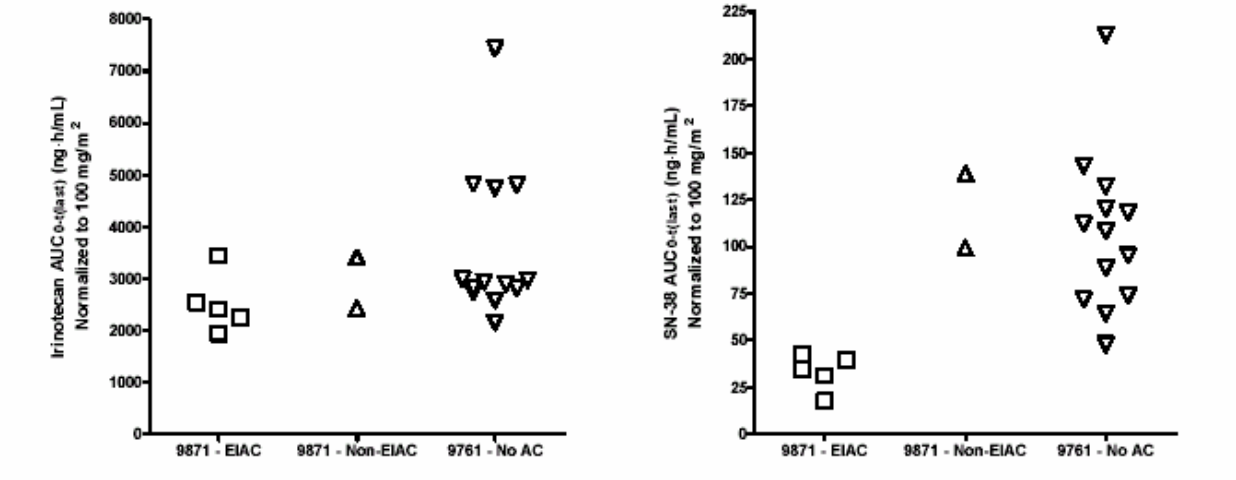


Figure S3: Scatter plots of irinotecan (left) and SN38 (right) AUC(0-tlast) in the P9871 EIAC stratum, P9871 non-EIAC stratum and P9761 no-AC comparison group.



Efficacy results:

The best overall tumor response was determined by the Applicant by selecting the best category from those observed by the investigator for each patient. One (11.1%) patient (706662) experienced a partial response (PR) and this patient received >20 cycles of irinotecan. One patient (700986) with SD received ε15 cycles of treatment and the other 3 SD patients received 2 cycles each. Four other patients had PD as their best response.

Conclusions:

- Using either the protocol definition of DLT or the FDA's preferred definition, the MTD was not reached for any of the 3 strata in this study.

- The overall safety profile was similar to that observed with irinotecan treatment in adults. Across all cycles of therapy, the most common nonhematologic AE was diarrhea. There was no apparent difference in toxicity between the different group categories.

- Concomitant treatment with EIACs had a major impact on SN-38 exposure. Dose-adjusted mean SN-38 $AUC_{0\text{-}t(last)}$ and Cmax values in EIAC patients were significantly lower than in no-AC patients. Results suggest that EIACs induce the oxidative metabolism pathway at the expense of the carboxylesterase-mediated hydrolysis reaction leading to SN-38.

- The PK findings of this trial are consistent with the results of another study in 10 glioma patients on EIACs and 21 no-AC glioma patients (Crews et al., 2002). There was a highly significant reduction in SN-38 AUC0-7 of both lactone and total species in addition to significant reduction in irinotecan lactone AUC0-7 but not total AUC0-7. EIACs had no apparent effect on SN-38G or APC total or lactone exposure.

- The results of the current and other studies suggest that non-EIACs should be considered in pediatric glioblastoma patients who require ACs and who are candidates for an irinotecan-containing regimen.

Study #:	**P9571**
Title:	A trial of irinotecan in children with solid tumors: A Pediatric Oncology Group (POG) Phase 1 Cooperative Agreement Study
Protocol Number:	POG #9571; Pharmacia # M/6475/056
Principal Investigator:	Susan Blaney, M.D. Texas Children's Cancer Center Houston, TX 77030
Study Centers:	19 participating centers in the US and Canada Coordinating Center: Texas Children's Cancer Center (TCCC) 6621 Fannin street, MC 3-3320 Houston, TX 77030

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 conducted by the Pediatric Oncology Group (POG) in 19 cancer centers in the US and Canada.
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 perprotocol 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 Statum 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.

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.

Drug Administration:
The test product was a commercial supply of CAMPTOSAR Injection. Irinotecan was administered as a 60 min IV infusion. The appropriate volume of 20 mg/mL solution was mixed with 5% dextrose to a final concentration of 0.12 mg/mL to 1.1 mg/mL irinotecan.
Starting dose levels for each stratum is shown in the following table.

Table S-XI: Starting dose levels by stratum

Level	Starting Dose $mg/m^2/day$
1	30
2	39
3	50
4	65
Subsequent Escalations	30% increments

Safety Evaluations and Procedures:
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.

Please see following table for schedule of study evaluations and PK assessments.

Efficacy was assessed using standard, bidimensional, solid tumor response criteria.
Concomitant medications included atropine for early-onset diarrhea, loperamide for treatment of late-onset diarrhea, antiemetics including dexamethasone, ondansetron, and growth factors at the discretion of the individual investigator (but not during cycle 1). Medications that could interfere with CYP P450 metabolism (inhibitors, inducers, substrates) were avoided.

Table S-XII: Study evaluations and PK assessments

Evaluation	Pre-Study	On Study	Off Study
Med/Onc History	X		
Physical examination, PS, symptoms	X	Weekly	X
Tumor evaluation	X	Q 3 weeks[a]	X
CBC, diff platelets	X	2 x weekly[b]	X
Urinalysis	X	Q 3 weeks[a]	X
Electrolytes (Ca^{+2}, PO_4, Mg^{+2}	X	Q 3 weeks[a]	X
Creatinine, SGPT, Bili	X	Weekly[c]	X
Total protein/albumin	X	Q 3 weeks[a]	X
Chest X-Ray	X	As indicated	
Bone marrow aspirate if needed	X	At Wk 3, Wk 6, then every 2 cycles and PRN	X
Additional studies as needed	X	At Wk 3, Wk 6, then every 2 cycles and PRN	X

[a] Prior to each cycle for first 2 cycles, Q 6-9 wk as required thereafter.
[b] Could decrease to weekly for the 3rd & subsequent cycles if no dose-limiting myelosupression in the first 2 cycles.
[c] After first 2 cycles, prior to each course, unless abnormal.
Abbreviations: CBC= Complete blood count, SGPT= (ALT) Alanine transferase, PS= Performance status

Pharmacokinetics (PK):
Enrolled patients who consented to the PK correlative study had blood draws performed on Day 1 of Cycle 1. In addition, patients > 20 kg underwent PK sampling on day 4 of cycle 1 as well. Blood samples (3-5 mL) were collected in heparinized, green-top tubes from a vein contralateral from the infusion site. Samples were centrifuged immediately and the decanted plasma was immediately stored at -20 ^{o}C. Blood draw times were: prior to the irinotecan infusion, at the end of the 60 min infusion, and at 5, 15, and 30 min and 1, 2, 4, 6, 8, and between 10 to 12 h following the completion of the infusion.

Analytical Methods:
Plasma samples were assayed for total (lactone + carboxylate species) concentrations of irinotecan, SN-38, APC, and SN-38G using validated, sensitive, specific, isocratic, high-performance, liquid chromatographic methods with fluorescence detection (HPLC-FL). Assays were carried out by Clinical Pharmacology, Pfizer.

Data Analysis:
Irinotecan, SN-38, SN-38G, and APC plasma-concentration data were analyzed by noncompartmental methods using Kinetica 2000, version 3.1 (InnaPhase Corp). Cmax,Tmax, lambda, t1/2, AUC(0-last), AUC(inf), CL and Vz were measured or estimated. Metabolic ratio, defined as the ratio of SN-38 AUC0-inf to irinotecan AUC0-inf, was used as a measure of the

relative extent of conversion of irinotecan to SN-38. The relative extent of SN-38 metabolism to SN-38G was defined as the ratio of SN-38G AUC0-inf to SN-38 AUC0-inf. The relative extent of conversion to APC was defined as the ratio of APC AUC0-inf to irinotecan AUC0-inf.

Results

Subject Disposition:
A total of 33 patients were enrolled in the study. The following tables show the number of patients per stratum, and demographic and baseline characteristics of the patients.

Table S-XIII: Number of patients by stratum and starting dose level.

Starting Dose Level (mg/m^2/week)	Heavily Pretreated	Less Heavily Pretreated	<6 Years	Total Patients
30 mg/m^2	5	-	-	5
39 mg/m^2	4	-	4	8
50 mg/m^2	5	6	3	14
65 mg/m^2	-	6	-	6
Total	**14**	**12**	**7**	**33**

Table S-XIV: Patient demographics and baseline characteristics

Characteristics	Categories	Stratum 1	Stratum 2	Stratum 3	All	(%)
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)
Gender	Male	11 (78.6)	9 (75.0)	3 (42.9)	23	(69.7)
	Female	3 (21.4)	3 (25.0)	4 (57.1)	10	(30.3)
Ethnic Origin	White	11 (78.6)	7 (58.3)	5 (71.4)	23	(69.70)
	African American	2 (14.3)	2 (16.7)	2 (28.6)	6	(18.2)
	Other	1 (20.0)	3 (25.0)	-	4	(12.1)
ECOG PS	ECOG 0	3 (21.4)	1 (8.3)	2 (28.6)	6	(18.2)
	ECOG 1	-	2 (16.7)	1 (14.3)	3	(9.1)
	ECOG 2	3(21.4)	2. (16.7))	1 (14.3)	6	(18.2)
	No data	8 (57.1)	7 (58.3)	3 (42.9)	18	(54.5)
Prior ChemoTxt	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)

The most frequent initial primary diagnosis was brain tumors (45.5%), followed by soft tissue (15.2%) and bone tumors (15.2%). More than half of the patients (54.5%) had metastasis at baseline and bone was the most frequent metastatic site (21.2%) followed by lymph nodes

(18.2%). Most of the patients (66.7%) received a previous treatment including the combination of surgery, radiotherapy and chemotherapy. Most of the patients (78.8%) had received >2 previous regimens of chemotherapy.

Safety evaluation:
For patients in stratum 1, DLT of grade 4 neutropenia were seen in 2/5 patients at the 50 mg/m^2 dose. The MTD was established at 39 mg/m^2 for the heavily pretreated group. However, per the protocol, additional patients should have been evaluated at the 39 mg/m^2 dose before declaring it as the MTD.
In the less heavily pretreated stratum, DLTs were observed in 3/6 patients at 65 mg/m^2 (2 patients with grade 4 neutropenia and 1 patient with grade 4 thrombocytopenia). The MTD was established at 50 mg/m^2 for the heavily pretreated group.
In the patients <6 years, 1 DLT was seen at the 39 mg/m^2 dose. At the 50 mg/m^2 dose, one patient showed multiple severe DLTs (grade 4 thrombocytopenia, grade 4 infection and grade 4 erythema), and another showed grade 3 diarrhea. The MTD was established at 39 mg/m^2 in this group.

The overall safety profile was similar to that observed with irinotecan treatment in adults and most adverse experiences were predictable and manageable. A total of 13 (of 33) 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.

Pharmacokinetics:
Plasma concentration vs. time profiles for irinotecan and its metabolites SN38, SN38G and APC, following doses of 39 and 50 mg/m^2, are shown in the following figure. Maximum plasma concentrations (Cmax) were observed at the end of the infusion for irinotecan and within 2 h after the end of infusion for the 3 metabolites. Thereafter, concentrations of irinotecan and its metabolites declined in a biphasic manner and were still quantifiable at the last time point (between 11 and 13 h after the start of infusion). The apparent upturn in the mean plasma concentrations of irinotecan and metabolites at 12 h in the 50 mg/m^2 dose group may be due to missing 12-h samples in several patients.

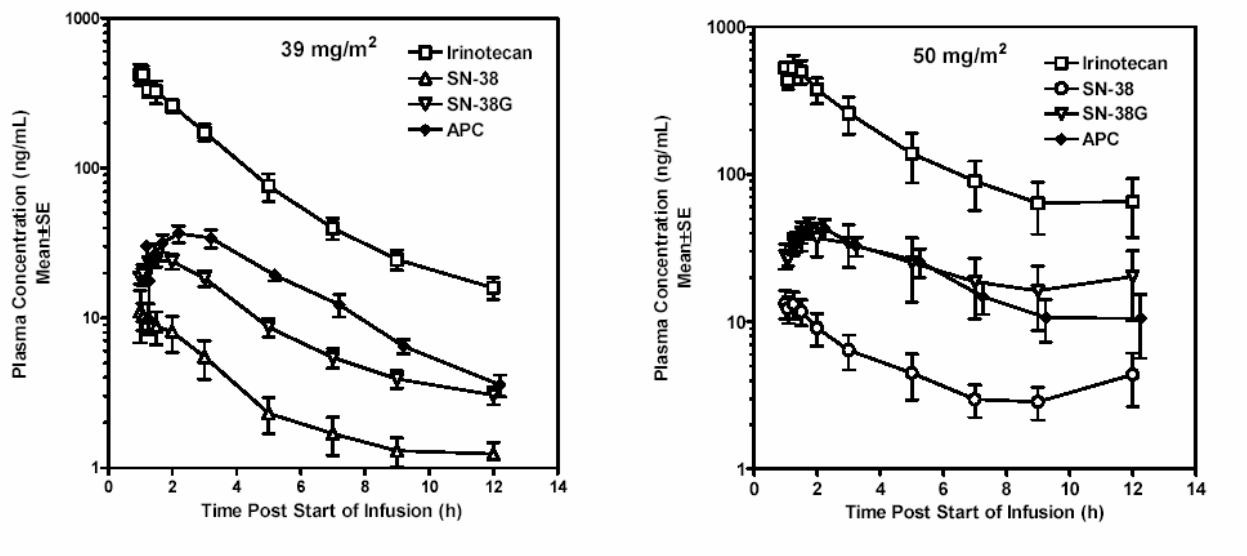
PK parameters for irinotecan and 3 metabolites are summarized in the table below.
Mean systemic exposure of patients to irinotecan and its metabolites (as reflected in AUC and Cmax) increased with dose. There was considerable inter- and intra-dose group variability associated with the PK parameters, especially for SN-38 and SN-38G. PK was comparable in children enrolled in the different protocol strata.

Table S-XV: PK parameters for irinotecan and metabolites.

Dose, mg/m^2	**30**		**39**		**50**		**65**	
Day	1	4	1	4	1	4	1	4
N[b]	2	2	8	4	10	7	5	5
Irinotecan								
t_{max} (h)[c]	1.08-1.08	1.17-1.25	1.11±0.115 (7)	1.11±0.066	1.24±0.341	1.17±0.17	1.06±0.083	1.05±0.072
C_{max} (ng/mL)	258-340	216-329	457±148 (7)	491±250	663±276	532±125	722±188	775±191
$AUC_{0\text{-}t(last)}$ (ng·h/mL)	869-1126	796-1047	1177±298 (7)	1121±259	2108±1535	1964±1169	2174±908	2119±771
SN-38								
t_{max} (h)	1.08-1.55	1.50-2.25	1.15±0.143*	1.48±0.052*	1.14±0.161	1.59±0.762	1.36±0.402	1.17±0.215
C_{max} (ng/mL)	10.8-30.3	9.13-21.0	10.6±6.29	5.50±2.47	13.4±7.72	9.50±3.40	14.2±6.15	10.4±2.61
$AUC_{0\text{-}t(last)}$ (ng·h/mL)	29.0-110	37.4-121	35.2±26.5	22.5±6.72	55.5±45.5	44.6±20.3	57.1±30.3	40.0±12.5
SN-38G								
t_{max} (h)	1.58-1.93	2.08-2.25	1.65±0.447 (7)	1.73±0.337	2.09±0.984 (8)	2.25±0.953 (5)	1.81±0.727	1.71±0.346
C_{max} (ng/mL)	15.6-28.4	12.8-24.6	27.0±6.26 (7)	23.1±9.15	44.3±24.1 (8)	34.2±21.2 (5)	38.0±16.9	44.0±48.6
$AUC_{0\text{-}t(last)}$ (ng·h/mL)	58.7-125	79.9-127	108±30.0 (7)	105±39.8	287±286 (8)	244±273 (5)	177±59	224±263
APC								
t_{max} (h)	ND[d]	ND	1.94±0.315 (3)	2.08 (1)	2.33±1.23 (5)	1.22-2.08 (2)	1.86±0.698	1.76±0.274
C_{max} (ng/mL)	ND	ND	36.5±8.25 (3)	14.7 (1)	46.3±13.1 (5)	24.1-29.3 (2)	109±102	138±190
$AUC_{0\text{-}t(last)}$ (ng·h/mL)	ND	ND	180±61.0 (3)	108 (1)	256±111 (5)	133-137 (2)	619±532	796±1106
$AUC_{0\text{-}t(last)}$ Ratios[e]								
SN-38/irinotecan	0.033-0.097	0.047-0.115	0.034±0.023 (7)	0.020±0.004	0.026±0.012	0.025±0.012	0.025±0.003	0.019±0.005
SN-38G/SN-38	0.53-4.30	0.66-3.40	4.05±2.58 (7)	4.62±0.860	5.55±3.19 (8)	5.11±3.85 (5)	3.76±1.87	5.34±4.87
APC/irinotecan	ND	ND	0.138±0.050 (7)	0.100 (1)	0.181±0.090 (5)	0.113-0.137 (2)	0.273±0.180	0.309±0.308

[a] Mean±SD unless N=2, in which case values given are the range.
[b] N is given in parentheses if different from the values in this row.
[c] Time relative to the start of the infusion.
[d] PK specimens were not assayed for APC.
[e] Relative extent of conversion (SN-38/irinotecan; REC); relative extent of glucuronidation (SN-38G/SN-38; REG); and relative extent of oxidation (APC/irinotecan; REO).
* p=0.0012; 2-sided, unpaired t-test.

Figure S4: Mean concentration-time profiles for irinotecan and metabolites. SN38, SN38G and APC following the 39 mg/m^2 (left panel) and 50 mg/m^2 (right panel). The apparent up-turn in concentrations at 12 hrs after the 50 mg/m^2 dose may be due to missing data at that time point.



Irinotecan and SN-38 accumulation was minimal based on comparisons of Day 1 and Day 4 exposures. Comparison of irinotecan and SN38 mean AUC0-t(last) values on Day 1 versus Day 4 showed no significant differences (figures S5 and S6). In addition pairwise comparisons did not reveal differences between Day 1 and Day 4 PK parameters with the exception of SN-38 Cmax, which was 35% *lower* on Day 4 than on Day 1 in patients with data on both days (p=0.002, paired t-test). The apparent change in Cmax may not be clinically significant since overall systemic exposure (AUC) was not different between Days 1 and 4. Graphs of Day 1 vs. Day 4 irinotecan and SN-38 Cmax and AUC0-t(last) values illustrate the intra-patient variability in these parameters.

Figure S5: Individual day 1 and day 4 irinotecan Cmax (left panel) and AUC (right panel).

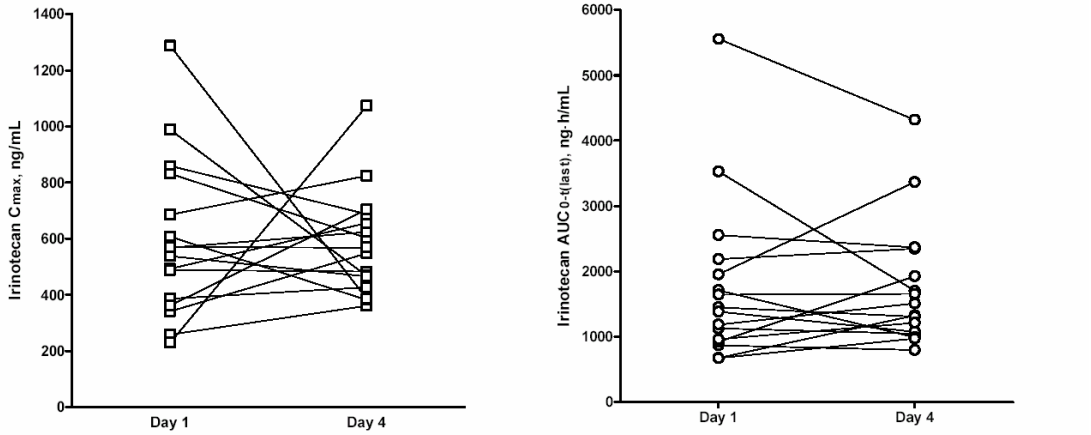
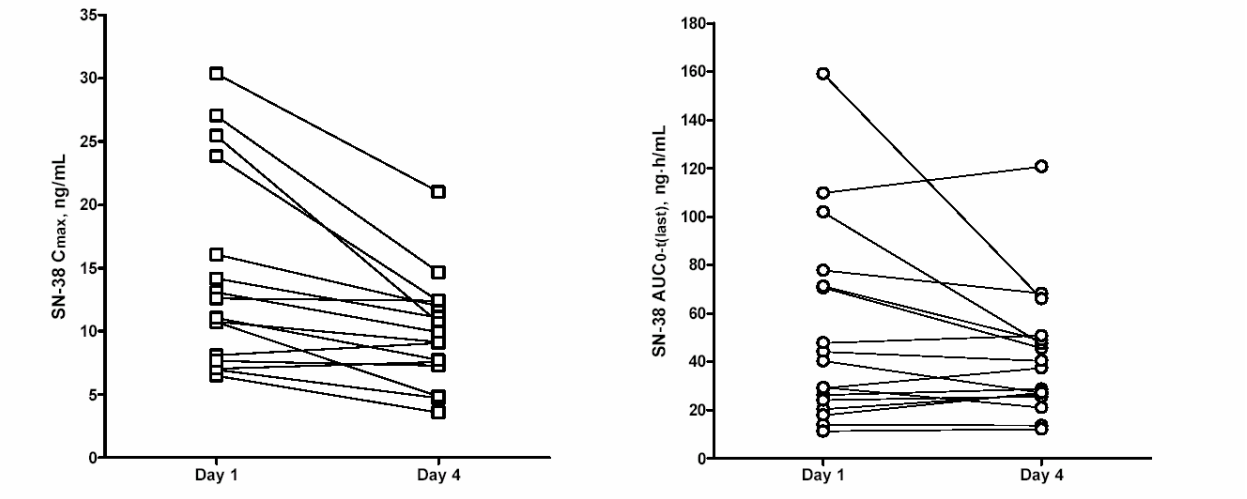


Figure S6: Individual day 1 and day 4 SN38 Cmax (left panel) and AUC (right panel).



There is a trend toward dose-proportional increases in AUC with dose. However there was substantial overlap of the 4 dose groups for both $AUC_{0\text{-}t(last)}$ and Cmax, especially for the active metabolite SN-38. The weak association between dose and systemic exposure may be due to the narrow dose range tested, the small size of the population, and the considerable interpatient PK variability. No formal statistical analysis of dose-proportionality was attempted.
There was no indication that irinotecan or SN38 PK varied among the different strata.

Efficacy results:
Four partial responses and 6 children with stable disease were observed in patients in Stratum 1 and 2. No child in Stratum 3 responded. One patient was not evaluable for response. 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.

Conclusions:

- The MTD was established by POG for heavily pretreated patients (Stratum 1) at 39 mg/m^2 daily for 5 days every 3 weeks. For less heavily pretreated patients (Stratum 2), the MTD was established by POG at 50 mg/m^2 daily for 5 days every 3 weeks. For children <6 years old, the MTD was established by POG at 39 mg/m^2 daily for 5 days every 3 weeks and myelosuppression was the main DLT.

- The overall safety profile was similar to that observed with irinotecan treatment in adults. The most common grade 3-4 nonhematologic AEs were gastrointestinal (30.3%): grade 3-4 diarrhea 15.2%, and grades 3-4 vomiting 3%, followed by infection (9.1%). Clinically important hematological toxicities were grade 3 (10.3%) and grade 4 (37.9%) neutropenia, grade 3 (12.1%) anemia, and grade 3 (15.2%) and grade 4 (3.0%) thrombocytopenia.

- Mean systemic exposure of patients to irinotecan and its metabolites (as reflected in AUC and Cmax) appeared to increase with dose, although there was considerable overlap between

the groups. There was substantial inter- and intra-dose group variability associated with the PK parameters, especially for SN-38 and SN-38G. PK was comparable in children enrolled in the different protocol strata. Irinotecan and SN-38 exposures determined on Day 1 and Day 4 of Cycle 1 were comparable, indicating minimal drug accumulation.

- The antitumor activity that was observed in this study was encouraging. Four objective partial tumor responses were seen, and stable disease was observed in 6 patients.

- The results of this phase I study suggest that single-agent irinotecan is well-tolerated in children with refractory cancer. The safety profile of irinotecan given daily for 5 days every 3 weeks was as expected and was consistent with that reported in adults. Although the data are limited, the schedule of administration was generally tolerable over multiple cycles and was associated with encouraging signs of disease control in some children with treatment-resistant solid tumors. Thus, phase II studies of irinotecan (alone or in combination with other anticancer agents) are warranted in children with refractory solid tumors and including CNS tumors.

Study #:	**ST JUDE: PNU-101440E**
Title:	A phase I study of irinotecan in pediatric patients with refractory solid tumors.
Protocol Number:	Pharmacia # CPTAIV-0020-453
Principal Investigator:	Wayne L. Furman, MD and Charles Pratt, MD Department of Hematology-Oncology St Jude Children's Research Hospital, Memphis, TN
Study Centers:	St Jude Children's Research Hospital 332 North Lauderdale Memphis, TN 38105

Objectives:

- To determine the maximum tolerated dose (MTD) of irinotecan when given intravenously (IV) daily x 5 for 2 consecutive weeks (Cycle Days 1-5 and 8-12 of a 21-day cycle).
- To determine the dose-limiting toxicities (DLTs) of irinotecan, including qualitative and quantitative toxicities, and to define their duration and reversibility.
- To characterize the pharmacokinetics (PK) of irinotecan in children with drug-resistant malignant solid tumors and evaluate the relationship between PK parameters and toxicity and/or response.
- To determine the dosage of irinotecan that may be used in subsequent phase II trials.

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 tumors unresponsive to conventional therapy. Sequential cohorts of 3 patients were enrolled to receive progressively higher starting dose levels of irinotecan as a 60 minute IV infusion on days 1-5 and 8-12 of each 3-week cycle. If 1 of 3 patients at a dose level developed DLT, 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 1. Throughout treatment, patients were evaluated for clinical and laboratory adverse events. Blood samples for PK 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. Patients were treated until progression of disease, unacceptable toxicity, or a decision by the physician or patient to discontinue therapy.

Drug Administration:

The test product was commercial CAMPTOSAR for injection. Irinotecan was administered as a 60 min IV infusion daily x5 for 2 weeks of a 3-week cycle.
Successive cohorts of 3 or more patients were to be enrolled to progressively higher doses of irinotecan 20, 24, 29 and 35 mg/m^2. If MTD was exceeded at the first dose level, subsequent patients could be enrolled at 16 mg/m^2. A DLT was defined as the occurrence of grade 4 non-hematological or grade 3 or 4 non-hematological toxicity.

Safety Evaluations and Procedures:

Toxicities were graded by the investigators according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), Version 1. Throughout treatment, patients were evaluated for clinical and laboratory adverse events.
Please see following table for schedule of study evaluations and PK assessments.

Efficacy was assessed using standard, bidimensional, solid tumor response criteria.
Concomitant medications included atropine for early-onset diarrhea, loperamide for treatment of late-onset diarrhea, antiemetics including dexamethasone, ondansetron, and growth factors at the discretion of the individual investigator (but not during cycle 1). Medications that could interfere with CYP P450 metabolism (inhibitors, inducers, substrates) were avoided.

Table S-XVI: Schedule of evaluations.

Evaluation	Prestudy	Weekly	Twice Weekly	Every 3-4 Weeks and End of Study
Medical History	X			
Physical Examination	X			
CBC, Differential, Platelets	X		X	
Clinical Labs	X			X
BUN, Creatinine, SGOT, Alk Phos		X[a]		
Urinalysis	X			X
Stool Sample[b]	X			
Tumor Evaluation	X			X
PK Sample Collection[c]				

[a] Subset of clinical labs
[b] Patients with diarrhea only, obtained for potassium, sodium, and osmolality
[c] After the first and tenth dose of Cycle 1 only
Abbreviations: CBC = complete blood count; BUN = blood urea nitrogen; SGOT = (AST) aspartate aminotransaminase; Alk Phos = alkaline phosphatase; PK = pharmacokinetic

Pharmacokinetics (PK):
Enrolled patients who consented to the PK correlative study had blood draws performed on Day 1 and day 10 of Cycle 1. Blood samples (3 mL) were collected in heparinized tubes from a vein contralateral from the infusion site. Blood draw times were: prior to the irinotecan infusion, at the end of the 60 min infusion, and at 0.25, 0.5, 1, 2, 4 and 6 h following the completion of the infusion. Samples were centrifuged immediately following collection. Plasma was separated and proteins were precicipitated by addition of 0.2 ml sample to 0.8 ml cold methanol (-30^{o}C) followed by vigrous agitation and repeat centrifugation. The supernatent was decanted and immediately stored at –20^{o} C until analysis.

Analytical Methods:

Plasma samples were assayed specifically for the lactone forms of irinotecan, SN-38 and APC using a previously described (Rivory, 1994) validated, sensitive, specific high-performance liquid chromatographic method with fluorescence detection (HPLC-FL). Assays were carried out (b) (4)

Data Analysis:
Irinotecan, SN-38, SN-38G, and APC plasma-concentration data were analyzed by noncompartmental methods using Kinetica 2000, version 3.1 (InnaPhase Corp). Cmax, Tmax and AUC(0-last) were measured or estimated. Metabolic ratio, defined as the ratio of SN-38 AUC0-last to irinotecan AUC0-last, was used as a measure of the relative extent of conversion of irinotecan to SN-38. Other PK parameters (CL, Vz, t1/2) were not estimated due to the short duration of sampling.

Results:

Subject Disposition:
A total of 26 patients were enrolled in the study, however data is available for 22 patients (1 patient did not receive irinotecan, 1 dropped out after she was discovered to be pregnant, and 2 did not have parental re-consent). The following tables show the number of patients per stratum, and demographic and baseline characteristics of the patients.

Table SXVII: Number of patients enrolled by starting dose level. Total patients includes number of patients with PK data.

Starting Dose Level (mg/m^2)	Total Patients
20	8/9
24	11/12 [b]
29	2/2
Total	21/23

[a]This report does not include plasma concentration-time data or PK parameters for 2 patients treated with 24 mg/m^2 whose families did not consent to provision of their child's results to the Sponsor.
[b]This report includes PK data, but not clinical data, from patient #13426 (24 mg/m^2 group) who was withdrawn from the trial after Day 3 of Cycle 1 due to pregnancy.

Table S-XVIII: Patient demographics and baseline characteristics.

Characteristics	Categories	Dose Level (mg/m^2)			Total	
		20	24	29	N	(%)
Age	1 month - <2 years	-	1	-	1	(4.5)
	2 - <12 years	3	4	2	9	(40.9)
	12 - <16 years	4	3	-	7	(31.8)
	≥16 years	2	3	-	5	(22.7)
Gender	Male	5	6	2	13	(59.1)
	Female	4	5	-	9	(40.9)
Ethnic Origin	White	7	6	2	15	(68.2)
	African American	1	4	-	5	(22.7)
	Other	1	1	-	2	(9.1)
ECOG PS	ECOG 0	4	4	1	9	(40.9)
	ECOG 1	3	5	-	8	(36.4)
	ECOG 2	1	-	-	1	(4.5)
Tumor Type	Carcinoma of larynx	-	1	-	1	(4.5)
	Anaplastic astrocytoma	-	1	-	1	(4.5)
	Astrocytoma	-	1	-	1	(4.5)
	Medulloblastoma	-	1	-	1	(4.5)
	Neuroblastoma	2	1	2	5	(22.7)
	Oligodendroglioma	-	1	-	1	(4.5)
	PNET	1	1	-	2	(9.1)
	Rhabdomyosarcoma	1	2	-	3	(13.6)
	Osteosarcoma	4	1	-	5	(22.7)
	PNET	-	1	-	1	(4.5)
	Hepatoblastoma	1	-	-	1	(4.5)
Primary Sites	Abdominal	-	1	-	1	(4.5)
	Adrenal gland	2	-	2	4	(18.2)
	Bone	4	2	-	6	(27.3)
	Brain	-	6	-	6	(27.3)
	Gonad	1	-	-	1	(4.5)
	Head and neck	-	1	-	1	(4.5)
	Liver	1	-	-	1	(4.5)
	Pelvis	1	1	-	2	(9.1)
Prior ChemoTxt	0 regimen	3	1	-	4	(18.2)
	1 regimen	1	3	-	4	(18.2)
	≥2 regimen	5	7	2	14	(63.6)
Prior Therapy	ChemoTxt only	1	3	-	4	(18.2)
	ChemoTxt + Surgery	4	3	-	7	(31.8)
	ChemoTxt + XRT	-	2	-	2	(9.1)
	ChemoTxt + XRT + Surgery	4	3	2	9	(40.9)

Source Appendix 2.2, Tables 2.1, 2.2, 2.3, 2.4, 2.5

Abbreviations: PNET= Primitive neuroectodermal tumor, Chemo TxT= Chemotherapy, XRT= Radiation

Safety evaluation:
The original protocol included a separate stratum for patients who had received prior craniospinal or pelvic (> 50Gy to >50% of the pelvis) due to possible hematologic toxicity. However, after a number of patients had been enrolled and assessed, it was noted that the myelosuppression was no different in these patients than in patients with little or no prior irradiation. Therefore the protocol was amended and the stratification was removed.

A total of nine patients were enrolled at the starting dose level of 20 mg/m^2, of which 5 experienced a DLT (1 patient with febrile neutropenia + grade 3 hypotension, 1 with grade 3 vomiting, 2 with grade 3 diarrhea, 1 with grade 4 diarrhea + grade 3 nausea and vomiting). Eleven patients were treated at the 24 mg/m^2 dose level, of which 6 patients 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 non-hematological 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 in 2 patients, however both showed grade 4 toxicites (diarrhea and neutropenia).

Due to the number of patients showing DLTs at 24 mg/m^2, the MTD was set at 20 mg/m^2. If the data from the prior stratification are combined, it appears that both 20 and 24 mg/m^2 dose showed similar rates of DLTs. The applicant concluded that the lower dose of 20 mg/m^2 daily x5, for 2 weeks of a 3-week schedule would be then appropriate dose for further phase 2 studies.

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.

Pharmacokinetics:
The following figure shows the mean concentration-time profile for patients at the 24 mg/m^2 dose level. Cmax was observed at the end of the infusion and shortly thereafter for SN38. Post-infusion, concentrations declined in a multi-exponential manner.

Table S-XIX lists the descriptive PK parameters of irinotecan lactone and SN-38 lactone at the three irinotecan dose levels on Days 1 and 10 of Cycle 1. For all dose levels, there is a substantial
interpatient variability in Cmax and AUC0-t(last) for irinotecan and SN-38 lactones. Mean Cmax and AUC0-t(last) for both irinotecan and SN-38 lactones were lower on Day 10 compared to those on Day 1; however there was a significant overlap between Day 1 and Day 10. The evaluation of dose-proportionality is not possible with the present data because of the substantial interpatient variability, narrow dose range evaluated, and very small number of patients at each dose level. There is a significant overlap in the systemic exposure to irinotecan and SN-38 lactones at the 3 dose levels.
Exploration of the data did not show any association between irinotecan or SN-38 lactone exposure and efficacy or severity of diarrhea or neutropenia.

Figure S7: Mean concentration-time profiles for irinotecan lactone and SN38 lactone following 24 mg/m^2 (n=10).

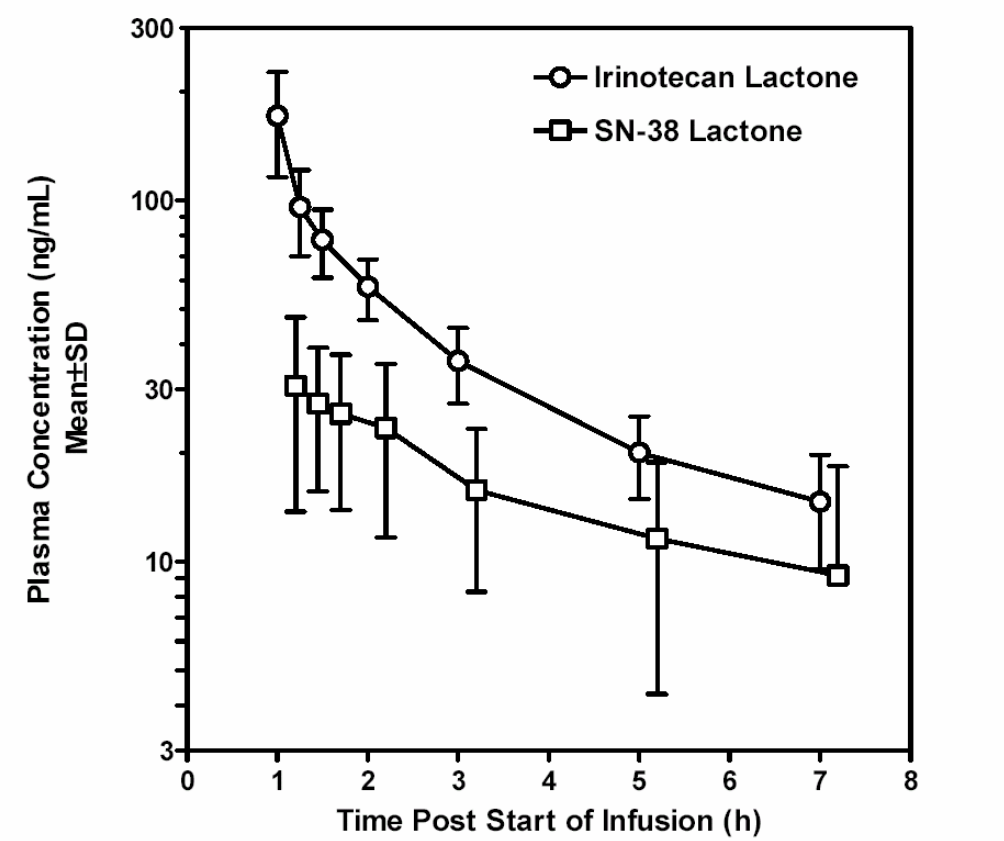


Table S-XIX: Mean pharmacokinetic parameters for irinotecan and SN38 lactones.

Dose, mg/m^2	20		24		29	
Day	1	10	1	10	1	10
N	9	9	10	8	2	2
Irinotecan						
tmax, h	1.06±0.072	1.09±0.099	1.04±0.043	1.04±0.032	1.00-1.02	1.02-1.03
Cmax, ng/mL	199±92.1	116±37.2	171±55.2	128±59.1	493-549	175-179
AUC0-t(last), ng·h/mL	337±163	253±82.9	303±67.6	250±118	602-948	302-496
SN-38						
tmax, h	1.74±1.26	1.81±0.669	1.42±0.672	1.61±0.723	1.00-1.25	1.02-2.95
Cmax, ng/mL	42.7±41.7	13.9±9.42	33.0±16.8	18.8±8.97	23.4-247	3.38-38.8
AUC0-t(last), ng·h/mL	121±125	58.8±42.4	102±51.1	65.3±43.8	81.2-311	14.4-170
Ratio: SN-38 AUC0-t(last)/ Irinotecan AUC0-t(last)	0.384±0.311	0.250±0.212	0.341±0.151	0.294±0.138	0.086-0.516	0.048-0.342

[a] Mean±SD unless N=2 in which case values are the range.

Efficacy results:
Of the 22 patients evaluable for efficacy, 4 showed a partial response (1 each at 20 and 29 mg/m^2 and 2 at 24 mg/m^2). There were 15 patients with stable disease.

Conclusions:

- The MTD for irinotecan was established at 20 mg/m^2 due to the number of DLTs observed for the 24 mg/m^2. However, it does appear that the DLT were similar for both the 20 and 24 mg/m^2 dose levels.

- The most common grade 3 or 4 AEs were diarrhea (41%), pyrexia (23%), hypotension and vomiting (14% each), and hematologic toxicities included neutropenic fever (3 patients), neutropenia (13 patients, 59%), leukopenia (10 patients, 46%), anemia (9 patients, 41%) and thrombocytopenia (3 patients, 14%).

- Substantial interpatient variability in exposure to the lactone (bioactive) forms of irinotecan and SN-38 was noted.
  - While no formal analysis of dose-proportionality was done due to the narrow dose range and few patients studied as well as the limited duration of sampling, neither irinotecan lactone AUC0-t(last) nor SN-38 AUC0-t(last) tended to increase with dose.
  - In patients with repeat PK assessments, a statistically lower SN-38 AUC was noted on Day 10 compared to Day 1.
  - There was no association between irinotecan or SN-38 lactone exposure and efficacy or severity of diarrhea or neutropenia.

- Four (18.2%) partial tumor responses (PRs) were reported. Fifteen (68.2%) of the 22 patients had SD as a best response. There was no association between irinotecan or SN-38 exposure and tumor response.

- The results of this phase I study suggest that the protracted schedule of administration evaluated in this phase 1 study, i.e., daily x5 for 2 weeks of a 3-week cycle appears to be generally tolerable. Irinotecan might have some therapeutic activity in the tumor types seen most frequently in children, particularly rhabdomyosarcoma with 2 PRs and 1 SD noted. This regimen was evaluated in a phase 2 study in patients with rhabdomysosarcoma (D9802).

Study #:	**D9802: PNU-101440**
Title:	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 "Up-Front Window" Irinotecan Single Agent Irinotecan (SAI) Treatment.
Protocol Number:	Pharmacia # 440E-ONC-0020-207
Principal Investigator:	Alberto Pappo, MD St Jude Children's Research Hospital, Memphis, TN
Study Centers:	St Jude Children's Research Hospital 332 North Lauderdale Memphis, TN 38105

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 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 min 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 were presented in this report.

Drug Administration:
Commercial sources of CAMPTOSAR were used for this trial. Irinotecan was to be administered IV in 5% dextrose solution over 60 min. The appropriate volume of irinotecan was mixed with 5% dextrose to a final concentration of irinotecan not to exceed 0.12-1.1 mg/mL. Irinotecan at a starting dose of 20 mg/m^2 was administered daily x5, x2 repeated every 3 weeks.

Duration of Treatment: The duration of treatment during the SAI window phase was based on tumor response. The SAI window was to be discontinued if the following occurred:

- PD at Week 3 or Week 6: the patient was to start VAC and continue on study
- Unacceptable toxicity: the Study Chairman would decide whether the patient should be removed from the study or continue.

All patients were to be followed until death or until lost to follow-up. Any pertinent information about late problems deriving from or related to therapy had to be documented.

Study Treatment: Single-agent irinotecan (SAI) was administered at a dose of 20 mg/m^2 x5 days for 2 weeks of a 3 week cycle. Two cycles of SAI were given, followed by tumor assessment. Then depending on their response to SAI, patients went onto multiagent, multimodal therapy per protocol. Patients completing the 2 irinotecan cycles were to continue as medically recommended to either of the two 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 (vincristine+irinotecan) alternating with V (vincristine) and VAC (vincristine+actinomycin d+cyclophosphamide) schema
• Radiotherapy (Weeks 15-22)
• Continuation (Weeks 26-44) VCPT alternating with V and VAC schema

Treatment Assignment B: patients rated as non-responder or with stable disease or with progressive disease (NR/SD/PD) were to receive multimodal, multiagent therapy as follows (see protocol section 6.0):
• Induction treatment (Weeks 6-14) VAC alternating with V schema
• Radiotherapy (Weeks 15-22)
• Continuation (Weeks 26-44) VAC alternating with V schema
If a patient had clinical evidence of progressive disease (PD) at Week 3, appropriate imaging had to be obtained. Subsequently if progression was confirmed patient had to begin VAC chemotherapy as outlined above for Treatment Assignment B.

Based on clinical trials in adults, there do not appear to be overlapping toxicities between vincristine and topoisomerase inhibitors. Addtionally, preclinical studies suggest that the combination may be synergistic.

Evaluations and Procedures:

Safety evaluations:

Toxicities were graded by the investigators according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), Version 2. Throughout treatment, patients were evaluated for clinical and laboratory adverse events.

Concomitant medications included atropine for early-onset diarrhea, loperamide for treatment of late-onset diarrhea, and antiemetics including ondansetron or granisetron.

Efficacy evaluations:

The primary objective of this protocol was to evaluate the RR to SAI when used in an upfront treatment window. Patients were required to have measurable disease to be eligible for study entry. The criteria evaluated for this report were:

- Tumor response after 2 cycles of SAI window (response confirmation not required)
- Time to response
- Survival

Other time-related parameters like response duration, time to progression or time to treatment failure were not analyzed for this report.

Tumor response was evaluated according to modified World Health Organization (WHO) criteria as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). All disease sites noted at baseline were to be re-evaluated prior to assignment of CR, PR, SD or PD.

- Complete Response (CR): Complete disappearance of all clinically detectable malignant disease for ≥3 weeks. No new lesions could appear during this time.
- Partial Response (PR): A ≥50% decrease of the sum of the products of perpendicular diameters of all measurable lesions. No new lesions could develop and there could be no progression of evaluable disease. All lesions and sites were required to be assessed.
- No Response – No Remission (NR)/Stable Disease (SD): A <50% decrease in the sum of products of the maximum perpendicular diameters of all measurable lesions with no evidence of progression in any lesion and no new lesions.
- Progressive Disease (PD): A ≥25% increase in the sum of products of maximum perpendicular diameters of measurable lesions at any involved site and/or appearance of any new lesions. For patients who had previously attained a PR, >50% increase in tumor size from what was measured at the time of maximum tumor regression.
- Relapse/Recurrence (R): Appearance of new lesions or reappearance of an old lesion for patient in CR.

Please see following table for schedule of study evaluations and PK assessments.

Table S-XX: Schedule of evaluations

	Pre Study	Induction						Continuation	End of TxT	Off Study
	Wks 0-5		Eval 5	6-14	Eval 14	15-25	Eval 25	26-44	Eval 44	
Hx/Px/Ht/Wt	x	Q 3wks	x	Q 3wks	x	Q 3wks	x	Q 3wks	x	x
Clinical Assessment	x	Q 3wks	x	Q 3wks	x	Q 3wks	x	Q 3wks	x	x
CBC/Diff/Plt	x	wkly	x	Wkly[1]	x	Wkly[1]	x	Wkly[1]	x	-
Urinalysis, Creatinine, ALT/SGPT, ALK, LDH	x			Before each course					x	-
Lytes (Na,K,Cl, CO2)	x		Before each course and as indicated						-	-
Ca/Phos/TP/Alb	x		x	-	x	-	x	Q 12 wks	-	-
Bil BM BX/ASP	x	-	x^2		x^2	-	x^2	Q 12 wks[2]	x^2	x^2
Chest XRT	x	-	x		x	-	x	Q 12 wks	x	x
MRI/CT of primary tumor	x	x^2	x^2	-	x^2	-	x^2	Q 12 wks	x	x^2
CT Chest	x		x^2		x^2	-	x^2	Q 12 wks[2]	x	x^2
CT or US liver[3]	x	-	x^2		x^2	-	x^2	Q 12 wks[2]	x^2	x^2
MRI or CT Head[4]	x	-	x^2	-	x^2	-	x^2	Q 12 wks[2]	x^2	x^2
CT or US Retro[5]	x^3	-	x^2	-	x^2	-	x^2	Q 12 wks[2]	x^2	x^2
Bone Scan	x	-	x^2	-	x^2	-	x^2	Q 12 wks[2]	x	x
LP[6]	x	-	-	-	-	-	-	-	-	-
PK[7]				Day 1 of Weeks 0, 9 and 26						

1During chemotherapy (VAC), 2x/wk while on G-CSF
2 Only if previous study was abnormal or clinically indicated. If the CXR was abnormal, CT chest did not need to be repeated
3 For abdominal/pelvic tumors only
4 Only if symptomatic at time of diagnosis or met criteria in Section 4.1.1
5 For lower extremity, GU, pelvic and abdominal tumors only
6 Required in metastatic parameningeal tumors and/or multiple intracranial metastases at initial diagnosis only
7 Selected institutions (Phase I consortium institutions) obtained PK samples on Day 1 of wks 0 and 9. Only PK from wk 0 are presented in this report. Week 9 PK studies were to be performed only in patients who responded to the CPT-11/Vincristine window. Other studies were obtained as frequently as necessary for optimal patient care.
Post pubertal males were encouraged to consider having their sperm banked prior to chemotherapy.
Abbreviations: ALK= Alkaline phosphatase, Bilat BM BX/ASP=Bilateral bone marrow biposy/aspirate, CBC= Complete blood count, Diff= Differential, Hx= History, LDH= Lactate dehydrogenase, Plt = Platelet count, PK= Pharmacokinetics, Px = Physical Exam; ALT/SGPT= Alanine aminotransferase, TxT=Treatment

Pharmacokinetics (PK):

PK blood samples were obtained in a subset of patients on day 1 of week 0 (first cycle) and later during weeks 9 and 26 (these data are not included in the report). Blood samples (3 mL) were collected in heparinized tubes from a vein contralateral from the infusion site. Blood draw times were: prior to the irinotecan infusion, at the end of the 60 min infusion, and at 0.25, 0.5, 1, 2, 4 and 6 h following the completion of the infusion. Samples were centrifuged immediately following collection. Plasma was separated and proteins were precipitated by addition of 0.2 ml

sample to 0.8 ml cold methanol (-30°C) followed by vigrous agitation and repeat centrifugation. The supernatent was decanted and immediately stored at –20° C until analysis.

Analytical Methods:
Plasma samples were assayed irinotecan, SN-38 and APC using a validated, sensitive, specific high-performance liquid chromatographic method with fluorescence detection (HPLC-FL), which quantified the lactone and carboxylate species.Assays were carried out (b) (4)

Data Analysis:
Irinotecan, SN-38, SN-38G, and APC plasma-concentration data were analyzed by noncompartmental methods using Kinetica 2000, version 3.1 (InnaPhase Corp). Cmax, Tmax and AUC(0-last) were measured or estimated. Metabolic ratio, defined as the ratio of SN-38 AUC0-last to irinotecan AUC0-last, was used as a measure of the relative extent of conversion of irinotecan to SN-38. Other PK parameters (CL, Vz, t1/2) were not estimated due to the short duration of sampling.

Results:

Subject Disposition:
The study enrolled 21 patients across 20 centers into the single-agent irinotecan window of treatment. The following table shows the patients demographics and baseline characteristics.

Table S-XXI: Patient demographics

		SAI Window		
		N		**%**
Age Group				
	1 mo-< 2 y	3		14.3
	2-<12 y	4		19.0
	12-<16 y	7		33.3
	≥16 y	7		33.3
Age				
	Min		0.8	
	Median		12.8	
	Max		19.2	
Gender				
	Male	10		47.6
	Female	11		52.4

Table XXII: Baseline characteristics and Disease diagnosis

		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
* 1 patient could have more >1 metastatic site			

Efficacy Results:
The following table summarizes the best overall tumor response to SAI. The best overall tumor response rate (CR + PR) was 42.9% (9/21 patients); the overall SD rate was 28.6% (6/21 patients) and 6 patients (28.6%) had PD as best response. Despite the RR of 42.9% due to the high rate (28.6%) of PD during SAI window treatment and the early deaths (14%) associated with PD, the SAI window was closed to accrual and the protocol was amended to change the up-front window treatment to the combination of VCPT.

Table S-XXIII: Best overall tumor response during single-agent Irinotecan treatment

	N	%
Total	21	100.0
CR+PR	9	42.9
CR	0	0
PR	9	42.9
SD	6	28.6
PD	6	28.6
Abbreviations: CR=Complete response, PD=Progressive disease, PR=Partial response, SAI=Single-agent irinotecan, SD=Stable disease		

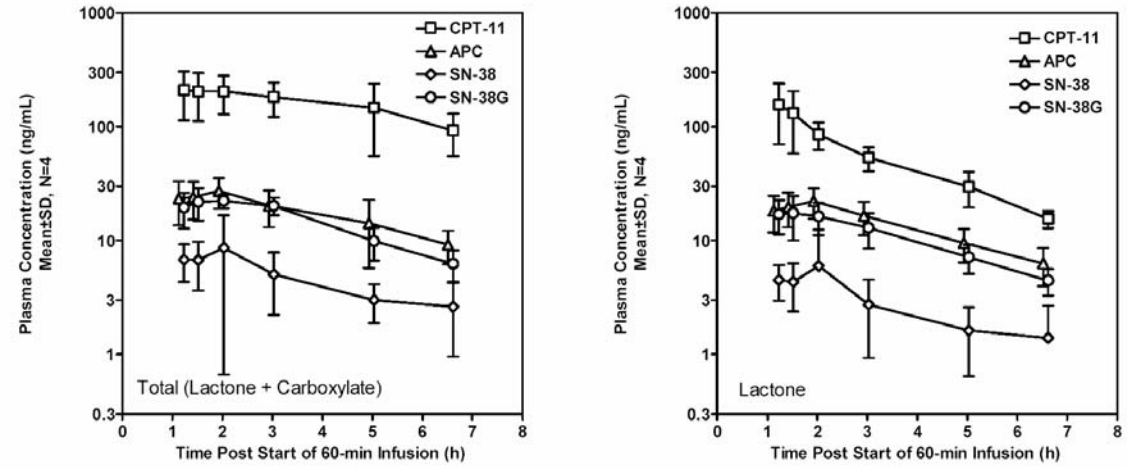
Safety Results:
The majority (90.5%) of patients experienced at least 1 AE. The most common (66.7%) Aes were metabolism disorders. The second most common (61.9%) AEs were gastrointestinal disorders. The overall incidence of grade 3-4 AEs was 66.7% (14 patients).

- Diarrhea occurred in 11 (52.4%) patients with only 2 (9.5%) patients experiencing grade 3 diarrhea. No grade 4 diarrhea was reported.
- Grade 3 vomiting was experienced by 4 (19.0%) patients.

- Metabolism and nutrition disorders were reported in 14 (66.7%) patients and 10 (47.6%) patients were reported with severe disorders (grade 3-4) including 6 patients (28.6%) with dehydration, 5 patients (23.8%) with hypokalemia and 3 patients (14.3%) with hyponatremia.
- Investigational disorders (increase of AST, ALT, bilirubin) were experienced by 7 (33.3%) patients but no grade 3-4 events were reported except for 1 patient (4.8%) with prolonged activated partial thromboplastin time (aPTT).

PK Results:
The following figure shows the concentration-time profiles for total (left panel) and lactone forms (right panel) of irinotecan and metabolites APC, SN38 and SN38G following the 20 mg/m^2 dose in the 4 patients who had PK evaluations during the study.

Figure S-8: Plasma concentration-time profiles for irinotecan and metabolites (mean + SD, n=4) in patients receiving 20 mg/m^2 as a 60-min IV infusion (left panel: total forms, right panel: lactone forms)



The following table shows the descriptive parameters for the total and lactone forms of irinotecan and metabolites in the patients. Based on mean AUCs (through 7 hrs post-start of infusion), lactone:total ratios were 0.37 for irinotecan and 0.60 for SN38. There was substantial variability in Cmax and AUC(0-7h). Due to the short duration of sampling, CL, Vz and t1/2 could not be computed for the subjects.

Table S-XXIV: PK parameters for Irinotecan and metabolites. Week 0 Day 1 (SAI window) Dose=20 mg/m^2

	Lactone	**Total**
Irinotecan		
tmax[b] (h)	1.25±0	1.85±0.784
Cmax (ng/mL)	155±85.0	236±73.2
AUC(0-tlast) (ng·h/mL)	387±134	1044±429

SN38		
tmax (h)	1.58±0.514	1.58±0.514
Cmax (ng/mL)	6.75±5.96	9.41±7.39
AUC(0-tlast) (ng·h/mL)	18.3±12.4	30.7±16.7
SN38G		
tmax (h)	1.50±0.354	1.69±0.375
Cmax (ng/mL)	18.2±6.22	23.6±3.98
AUC(0-tlast) (ng·h/mL)	70.7±21.2	90.2±16.6
APC		
tmax (h)	1.96±0.344	1.96±0.344
Cmax (ng/mL)	23.6±7.04	28.6±8.72
AUC(0-tlast) (ng·h/mL)	87.9±24.0	115±38.4
AUC Ratios		
SN-38/irinotecan	0.062±0.065	0.035±0.026
SN-38G/SN-38	5.15±3.29	3.58±1.83
APC/irinotecan	0.261±0.134	0.114±0.032

[a] PK blood samples were collected through 7 h post start of infusion.
[b] tmax values for irinotecan and all metabolites are relative to the start of the 60-min infusion.
[c] Ratio of metabolite $AUC_{0\text{-}t(last)}$ to irinotecan $AUC_{0\text{-}t(last)}$. Also known as relative extent of conversion (SN-38/irinotecan); relative extent of glucuronidation (SN-38G/SN-38); and relative extent of oxidation (APC/irinotecan).

CONCLUSIONS

- The primary objective of this nonrandomized phase II study was to determine the efficacy of SAI when administered as a 2-cycle up-front window of therapy to children with metastatic RMS. This up-front, single-agent window was to be followed by multimodal, multiagent therapy.

- The assessment of the overall tumor RR was the primary efficacy endpoint. The RR was 42.9% and the median time to response was 5.0 weeks [range 3.0-6.3]. In addition, 28.6% of patients had stabilization of their disease. Six patients (28.6%) had progressive disease as their best response. The median survival of patients treated on the SAI window was 76.3 weeks [95% CI: 57.7 – 115.0].

- Despite the RR > 40% (criteria for continuation of study, according to Simon 2-stage design), the high rate of progressive disease and the early death rate led to the closure of this arm of the study, and the protocol was amended to the combination VCPT (vincristine+irinotecan).

- 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.

- PK studies of irinotecan and SN-38 lactone and total (lactone + carboxylate) species in 4 patients suggest that ratios of lactone/total AUC for irinotecan and SN-38 are comparable to those reported in adults. Due to the small number of patients who underwent PK evaluations and extremely short duration of data collection, systemic parameters could not be estimated.

Study #:	**P9761**
Title:	A Phase II trial of Irinotecan in children with refractory solid tumors: A Children's Oncology Group Study – A Preliminary Report.
Protocol Number:	Pharmacia # 440E-ONC-0020-222
Principal Investigator:	Lisa Bomgaars, MD Baylor College of Medicine, Texas Children's Cancer Center Houston, TX
Study Centers:	80 centers in US and Canada

Primary Objective:
The primary objective of this phase II study was to determine the efficacy of irinotecan in the treatment of children with refractory neuroblastomas, sarcomas of soft tissue or bone and other solid or CNS tumors.

Secondary Objectives:
- To further evaluate the toxicity of irinotecan when given daily x 5, every 3 weeks.
- To further evaluate the PK/pharmacodynamics (PD) of irinotecan and its metabolites (SN-38, SN-38G, and APC.
- To develop a population PK model for irinotecan and metabolite plasma PK.

Study Design:
The study was a multi-center, open-label, uncontrolled, single-arm, phase II trial in children 1 to <22 years (y) of age with solid tumor malignancies, refractory to conventional therapeutic modalities or for which no standard therapy was available. In addition, patients with CNS tumors who had recurrent or refractory disease were eligible. Measurable disease was a requirement for study entry.

Irinotecan was administered using standard supportive care with loperamide, atropine and antiemetics used in prior studies with irinotecan in both adult and pediatric patients with solid tumors. The standard NCI definitions of toxicity (NCI CTC Version 2.0) were used in the trial, consistent with usual cooperative group practice in the phase 2 evaluation of cytotoxic agents. PK assessments included evaluation of irinotecan and its active metabolite, SN-38, as well as SN-38G and APC. The data were analyzed for associations between drug exposure and gender, age group, severity of Cycle 1 toxicity and overall tumor response.
Throughout therapy, patients were evaluated for clinical and laboratory adverse events (AEs). Blood samples for PK/ PD analysis were collected on Day 1 of Cycle 1. Repeated tumor measurements were obtained assess response to therapy.

A total of 170 patients were stratified into 2 categories and then into 9 substrata based on tumor histology:

Solid Tumor Strata:
- Ewing's Sarcoma/ PNET
- Neuroblastoma
- Osteosarcoma
- Rhabdomyosarcoma
- Other extracranial solid tumors, excluding lymphomas and brain tumors

CNS Tumor Strata:
- Medulloblastoma/ PNET
- Brain Stem Glioma
- Ependymoma
- Other CNS Tumors

Drug administration:
The test product was the commercially available Camptosar Injection.
Irinotecan at a starting dose of 50 mg/ m^2 was to be administered as a 60 min IV infusion, daily x 5, every 3 weeks.

Duration of Treatment: All patients who demonstrated a tumor response (CR or PR) or stable disease (SD) were to continue on treatment. Tumor response evaluations were performed after every other course of treatment or whenever clinically indicated.
The appropriate duration of treatment was based on repeated evaluations of response and toxicity. The study treatment was to be discontinued in the event that any of the following occurred: tumor progression, unacceptable toxicity, withdrawal of patient consent, failure to recover toxicities at 4 weeks from the last prior irinotecan administration

In the absence of progressive disease (PD), patients were to receive at least 2 cycles of irinotecan prior to their first on- study tumor evaluation.

Safety evaluations:
Toxicities were graded by the investigators according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), Version 2. Throughout treatment, patients were evaluated for clinical and laboratory adverse events.

Concomitant medications included atropine for early-onset diarrhea, loperamide for treatment of late-onset diarrhea, and antiemetics including ondansetron or dexamethasone. No other medications were permitted. Patients who required anticonvulsants after enrollment were to be taken off study and if such a patient was deemed by the investigator to show evidence of clinical benefit from treatment with irinotecan, he/ she was eligible for enrollment on a parallel COG phase I study (P9871).

Efficacy Evaluations: The primary objective of this protocol was to evaluate the tumor response to irinotecan. Patients were required to have measurable disease to be eligible for study entry.

Tumor response was evaluated according to modified World Health Organization (WHO) criteria as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). All disease sites noted at baseline were to be re-evaluated prior to assignment of CR, PR, SD or PD.

• Complete Response (CR): Complete disappearance of all clinically detectable malignant disease for ≥3 weeks. No new lesions could appear during this time.

• Partial Response (PR): A ≥50% decrease of the sum of the products of perpendicular diameters of all measurable lesions. No new lesions could develop and there could be no progression of evaluable disease. All lesions and sites were required to be assessed.

• No Response – No Remission (NR)/Stable Disease (SD): A <50% decrease in the sum of products of the maximum perpendicular diameters of all measurable lesions with no evidence of progression in any lesion and no new lesions.

• Progressive Disease (PD): A ≥25% increase in the sum of products of maximum perpendicular diameters of measurable lesions at any involved site and/or appearance of any new lesions. For patients who had previously attained a PR, >50% increase in tumor size from what was measured at the time of maximum tumor regression.

• Relapse/Recurrence (R): Appearance of new lesions or reappearance of an old lesion for patient in CR.

PK Assessments: Enrolled patients who consented to the PK study had blood samples taken on Day 1 of Cycle 1. PK blood draws in the first 12 patients enrolled were made according to a "full sampling" schedule whereas a " limited sampling" schedule was used in the remaining patients. Blood draw times in the " full sampling" group were: prior to the irinotecan infusion, at the end of the 60- min infusion, and at 5, 15, and 30 min and 1, 2, 4, 6, 8, and between 10 to 12 h following the completion of the infusion. Draw times in the " limited sampling" group were pre-infusion, end of 1- h infusion, and 1.5, 4.5, 6, and 24 h after the end of the 1- h infusion. Blood samples (3- 5 mL) were collected in heparinized, green- top tubes from a vein contralateral from the infusion site. Samples were centrifuged immediately and the decanted plasma was immediately stored at - 20oC.

Analytical Methods:

Plasma samples were assayed for irinotecan, SN-38 and APC using a validated, sensitive, specific high-performance liquid chromatographic method with fluorescence detection (HPLC-FL).

Data Analysis:

Irinotecan, SN-38, SN-38G, and APC plasma-concentration data were analyzed by noncompartmental methods using Kinetica 2000, version 3.1 (InnaPhase Corp).

For the "limited sampling" data sets, apparent terminal elimination rate constants (λ_z) were determined by linear least-squares regression of plasma concentration-time points in the terminal log-linear region of each patient's plasma concentration-time profile. The apparent terminal half-life (t1/2z) was calculated as $0.693 \cdot \ln 2/\lambda z$. Area under the plasma concentration-time curve ($AUC_{0\text{-}t(last)}$) was determined using the linear trapezoidal rule from time=zero to the last sampling time at which quantifiable drug concentrations occurred. Area under the irinotecan plasma concentration-time curve through infinite time ($AUC_{0\text{-}\infty}$) was alco

calculated. Clearance (CL) and volume of distribution (V_z) of irinotecan were calculated as dose/$AUC_{0-\infty}$ and CL/λ_z, where the administered dose of irinotecan was expressed in free-base equivalents. Metabolic ratio, computed as the ratio of SN-38 $AUC_{0-\infty}$ to irinotecan $AUC_{0-\infty}$, was used as a measure of the relative extent of conversion of irinotecan to SN-38 (REC). The relative extent of SN-38 metabolism to SN-38G (REG) was calculated as the ratio of SN-38G $AUC_{0-\infty}$ to SN-38 $AUC_{0-\infty}$. The relative extent of irinotecan conversion to APC (REO) was defined as the ratio of APC $AUC_{0-\infty}$ to irinotecan $AUC_{0-\infty}$.

For the "full sampling" data sets, $AUC_{0-t(last)}$ was determined using the linear trapezoidal rule from time=zero to the last sampling time at which quantifiable drug concentrations occurred. Irinotecan and metabolite t1/2,Z and AUC0-∞ values and irinotecan CL and Vz were not computed because blood sampling was carried out through 13 h post start of infusion at the latest. Metabolic ratio, computed as the ratio of SN-38 $AUC_{0-t(last)}$ to irinotecan $AUC_{0-t(last)}$, was used as a measure of the REC. The REG was calculated as the ratio of SN-38G $AUC_{0-t(last)}$ to SN-38 $AUC_{0-t(last)}$. The REO was defined as the ratio of APC $AUC_{0-t(last)}$ to irinotecan $AUC_{0-t(last)}$**.** Please see following table for schedule of study evaluations and PK assessments.

Table SXXV: Schedule of assessments.

	Pre-study	Start of each treatment course	Weekly	Every other course	Off-Study
Complete history, height	X				X
Symptoms, performance and physical exam (TPR, BP, Wt)	X	X			X
CT or MRI of measurable lesions	X			X	X
CBC, differential, platelets	X	X	X		X
Urinalysis	X				
Electrolytes, Ca, PO4, Mg	X		X		X
BUN/creatinine	X		X		X
Toital protein, albumin	X		X		X
SGPT	X		X		X
Bilirubin (T/D)	X		X		X
Skeletal survey	X			X	
Bone scan	X			X	
Chest X-ray	X				
BMA/BX	X			X	
Pregnancy test	X				
Additional studies (CSF, cell counts, ultrasound as needed for tumor evaluation and patient care	X				X
Document concomitant medications	X				

RESULTS:

Disposition of Patients: The study enrolled 170 patients from 80 centers. The accrual to each substrata and patient demographics and characteristics are presented in the tables below:

Table S-XXVI: Patient Accrual by stratum

All Strata	**ES/ PNET**	**NBL**	**OSA**	**RMS**	**Other Solid**	**MBL**	**BSG**	**EPM**	**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									

Table S-XXVII: Patient demographics and baseline characteristics.

	ES/ PNET	**NBL**	**OSA**	**RMS**	**Other Solid**	**MBL**	**BSG**	**EPM**	**Other CNS**	**All Strata**
N	18	18	12	19	43	21	9	10	20	170
(%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)
Age										
1 mo-<2 y	-	-	-	-	1 (2.3)	2 (9.5)	-	-	1 (5.0)	4 (2.4)
2-<12 y	5 (27.8)	17 (94.4)	4 (33.3)	15 (78.9)	25 (58.1)	10 (47.6)	5 (55.6)	6 (60.0)	12 (60.0)	99 (58.2)
12-<16 y	5 (27.8)	1 (5.6)	4 (33.3)	1 (5.3)	10 (23.3)	6 (28.6)	4 (44.4)	2 (20.0)	4 (20.0)	37 (21.8)
≥16 y	8 (44.4)	-	4 (33.3)	3 (15.8)	7 (16.3)	3 (14.3)	-	2 (20.0)	3 (15.0)	30 (17.6)
Gender										
Male	13 (72.2)	13 (72.2)	7 (58.3)	9 (47.4)	29 (67.4)	11 (52.4)	6 (66.7)	6 (60.0)	8 (40.0)	102 (60.0)
Female	5 (27.8)	5 (27.8)	5 (41.7)	10 (52.6)	14 (32.6)	10 (47.6)	3 (33.3)	4 (40.0)	12 (60.0)	68 (40.0)
Ethnic Origin										
White	12 (66.7)	10 (55.6)	7 (58.3)	14 (73.7)	24 (55.8)	15 (71.4)	3 (33.3)	9 (90.0)	12 (60.0)	106 (62.4)
Black	2 (11.1)	3 (16.7)	2 (16.7)	1 (5.3)	9 (20.9)	1 (4.8)	2 (22.2)	1 (10.0)	4 (20.0)	25 (14.7)
Other	4 (22.2)	5 (27.8)	3 (25.0)	4 (21.1)	9 (20.9)	5 (23.8)	4 (44.4)	-	4 (20.0)	38 (22.4)
No data	-	-	-	-	1 (2.3)	-	-	-	-	1 (0.6)
ECOG PS										
0	12 (66.7)	16 (88.9)	6 (50.0)	10 (52.6)	34 (79.1)	16 (76.2)	5 (55.6)	5 (50.0)	12 (60.0)	116 (68.2)
1	5 (27.8)	1 (5.6)	4 (33.3)	7 (36.8)	6 (14.0)	2 (9.5)	2 (22.2)	3 (30.0)	4 (20.0)	34 (20.0)
2	1 (5.6)	1 (5.6)	2 (16.7)	2 (10.5)	2 (4.7)	3 (14.3)	2 (22.2)	2 (20.0)	3 (15.0)	18 (10.6)
No data	-	-	-	-	1 (2.3)	-	-	-	1 (5.0)	2 (1.2)
Abbreviations: BSG = Brain stem glioma, EPM = Ependymoma, ES = Ewing's sarcoma, MBL = Medulloblastoma, NBL = Neuroblastoma, No Mets = No metastatic site, OSA = Osteosarcoma, PNET = Primitive neuroectodermal tumor, PS = Performance status, RMS = Rhabdomyosarcoma, UNK = Unknown										

Efficacy Results:

Table XXVIII: Efficacy results: response rates, by stratum.

	ES/				**Other**				**Other**	**All**

	PNET	NBL	OSA	RMS	Solid	MBL	BSG	EPM	CNS	Strata
N	18	18	12	19	43	21	9	10	20	170
(%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)
CR+PR	-	1	-	3	1	3	-	-	1	9
		(5.6)		(15.8)	(2.3)	(14.3)			(5.0)	(5.3)
CR	-	-	-	1	1	-	-	-	-	2
				(5.3)	(2.3)					(1.2)
PR	-	1	-	2	-	3	-	-	1	7
		(5.6)		(10.5)		(14.3)			(5.0)	(4.1)
SD	12	7	4	6	19	13	6	3	10	80
	(66.7)	(38.9)	(33.3)	(31.6)	(44.2)	(61.9)	(66.7)	(30.0)	(50.0)	(47.1)
PD	5	10	6	10	20	4	2	6	8	71
	(27.8)	(55.6)	(50.0)	(52.6)	(46.5)	(19.0)	(22.2)	(60.0)	(40.0)	(41.8)
NA	-	-	1	-	-	-	-	-	-	1
			(8.3)							(0.6)
UNK	1	-	1	-	3	1	1	1	1	9
	(5.6)		(8.3)		(7.0)	(4.8)	(11.1)	(10.0)	(5.0)	(5.3)

Abbreviations: BSG = Brain stem glioma, CR = Complete response, EPM = Ependymoma, ES = Ewing's sarcoma, MBL = Medulloblastoma, NA = Not assessed, NBL = Neuroblastoma, OSA = Osteosarcoma, PD = Progressive disease, PNET = Primitive neuroectodermal tumor, PR = Partial response, RMS= Rhabdomyosarcoma, SD = Stable disease, UNK = Unknown

The RR across all substrata was 5.3%. The RR for all solid tumors was 4.5% (5/110) and the RR was 6.7% (4/60) for all CNS tumors. Within the substrata, the RR (CR + PR) was 15.8% (3/19) for rhabdomyosarcoma patients and 14.3% (3/21) for medulloblastoma patients. There were no responders in the Ewing's sarcoma/PNET, osteosarcoma, brain stem glioma and ependymoma substrata. The overall SD rate was 47.1% (80/170) with a high rate of stabilization in glioma (66.7%), Ewing's sarcoma (66.7%) and medulloblastoma (61.9%) patients.

Safety Results:

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.

PK Results:

PK plasma samples were collected from each patient according to one of 2 sampling schedules. For 13 patients, 10 plasma samples were collected up to 12 h after the end of the infusion; this schedule is referred to as the "full sampling" schedule in this report. The other schedule, where 6 plasma samples were collected over the 24-h period following the end of the infusion, was used in 48 patients and is referred to as the "limited sampling" schedule in this report. The plasma concentration-time profiles of irinotecan and SN-38 during the first 12-h sampling period appeared to be similar in the "full" and "limited" groups [Appendices 2.8 and 3.5]. However it was obvious that the "full" schedule did not capture a substantial portion of the drug exposure occurring in the terminal phase of drug disposition [Appendix 2.8]. Thus, in subsequent analyses, only descriptive parameters were computed from the data from the "full sampling" patients. Mean plasma concentration-time profiles of irinotecan and the metabolites SN-38, SN-38G, and APC following the end of the 60-min infusion of irinotecan at 50 mg/m^2 are shown in Figure 1 for the "limited sampling" group. After the infusion stopped, plasma concentrations of irinotecan and SN-38 declined biexponentially and were still quantifiable at the 24-h time point. Mean concentration-time profiles of SN-38G and APC followed a similar pattern of biphasic decline.

Figure S-9: Mean (+/- SE) plasma concentration time profiles for irinotecan and metabolites.

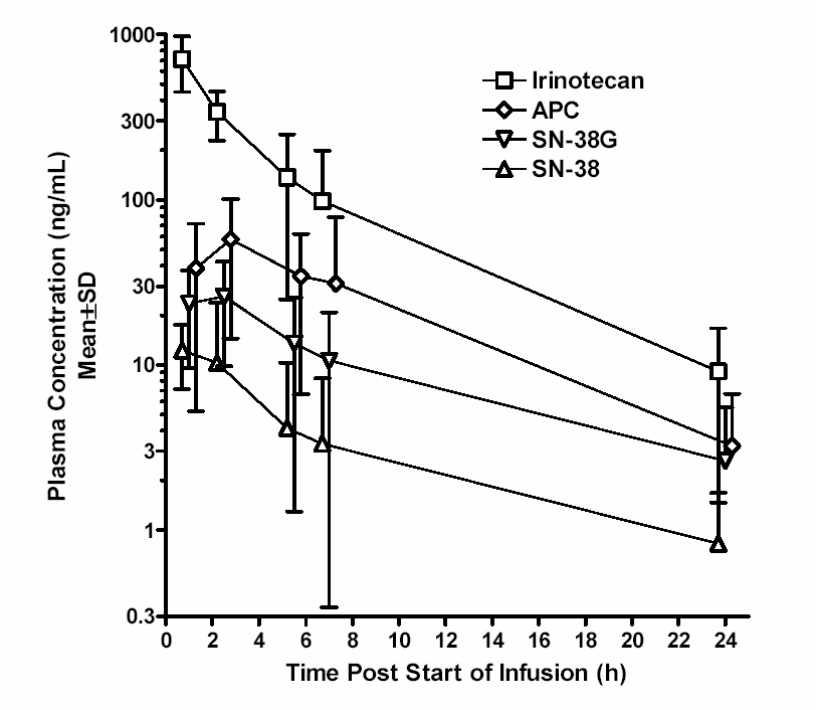


Table S-XXIX: Pharmacokinetics of irinotecan and metabolites.

	Mean ± SE

Irinotecan	
tmax[b], h	1.11±0.304
Cmax, ng/mL	685±264
AUC0-t(last), ng·h/mL	2899±1571
AUC0-∞, ng·h/mL	2963±1611
CL, L/h/m^2	17.3±6.72
Vz L/m^2	118±49.8
[t]1/2,z, h	4.71±0.658
SN38	
tmax, h	1.26±0.564
Cmax, ng/mL	14.2±12.6
AUC0-t(last), ng·h/mL	79.4±95.2
AUC0-∞ , ng·h/mL	95.0±100
t1/2,z , h	8.93±6.29
SN38G	
tmax, h	1.98±0.884
Cmax, ng/mL	27.8±16.4
AUC0-t(last), ng·h/mL	223±186
AUC0-∞ , ng·h/mL	264±216
t1/2,z , h	7.91±3.85
SN38G	
tmax, h	2.55±0.712
Cmax, ng/mL	60.9±54.8
AUC0-t(last), ng·h/mL	563±578
AUC0-∞ , ng·h/mL	593±595
t1/2,z , h	5.15±1.34
AUC Ratios	
SN-38/irinotecan	0.035±0.047
SN-38G/SN-38	3.68±2.82
APC/irinotecan	0.203±0.154

[a] N=53 for irinotecan SN-38G, and APC tmax and Cmax. N=52 for SN-38 tmax and Cmax.
[b] tmax values for irinotecan and all metabolites are relative to the start of the infusion.

DISCUSSION AND CONCLUSIONS

The primary objective of this single-agent, nonrandomized phase II study was to determine the efficacy of irinotecan in the treatment of children with refractory neuroblastomas, sarcomas of soft tissue or bone and other solid or CNS tumors. The secondary objectives were to further evaluate the toxicity and PK profile of irinotecan with this schedule. Irinotecan was infused over 60 minutes at a starting dose level of 50 mg/m^2 given daily for 5 consecutive days. Cycles were repeated every 21 days.

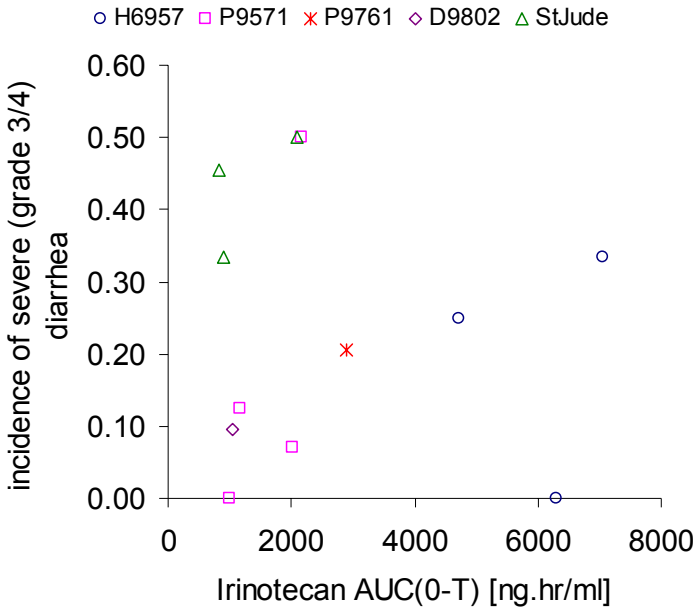
The overall tumor response rate (RR) was the primary efficacy endpoint. The RR was 15.8% in rhabdomyosarcoma patients, 14.3% in medulloblastoma patients and 5.6% in neuroblastoma patients. The RR across all substrata was 5.3%. The median duration of response was 24.7 weeks [95% CI 10.4 - 43.3]. In addition, 47.1% of patients had stabilization of their disease.

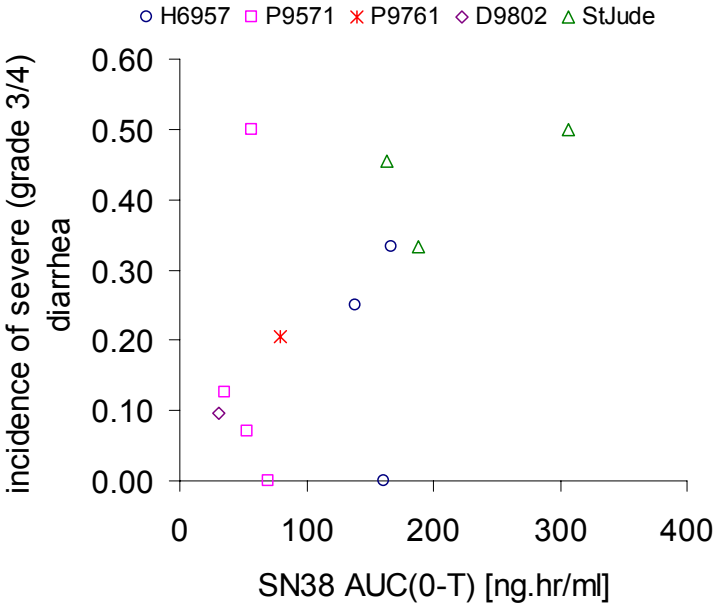
Across all cycles of therapy, the most common drug-related, grade 3 - 4 nonhematologic AEs were gastrointestinal, with 85.3% of the patients experiencing ≥1 AE. Diarrhea was the most frequent drug-related gastrointestinal event, however only 20.6% of the patients experienced grade 3-4 diarrhea. Neutropenia (38.8%) was the most frequent hematologic AE. Severe neutropenia (grade 3-4) was reported in 31.8% of the patients and was complicated by fever in 8.8% of the patients.

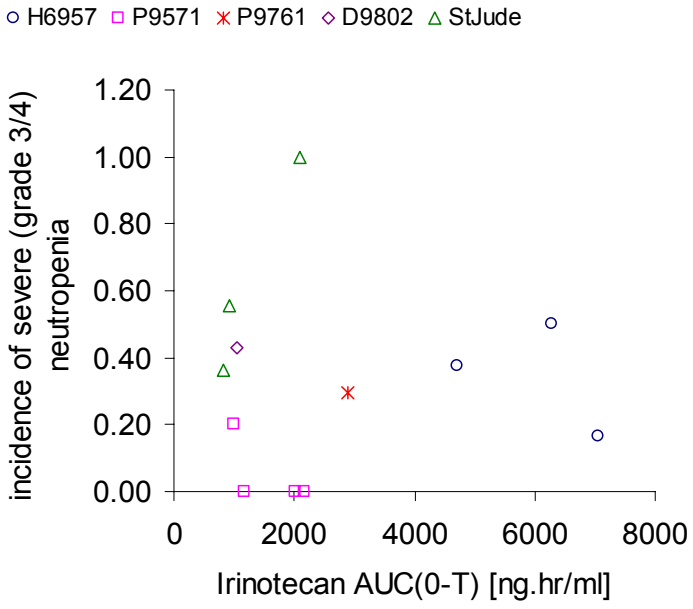
A secondary objective of this study was to determine the PK of irinotecan and its metabolites (SN-38, SN-38G and APC) and to look for potential associations between PK and toxicity or efficacy. PK results were characterized by substantial interpatient variability, as has been reported for adults. PK parameters in this pediatric trial were generally similar to those reported for adults with the possible exception that irinotecan CL may be slightly higher in the children in this trial. There was no apparent association between irinotecan or SN-38 PK and gender or age. Irinotecan and SN-38 AUC values were correlated with body weight, height, and surface area to generally the same degree. There was no apparent association between PK parameters and toxicity or efficacy.

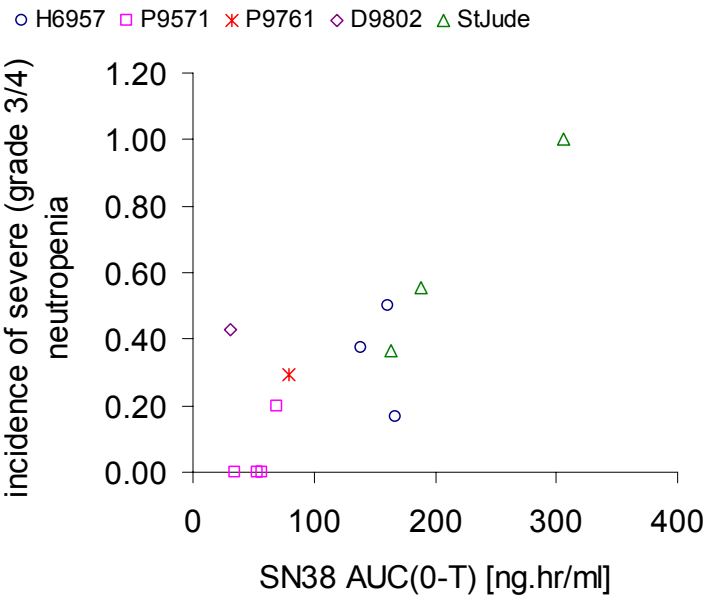
G. C. Pharmacometric Review

Summary of findings of Pharmacometric Analysis:
The proportion of pediatric patients with grade 3 and 4 diarrhea seems to increase with an increase in SN38 AUC. This is in accordance with data in adult patients. Conclusive identification of such a relationship is very important in "optimal" use of this drug. The Agency recommends that the applicant conduct sparse PK sampling to ensure reliable estimation of SN38 AUC in all future studies. The collected data should be analyzed to examine the exposure-response relationship for measures of toxicity of irinotecan.









OBJECTIVES

1. To characterize the pharmacokinetics of irinotecan and metabolites (SN38, SN38G) in pediatric patients.
   a) To develop a population pharmacokinetic model for irinotecan and its active metabolite SN38 in plasma.
   b) To determine the significance of covariates that could influence the PK of irinotecan such as body size metrics such as weight and body surface area, gender, age (within the pediatric population) and prior history of pretreatment (heavily vs. less heavily pretreated).

2. To examine the relationship between exposure to irinotecan (and SN38) and the incidence of severe adverse events, including diarrhea and neutropenia.

METHODS and RESULTS

Data:

Pharmacokinetic and safety (diarrhea and neutropenia incidence) data was obtained from the four phase 1 studies and two phase 2 studies submitted with this application. The phase 1 studies were conducted in pediatric patients with refractory solid tumors, and evaluated the safety and PK of three different regimens (weekly, 5 days every 3 weeks, and 5 days per week for 2 weeks every 3 weeks). One of the phase 2 studies was done in 170 pediatric patients with refractory solid tumors, stratified into 9 sub-strata based on tumor type. The other phase 2 study was done in 21 newly diagnosed rhabdomyosarcoma patients. Table PM-I lists the studies included in the analysis.

Software:

The following software were used in the pharmacometric analysis:
Database management and PK-PD analysis (logistic regression) - SAS®(Ver 8.0).
Population PK analysis - NONMEM® (Compiler: Visual Fortran Ver 6.5).

Table PM-I: List of studies included in Population PK and exposure-response analysis

Protocol #	**Schedule**	**PK Dose Levels (# PK Datasets Analyzed at Each Dose)**	**Analytes**	**# PK Samples (excl pre-dose)**
Inst: H6957 PHA: 98-6475-178	Weekly x 4 every-6-weeks	125 (6), 160 (4), 200 (2) [Total=12]	Total: CPT-11, SN-38, SN-38G, APC	13 over 25 h
Inst: P9571 PHA: M 6475 056	Daily x 5 every-3-weeks	30(2), 39 (8), 50 (10), 65 (5) [Day 1 total=26] Day 4: 30 (2), 39 (4), 50 (7), 65 (5) [Day 4 total=18]	Total: CPT-11, SN-38, SN-38G, APC	10 over 13 h
Inst: P9871 PHA: CPTAIV-0020-452	Daily x 5 every-3-weeks	30 (1), 50 (1), 100 (4), 130 (2) [Total=8] By stratum: 6 EIAC, 2 non-EIAC, 1 valproate	Total: CPT-11, SN-38, SN-38G, APC	10 over 13 h
Inst: St Jude PHA: CPTAIV-020-453	Daily x 5, x 2 every-3-weeks	20 (9), 24 (10), 29 (2) [Day 1 Total=21] [Day 10 Total=19]	Lactone: CPT-11, SN-38	7 over 7 h
Inst: P9761 PHA: 440E-ONC-0020-222	Daily x 5 every-3-weeks	50 (13 "Full sampling"; 48 "Limited sampling")	Total: CPT-11, SN-38, SN-38G, APC	"Full sampling": 10 over 13 h. "Limited sampling": 5 over 25 h.
Inst: D9802 PHA: 440E-ONC-0020-207	Daily x 5, x 2 every-3-weeks	20 (4)	Lactone & Total: CPT-11, SN-38, SN-38G, APC	6 over 7 h

Pharmacokinetic Model:

The applicant performed non-compartmental analysis of irinotecan and metabolite concentrations in the patients in individual studies. As the table above indicates, the studies had different infusion regimens and schedules and sampling ranged from rich to sparse across studies. The studies reported substantial variability in exposure and in the PK parameters estimated across the regimens. As a result, the examination of intrinsic and extrinsic covariates on the PK parameters in each study could not be done in a meaningful way. Additionally, since PK data was not collected in all the patients in the phase 2 studies, there was a need to obtain

estimates of the exposure in these patients. A population PK model would provide the basis for imputing the exposure to irinotecan and its active metabolite SN38 in all the patients, which in turn would allow a more complete examination of the exposure-toxicity relationship for irinotecan in pediatric tumor patients.

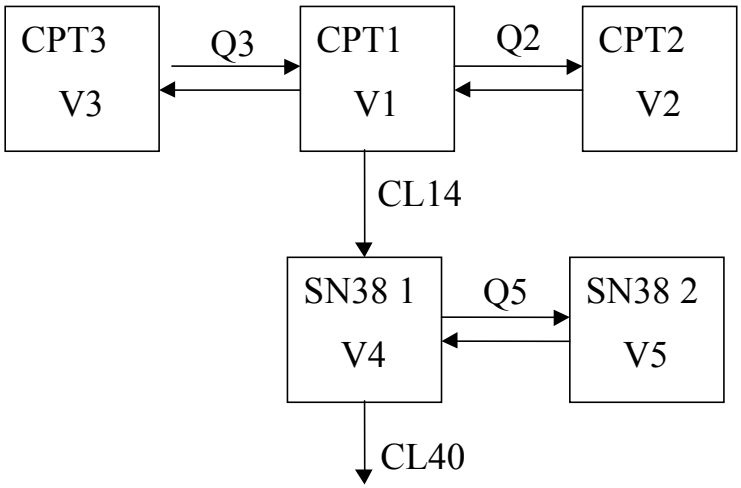
Model development and strategy:

A population model for irinotecan and its metabolites was recently published by Xie et al. (Clin Pharmacol Ther 72:265-75, 2002) using data from 109 patients who received doses ranging from 100 to 350 mg/m^2 of irinotecan, and concentrations of irinotecan and its metabolites were measured from 0 to 60 hours. The PK model employed by Xie et al. was used as the basis for modeling the data in the current analysis.

The model consisted of a 3-compartment model for irinotecan and a 2-compartment model for SN38 (figure PM-1). The strategy was to:

1) Fit the irinotecan data only to obtain the parameter estimates that best describe the disposition of irinotecan in the pediatric patients.
2) Examine the effect of covariates BSA (body surface area), body weight, age, gender and pretreatment on the PK parameters for irinotecan.
3) Fix the PK parameters for irinotecan at their best estimates obtained in step 2 and fit the 2-compartment model for SN38 to the data from the current submission. The effects of BSA and weight on the parameters for SN38 were also evaluated.

Figure PM1: Schematic of compartmental model for irinotecan and SN38.



Initial runs during the fitting of SN38 data resulted in poor fits with over-estimation of predicted SN38 concentrations. This was possibly due to the limited duration of PK sampling (13 hours following the start of infusion for most studies). Since the published PK model for irinotecan and SN38 (Xie et al.) was based on PK sampling for up to 60 hours post-start of infusion and better-estimated parameters, the volume and inter-compartment clearance for the peripheral compartment of SN38 (parameters V5 and Q5) were fixed to the final estimates published by Xie et al., and the central compartment volume and clearance for SN38 were estimated. Attempts to

estimate all of the SN38 parameters were unsuccessful. The reasons for this were unclear, but could be due to insufficient duration of time for SN38 sampling. Thus, the SN38 tissue compartment volume (V5) and inter-compartmental clearance (Q5) were fixed to estimates obtained by Xie et al, which had a rich sampling for SN38 up to 60 hours. The two parameters of interest that were estimated were SN38 central compartment volume (V4) and the SN38 Clearance (Cl4). Fm is defined as the fraction metabolized for SN38 which cannot be estimated from these data.

Covariate model selection was based on stepwise forward selection. According to the likelihood ratio test, the ratio of the likelihood from nested models is assumed to be asymptotically $\chi 2$-distributed with degrees of freedom equal to the difference in the number of model parameters. A critical change of 20 or greater (df=1) was used to guide covariate selection.

Covariates for irinotecan:

Examination of covariates for irinotecan showed that body size was a significant covariate for clearance and volumes for irinotecan. The best estimates were obtained for models incorporating body weight as a predictor for clearance as well as for the tissue compartment volumes for irinotecan (figure PM3a). For all parameters shown below, body weight provided a better fit (lower OFV) compared to models with body surface area as the predictor. Models for V1 and Q2 did not yield significant covariates. θ_{V2} is the population volume for the second tissue compartment for Irinotecan. θ_{V3} is the population volume for the third tissue compartment for Irinotecan. θ_{CL1} is the population clearance for Irinotecan. θ_{CL2} is the coefficient for clearance for Irinotecan.

$V2 = \theta_{V2} \bullet (WT/40)$

$V3 = \theta_{V3} \bullet (WT/40)$

$CL = \theta_{CL1} \bullet (WT/40)^{\theta CL2}$

$Q3 = \theta_{Q3} \bullet (WT/40)$

Estimates of inter-individual variability were high, ranging from 57 to 109% across parameters. Addition of other covariates to the model for clearance, including age, gender and pre-treatment did not result in significant changes in objective function value and indicate that these covariates were not significant predictors of CL of irinotecan, after the inclusion of weight in the model (see figures PM3b, 3c and 3d).

Figure PM3a: Individual estimates of irinotecan clearance vs. body weight

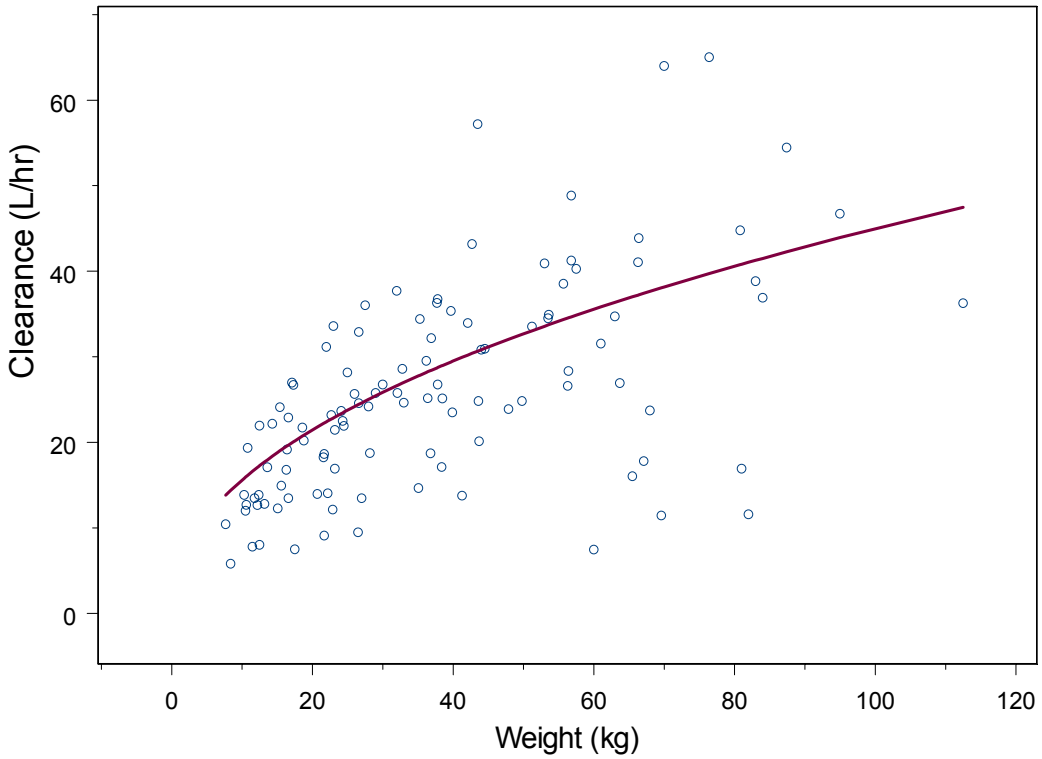


Figure PM3b: Individual estimates of irinotecan clearance vs. age

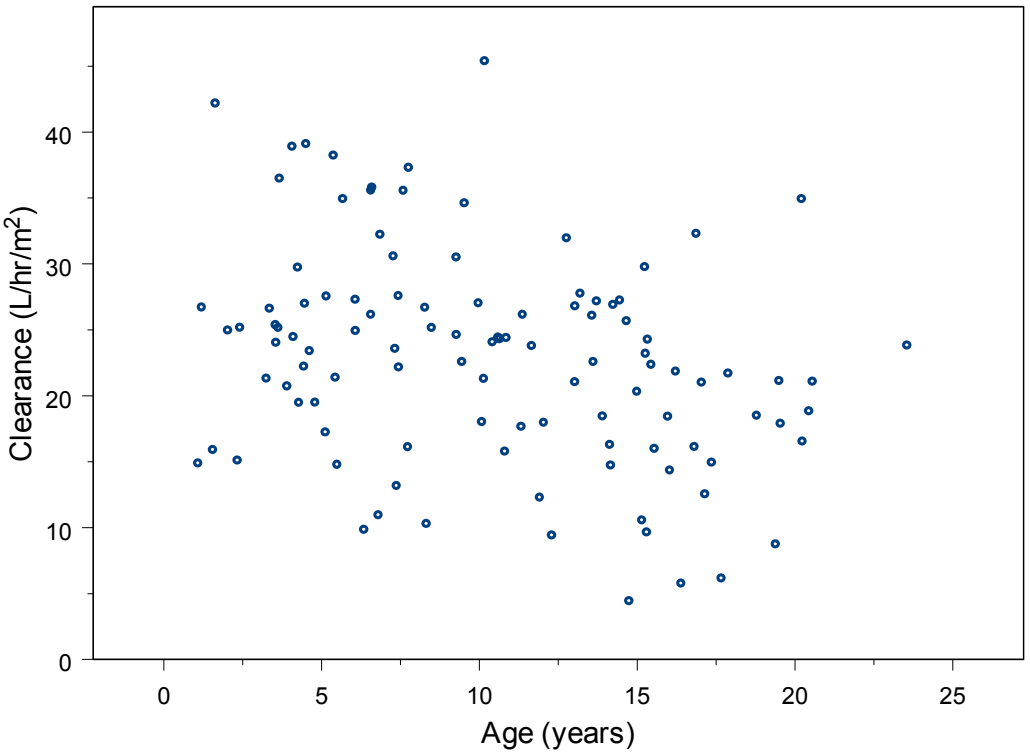


Figure PM3c: Individual estimates of irinotecan clearance vs. gender

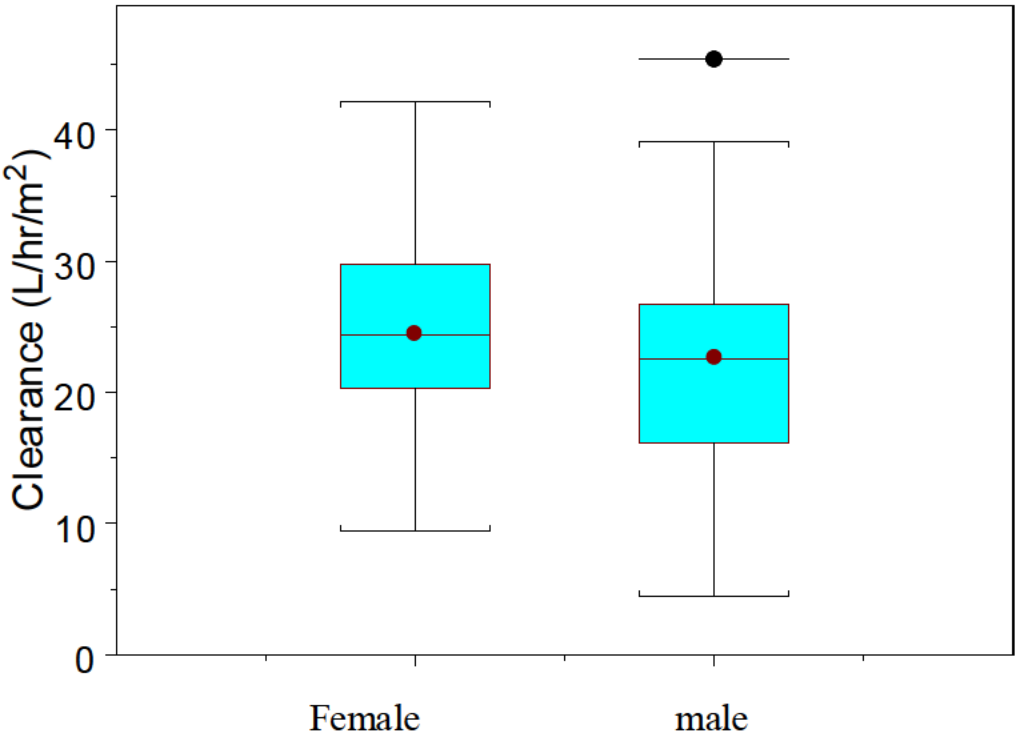
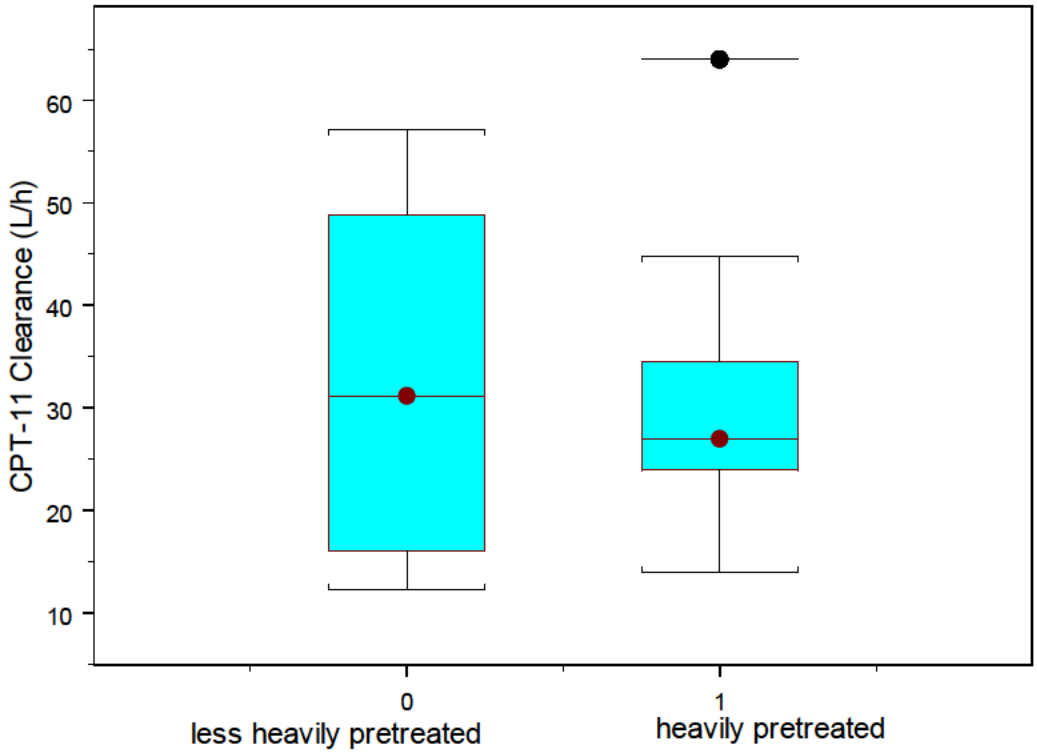


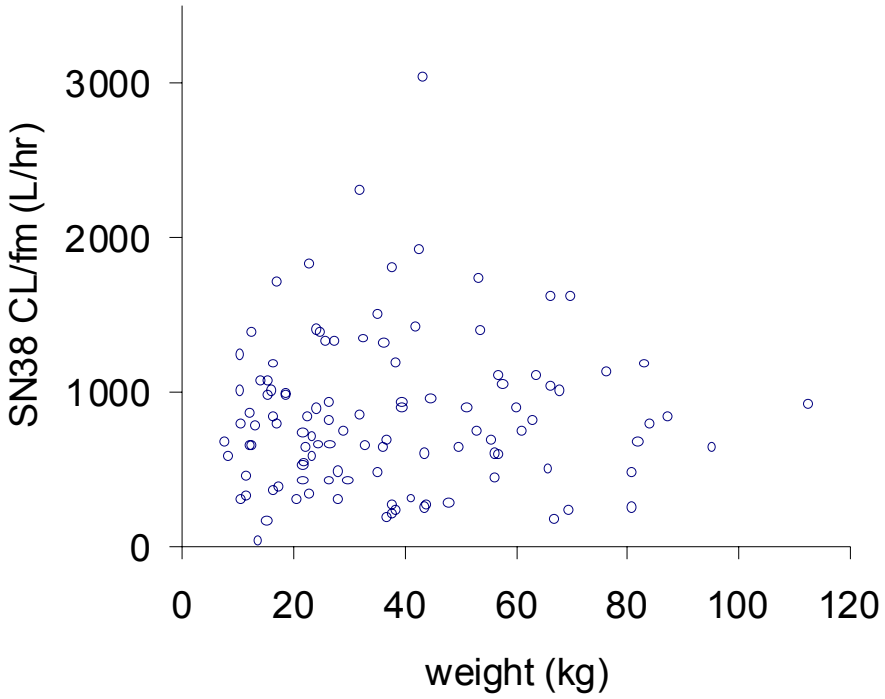
Figure PM3d: Individual estimates of irinotecan clearance vs. pre-treatment (heavily vs. less-heavily)



Covariates for SN38:

The final model for SN38 did not include body size (BSA or weight) as significant covariates for any of the clearance or volumes of SN38 (CL4, Q5, V4, V5). The inter-individual variability estimates in the parameters were substantial, ranging from 75 to 98%. Figure PM-4 illustrates the wide range of estimates of CL plotted as a function of body weight and there appears to be no trend as a function of weight. The reasons for lack of a relationship could be several:
1) The extent of SN38 formation is dictated by the extent of CPT-11 clearance, which already accounts for body size differences.
2) SN38 is reversibly converted to SN38G in the gut by bacterial glucuronidases. The model is simplified for practical reasons and the reversible conversion is not accounted for in the model.
3) This finding seemed to be consistent with Xie et al. These authors also did not find body size to be a determinant of SN38 exposure.

Figure PM4: Individual estimates of SN38 clearance vs. body weight



Results of PK analysis:

The model predicted irinotecan and SN38 concentrations are shown in figure PM-2 (scatterplots of observed and predicted irinotecan and SN38). Figure PM3 illustrates concentration vs. time profiles for representative patients for both CPT-11 and SN38.

Figure PM2a: Observed vs. individual predicted concentrations for Irinotecan

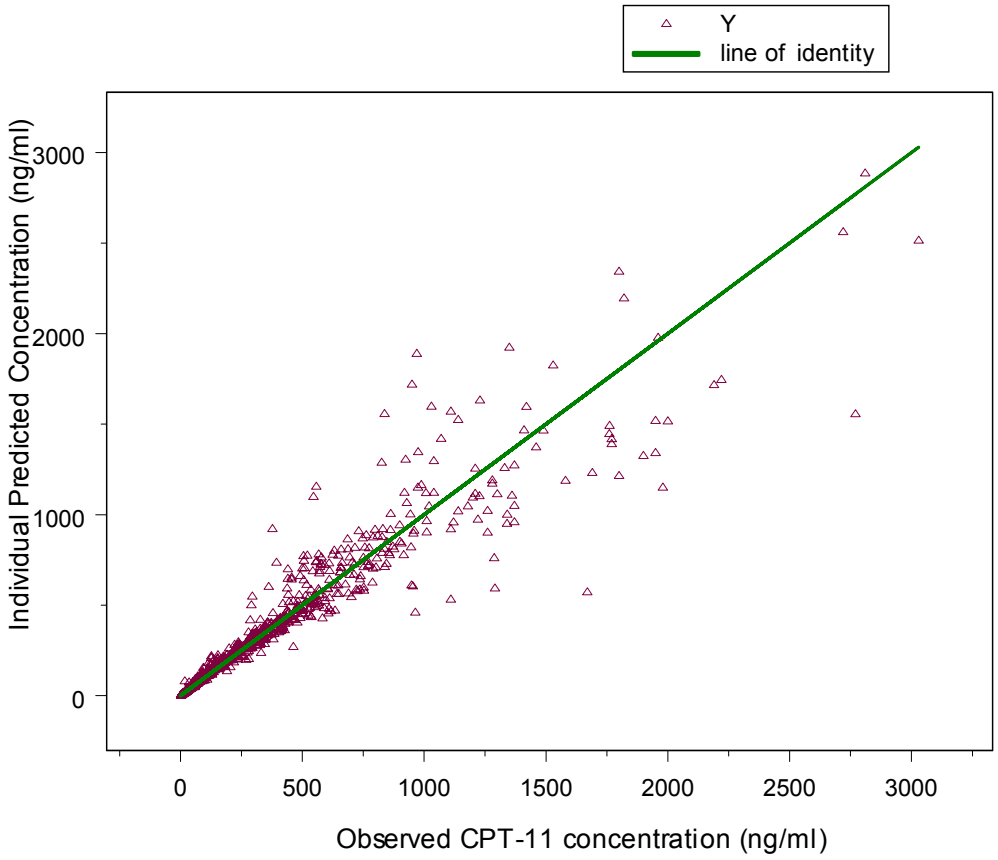


Figure PM2b: Observed vs. population predicted concentrations for Irinotecan

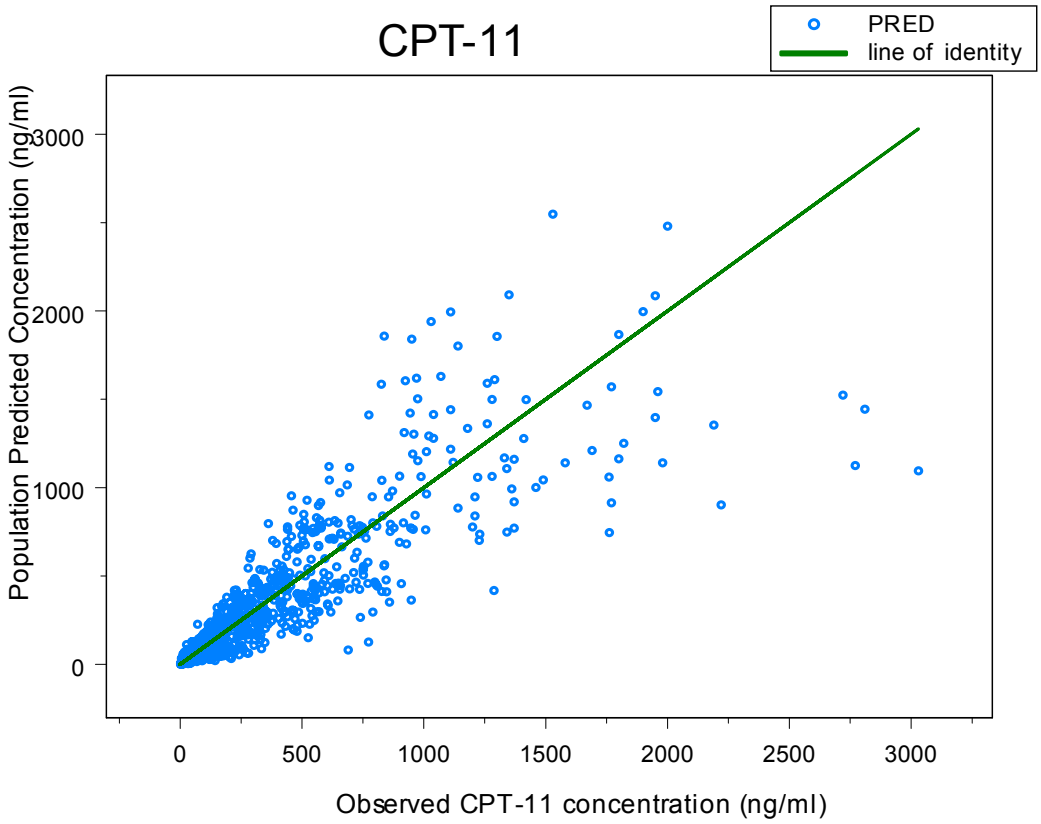


Figure PM2c: Observed vs. individual predicted concentrations for SN38

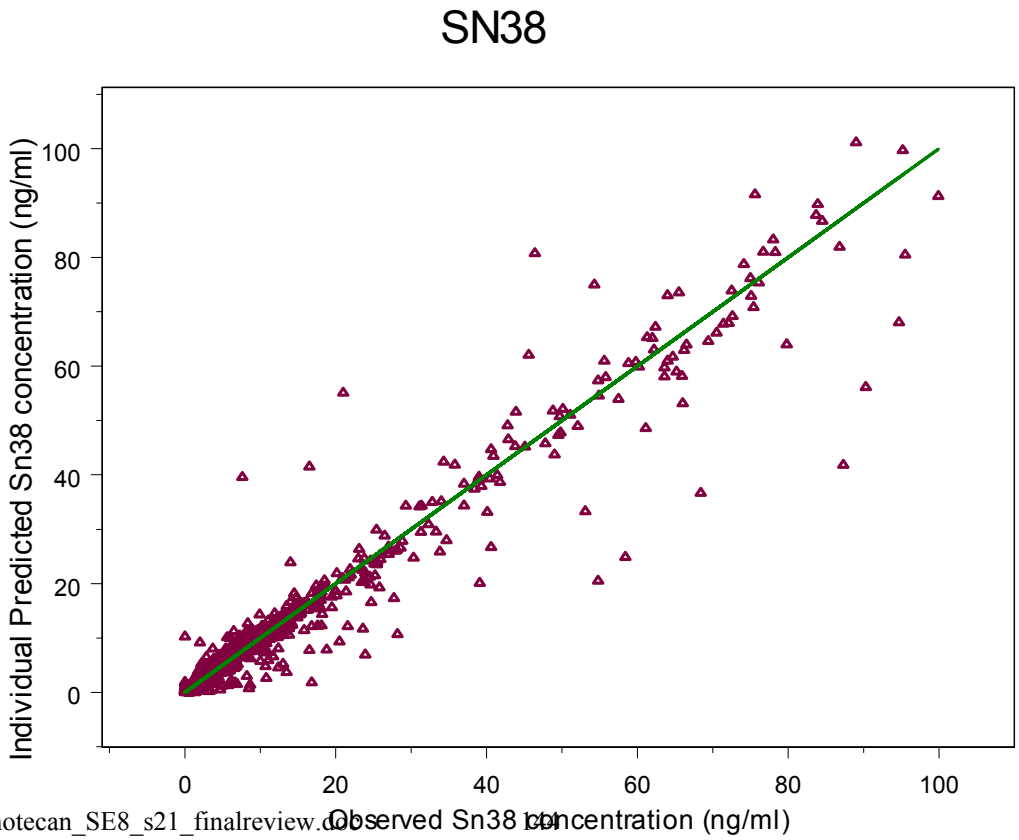
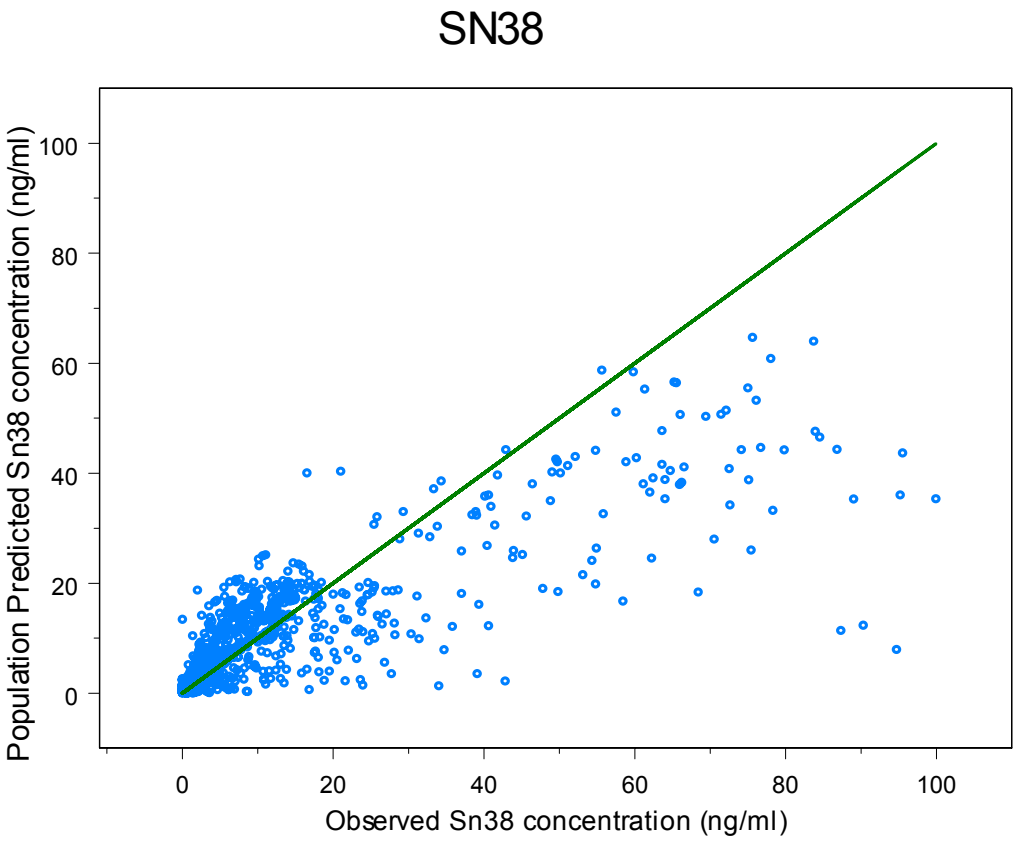


Figure PM2d: Observed vs. population predicted concentrations for SN38



The observed versus predicted (both individual predicted and population) for CPT-11 provided reasonable fits as seen in Figures PM2a and 2b. For SN38 the observed concentrations versus individual predicted concentrations showed good correlation as seen in figure PM2c. However, there was a bias in estimating the population predicted concentrations for SN38 when compared to observed concentrations. For the lower concentrations less than 20 ng/ml, the population predictions were overestimated and for the higher concentrations there was an underestimation.

Figure PM2e: Representative population predicted and individual predicted irinotecan-time plots

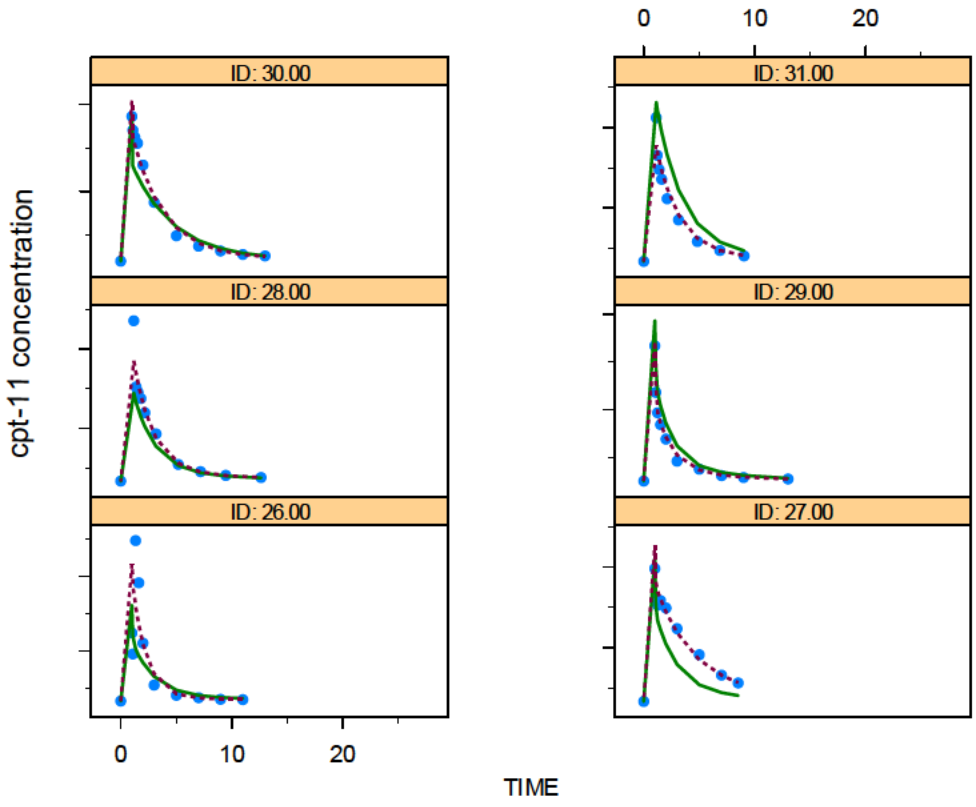


Figure PM2f: Representative population predicted and individual predicted SN38-time plots

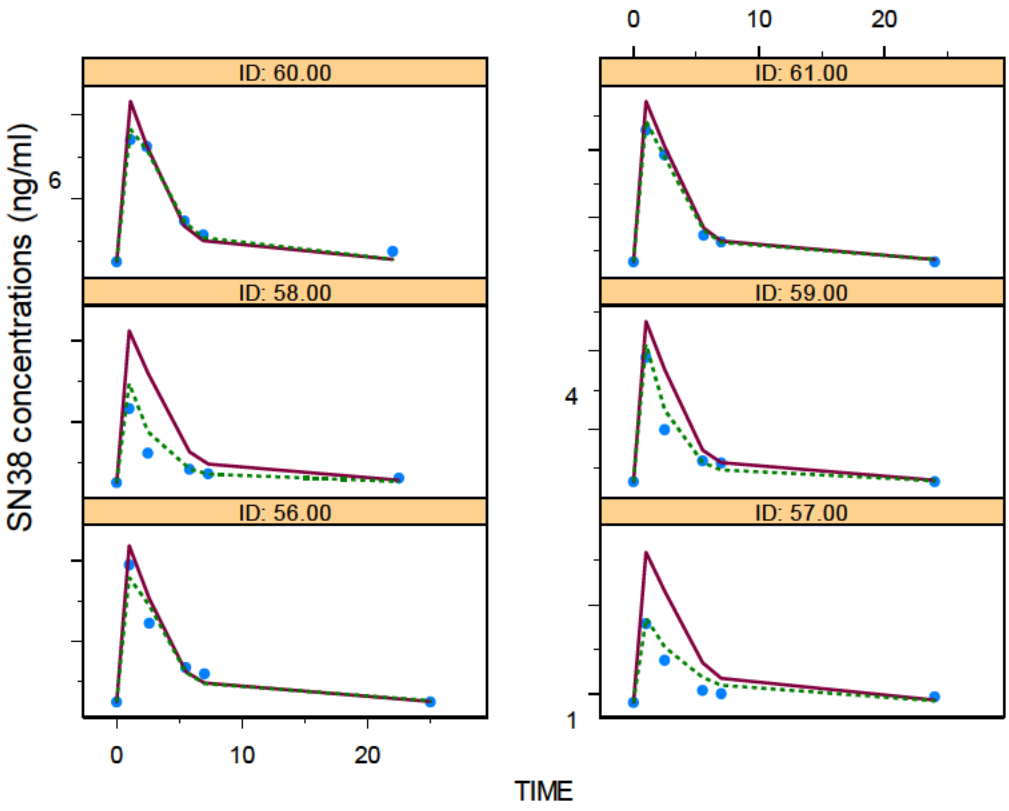


Table PM-II lists the final parameter estimates from the final PK model for irinotecan and SN38.

Table PM-II: Parameter estimates from NONMEM model fit.

Irinotecan		
Parameter	Population Mean	Interindividual Variability (% COV)
V1 [L]	6.4	106
V2 [L/40 kg]	78.9	75
V3 [L/40 kg]	72.8	57
CL [L/hr/40 kg]	29.5	81
Q2 [L/hr/40 kg]	5.1	87
Q3 [L/hr/40 kg]	175.0	109
CL2 [-]	0.46	-
Residual Variability		
ε1 [%]	45	
ε2 [ng/ml]	0.39	

SN38		
Parameter	Population mean	Interindividual variability
V4/Fm [L]	498	98
V5 /Fm [L]	71600 [1]	75 [1]
CL4 /Fm [L/hr]	641	85
Q5 /Fm [L/hr]	1530 [1]	77 [1]
Residual Variability		
ε3 [ng/ml]	5.7	

1: Estimates for V5 and Q5 were fixed to typical values obtained by Xie et al., 2002.

- Scatter-plots of individual predicted concentrations vs. observed data show a high degree of correlation. There does appear to be some over-estimation of population predicted SN38 concentrations (figure PM2b) but not for the individual predicted SN38 concentrations. This was not considered to be a limitation, since it was the individual predictions that were used in the exposure-response analysis.
- Since the final parameter model for SN38 clearance did not show significant effects of any covariates, it could not be used to estimate the AUC for the patients who did not have PK evaluations.

- The clearance and volume estimates obtained from the above fits are close to the parameter estimates reported using a rich dataset of irinotecan and SN38 concentrations in 109 adult patients (Xie et al., 2002).

Comparison between adult and pediatric data

Table PM-III: Comparison of parameter estimates between current dataset in pediatric and published results in adults.

Irinotecan		
Parameter	Estimate from current data in pediatrics	Estimate from Xie et al. in adults
V1	6.4 [L]	44 [L/1.2 m^2]
V2	78.9 [L/40 kg]	43.1 [L/1.2 m^2]
V3	72.8 [L/40 kg]	81.5 [L/1.2 m^2]
CL	29.5 [L/hr/40 kg]	20.28 [L/hr/1.2 m^2]
Q2	5.1 [L/hr/40 kg]	5.7 [L/hr/1.2 m^2]
Q3	175.0 [L/hr/40 kg]	73.2 [L/hr/1.2 m^2]
Inter-individual variability		
V1 [%]	106	26
V2 [%]	75	27
V3 [%]	57	45
CL [%]	81	32
Q2 [%]	87	74
Q3 [%]	109	47
ε1 [%]	45	16.7
ε2 [ng/ml]	0.39	1.3
SN38		
V4	498 [L]	408 [L]
V5	71600 [L] [1]	71600 [L] [1]
CL4	641 [L/hr]	712 [L/hr]
Q5	1530 [L/hr] [1]	1530 [L/hr] [1]
Inter-individual variability		
V4 [%]	98	89
V5 [%]	75 [1]	59
CL4 [%]	85	58
Q5 [%]	77 [1]	56
ε3 [ng/ml]	5.7	0.56

[1]1: Estimates for V5 and Q5 were fixed to typical values obtained by Xie et al., 2002.

- PK parameter estimates in the pediatric population are close to those obtained by Xie et al. in adults, particularly CL for irinotecan and SN38.
- Estimates of compartment volumes for irinotecan show some differences from the estimates obtained by Xie et al., although the Vss (V1+V2+V3) was similar (Vss=158.1 L for pediatrics and 168.6 L for the adults).
- Variability estimates are comparable for both groups and emphasize the substantial variability in PK of irinotecan as well as SN38 both in pediatrics and adult patients.

PK-PD analysis of irinotecan exposure vs. diarrhea relationship

Relationship between AUC of irinotecan/SN38 and incidence of severe diarrhea:
Diarrhea is the major dose-limiting non-hematologic toxicity of irinotecan. Following irinotecan treatment, diarrhea can be acute, occurring early and accompanied by cholinergic symptoms such as cramps, diaphoresis, salivation etc. It is short-lasting and rapidly suppressed by atropine. Late onset diarrhea can also occur, usually after the third day following irinotecan treatment, and tends to be unpredictable and severe. Thus there is a need to understand the pathophysiology of this late-onset diarrhea and its relationship to exposure to irinotecan and/or its metabolites. There are several mechanisms postulated for the occurrence of late-onset diarrhea (Saliba et al., J Clin Oncol 16:2745-51, 1998). Secretory diarrhea occurs when there is abnormal ion transport in the intestinal epithelial cells resulting in increased excretion of electrolytes (including Na+) and fluids. Exudative diarrhea occurs when there is disruption of the integrity of the intestinal mucosa, leading to protein loss, mucus and blood in stools. Another type of late-onset diarrhea occurs when there are abnormalities in GI motility (deranged motility diarrhea). In the case of irinotecan, diarrhea is thought to be secretory with an exudative component, due to the presence of watery stools accompanied with loss of alpha-1-antitrypsin, and also because irinotecan-induced diarrhea is treatable with loperamide, which has anti-secretory properties.

Studies examining the relationship between exposure to irinotecan or SN38 and diarrhea have yielded inconsistent findings, with some studies showing a significant relationship between irinotecan AUC and/or SN38 exposure and incidence of severe diarrhea, and other studies failing to determine a significant relationship. Some of the reasons for this inconsistency include: 1) variability in the ratio of AUCs of SN38 to SN38G (the biliary index) which reflects the SN38 concentrations in the bile. High ratios have been correlated with a higher incidence of severe diarrhea in some, but not all studies. 2) Inter-individual differences in local GI beta-glucuronidase activity, which would in turn reflect the degree of breakdown of SN38G in the GI tract back to the more active (and presumably toxic) metabolite SN38.

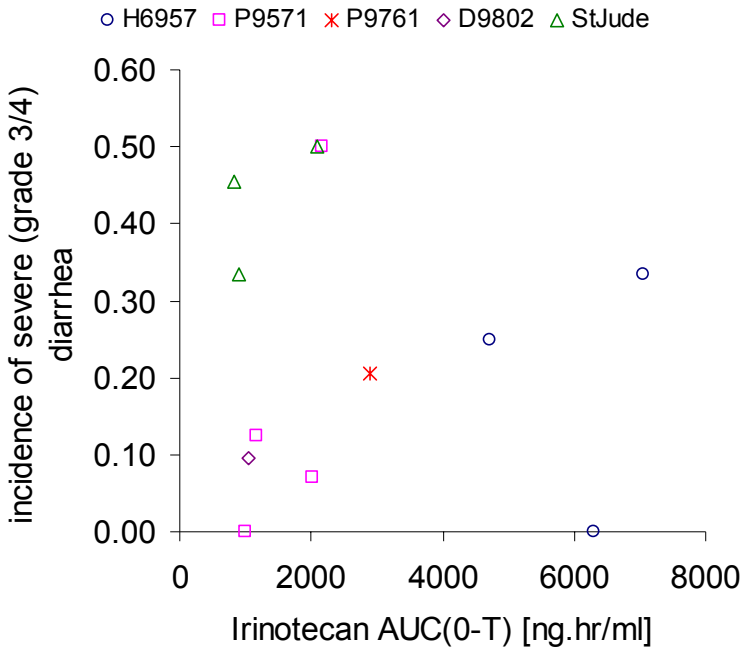
In all the studies included in the submission, treatment with atropine and/or loperamide was started for patients depending on the timing of symptoms relative to drug administration.

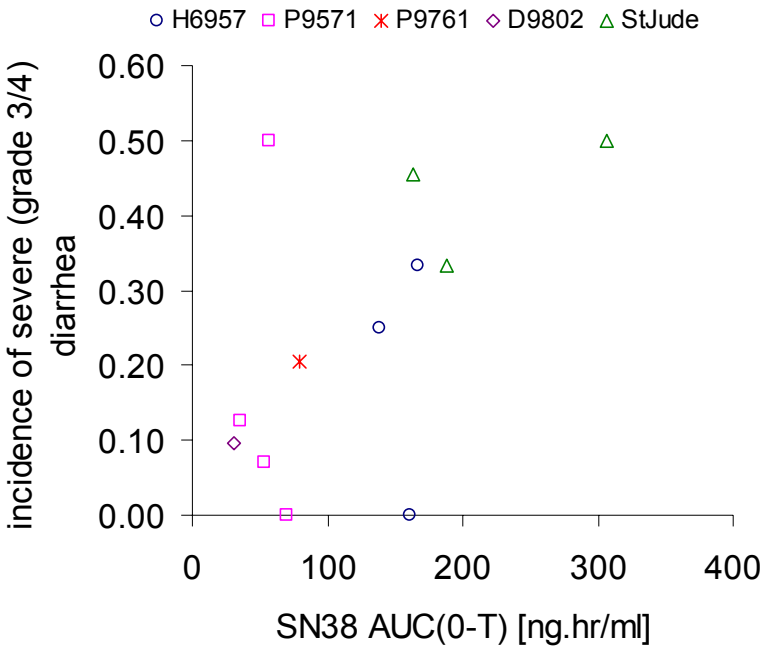
Figure PM-5 shows the incidence of severe diarrhea plotted as a function of mean AUC of irinotecan and mean AUC of SN38. The data are obtained from the PK data and safety data following different doses and regimens in the phase 1 and phase 2 studies included in the

submission (H6957, P9571, P9761, P9871 and D9802). Data from the STJUDE study were not included since all concentrations were measured as the lactone. The AUCs are from 0 to the last measured time point, since terminal slopes and extrapolation to infinity could not be obtained adequately for some studies.

The plots suggest a trend for a higher incidence of diarrhea with higher exposure (AUC), particularly for SN38. Two of the treatments included in this plot showed zero incidences of diarrhea. These are both obtained from the phase 1 studies which had relatively small numbers of patients per dose level, and are most likely not representative of the incidence of diarrhea usually seen with this drug.

Figure PM-5: Scatter-plots of incidence of severe (grade 3 or 4) diarrhea vs. mean AUC of irinotecan (upper panel) and mean AUC of SN38 (lower panel).





Estimation of exposure (AUC) for patients who did not have PK evaluation:
Across the 6 studies, only 122 of 267 subjects had PK evaluations and estimates of AUCs. In order to examine the relationship between exposure and diarrhea in the entire sample, the objective was to estimate (impute) AUCs for the remainder of the sample. Unfortunately, the PK model for SN38 did not result in a covariate model for clearance that could be used to impute SN38 clearance (see figure PM-3) and hence AUC for the patients in whom PK data was not collected.

Exposure-response preliminary analysis:
Logistic regression was used to examine the relationship between incidence of severe diarrhea and exposure to irinotecan and SN38, using AUCs derived from individual estimates of SN38 clearance obtained from the final fit of the population PK model for SN38. This analysis could only be conducted in the patients who had observed concentrations (n=122). This analysis did not show a significant relationship between SN38 AUC and incidence of diarrhea (p=0.245), probably due to the limitations of including only those patients with PK evaluations.

An attempt was made to model the entire dataset using SN38 AUCs imputed from the population mean SN38 clearance for patients who did not have PK evaluations. However, this analysis also did not yield significant results.

PK-PD analysis of irinotecan exposure vs. neutropenia relationship

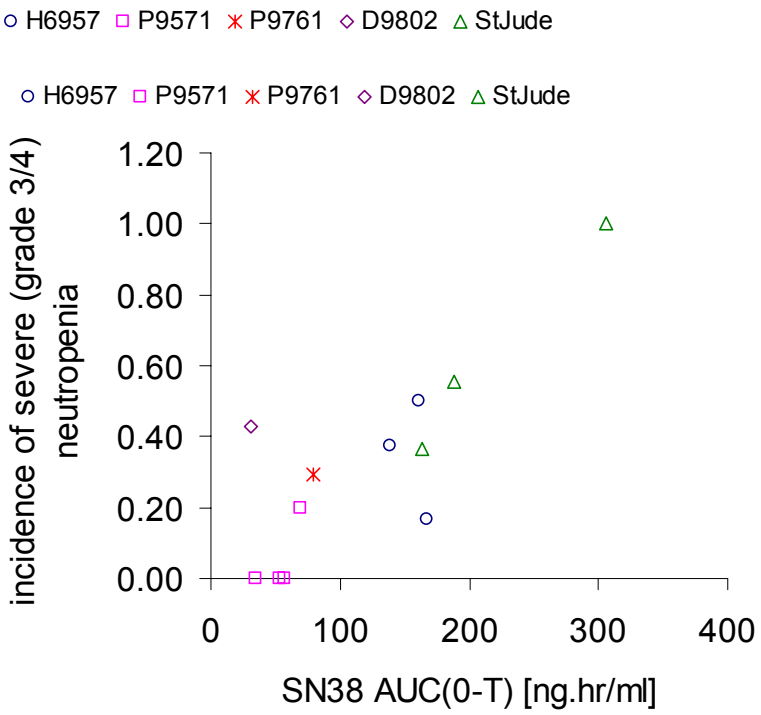
Relationship between AUC of irinotecan/SN38 and incidence of severe neutropenia:
Myelosuppression is commonly seen following treatment with irinotecan and results in neutropenia, leukopenia and anemia. Neutropenia is the major hematologic toxicity associated with irinotecan, and is commonly seen in 13% to 66% of patients on irinotecan either as a single

agent or in combination with 5-FU (package insert). In some cases, neutropenia is associated with infections and fever. Studies examining the relationship between exposure to irinotecan or SN38 and neutropenia have yielded inconsistent findings, with some studies showing a significant relationship between irinotecan AUC and/or SN38 exposure and incidence of severe grade 3 / 4 neutropenia, and other studies failing to determine a significant relationship. In all the studies included in the submission, patients were treated with G-CSF as well as with antibiotics in cases of infection.

Figure PM-6 shows the incidence of severe neutropenia plotted as a function of mean AUC of irinotecan and mean AUC of SN38. The data are obtained from the PK data and safety data following different doses and regimens in the phase 1 and phase 2 studies included in the submission (H6957, P9571, P9761, P9871 and D9802). Data from the STJUDE study were not included since all concentrations were measured as the lactone. The AUCs are from 0 to the last measured time point, since terminal slopes and extrapolation to infinity could not be obtained adequately for some studies.

The plots suggest a trend for a higher incidence of neutropenia with higher exposure (AUC) to SN38.

Figure PM-6: Scatter-plots of incidence of severe (grade 3 or 4) neutropenia vs. mean AUC of



irinotecan (upper panel) and mean AUC of SN38 (lower panel).

Estimation of exposure (AUC) for patients who did not have PK evaluation:

As described above in the diarrhea analysis, across the 6 studies, only 122 of 267 subjects had PK evaluations and estimates of AUCs. Since the PK model for SN38 did not result in a covariate model for clearance, the SN38 clearance and hence AUC could not be imputed for the patients in whom PK data was not collected.

Exposure-response preliminary analysis:
Logistic regression was used to examine the relationship between incidence of severe neutropenia and exposure to irinotecan and SN38, using AUCs derived from individual estimates of SN38 clearance obtained from the final fit of the population PK model for SN38. This analysis could only be conducted in the patients who had observed concentrations (n=122). This analysis did not show a significant relationship between SN38 AUC and incidence of severe neutropenia (p=0.435), probably due to the limitations of including only those patients with PK evaluations.

An attempt was made to model the entire dataset using SN38 AUCs imputed from the population mean SN38 clearance for patients who did not have PK evaluations. However, this analysis also did not yield significant results.

DISCUSSION

The objectives of this analysis were to characterize the PK of irinotecan and its metabolites in pediatric solid tumor patients and to examine the relationship between irinotecan (or its active metabolite SN38) exposure and the incidence of sever toxicity including diarrhea in this population.

The PK of irinotecan was best described by a 3-compartment model for irinotecan and a 2-compartment model for SN38. The final model parameters for irinotecan are consistent with estimates published for irinotecan in adult solid tumor patients (table PM-III), when normalized for body size. The main difference between the published parameters and the current parameters in children is the main covariate of the PK parameters. In the pediatric data, the parameters are all functions of body weight (with an exponent), while in adults, parameters were determined to be functions of body surface area, and were expressed per m^2. After accounting for body size, none of the other covariates examined (gender, age, prior treatments) was found to have a significant effect on the PK parameters.

There was a large degree of inter-individual variability in parameter estimates for both irinotecan and SN38. The parameters for SN38 were not as well estimated, compared to irinotecan, possibly due to the limited duration of PK sampling in most studies. Samples were collected for no more than 25 hours post-start of infusion, with sample collection for 7 to 13 hours post-start of infusion for most studies. The large inter-individual variability in SN38 PK is also probably related to the large interindividual variability in glucuronidation rates in the liver.

Due to the large inter-individual variability in clearance and the lack of a significant covariate model for clearance, the AUC could not be computed reliably for patients in whom PK was not performed. This was a major limitation in conducting an exposure-response relationship for

severe diarrhea and for severe neutropenia. A preliminary analysis of the mean data does suggest a relationship between SN38 exposure and incidence of grade 3/4 diarrhea or neutropenia, however, this will have to be verified in larger studies with PK sampling in all patients. Also, it might be more efficient to have samples in the terminal phase of SN38 elimination.

In summary, the goal of this analysis was to evaluate the PK and exposure-response relationship for irinotecan and its metabolite SN38. Knowledge of the PK as well as PK-PD relationship for irinotecan (and SN38) would aid in dose-selection for future pediatric trials with irinotecan and also aid in understanding the variability of irinotecan pharmacokinetics.

CONCLUSIONS:

The proportion of pediatric patients with grade 3 and 4 diarrhea seems to increase with an increase in SN38 AUC. This is in accordance with data in adult patients. Conclusive identification of such a relationship is very important in "optimal" use of this drug. The Agency recommends that the applicant conduct sparse PK sampling to ensure reliable estimation of SN38 AUC in all future studies. The collected data should be analyzed to examine the exposure-response relationship for measures of toxicity of irinotecan.

APPENDIX 1 TO PHARMACOMETRICS REPORT

NONMEM CONTROL STREAM FOR FINAL MODEL

```
THETA:      V1          V2          V3          CL          Q2
Q3          CL4         Q5          V4          V5
CLCOEFF
ETA:        V1          V2          V3          CL          Q2
Q3          CL4         Q5          V4          V5
ERR:        CEXP        CADD        SNADD
cptsnped_8_wt7b.out 12015.686 eval=224 sig=+3.3 sub=109 obs=1774
CCIL=NNNN NV1.0 PIV1.0
THETA     = 6.36c       78.9c       72.8c       29.5c       5.1c
175c        641         1530c       498         71600c
0.46c
ETASD     = 1.06301c    0.754983c   0.574456c   0.806226c
0.87178c    1.09087c    0.984886    0.748331c   0.851469
0.768115c
ERRSD     = 0.447214c   0.387298c   5.76194
THETA:se% = 0.0c        0.0c        0.0c        0.0c        0.0c
0.0c        29.3        0.0c        21.3        0.0c        0.0c
OMEGA:se% = 0.0c        0.0c        0.0c        0.0c        0.0c
0.0c        58.2        0.0c        57.5        0.0c
SIGMA:se% = 0.0c        0.0c        34.9
```

```
MINIMIZATION SUCCESSFUL

   user 9:54.79     real 9:54.79   tcl 0:3.02

;CPT-11 pediatric supplement
;Model base model, 3 comp for cpt-11 and 2cpt for SN-38
;Project Name: cpt-11
$PROB RUN# 20211
$INPUT ID TIME AMT RATE CMT DV MDV AGE SEX DROP=RACE HT WT BSA
PSUR PRAD PSYS ECOG
 HPRE STDY PID
$DATA ..\all_nmpk3_8.csv IGNORE=#
$SUBROUTINES ADVAN5 TRANS1
$MODEL COMP
       COMP
       COMP
       COMP
       COMP


$PK

TVV1=THETA(1)
V1=TVV1*EXP(ETA(1))
S1=V1

TVV2=THETA(2)*(WT/40)
V2=TVV2*EXP(ETA(2))

TVV3=THETA(3)*(WT/40)
V3=TVV3*EXP(ETA(3))

TVCL=THETA(4)*(WT/40)**THETA(11)
CL=TVCL*EXP(ETA(4))

TVQ2=THETA(5)
Q2=TVQ2*EXP(ETA(5))

TVQ3=THETA(6)*(WT/40)
Q3=TVQ3*EXP(ETA(6))

CL14=CL

TCL4=THETA(7)
CL4=TCL4*EXP(ETA(7))

TVQ5=THETA(8)
```

```
Q5=TVQ3*EXP(ETA(8))

TVV4=THETA(9)
V4=TVV4*EXP(ETA(9))
S4=V4

TVV5=THETA(10)
V5=TVV5*EXP(ETA(10))

K14 = CL/V1
K12 = Q2/V1
K21 = Q2/V2
K13 = Q3/V1
K31 = Q3/V3
K40 = CL4/V4
K45 = Q5/V4
K54 = Q5/V5


$ERROR

 IND1=0
 IND2=0
 IF (CMT.EQ.1) IND1=1
 CPT=A(1)/S1
 IF (CMT.EQ.4) IND2=1
 SN=A(4)/S4

 Y=(CPT*EXP(ERR(1)) + ERR(2))*IND1 + (SN + (ERR(3)))*IND2


$THETA (6.36 FIX)     ;V1 ; L
$THETA (78.9 FIX)     ;V2 ; L
$THETA (72.8 FIX)     ;V3 ; L
$THETA (29.5 FIX)     ;CL ;L/h
$THETA (5.1  FIX)     ;Q2 ;L/h
$THETA (175  FIX)     ;Q3 ;l/h
$THETA (0, 570  )     ;CL4;L/h
$THETA (1530 FIX)     ;Q5 ;L/h Karlsson estimate
$THETA (0, 500  )     ;V4 ;L
$THETA (71600 FIX)    ;V5 ;L Karlsson estimate
$THETA (0.46 FIX)     ;CLCOEFF


$OMEGA
1.13 FIX   ;V1
0.57 FIX   ;V2
```

```
0.33 FIX   ;V3
0.65 FIX   ;CL
0.76 FIX   ;Q2
1.19 FIX   ;Q3
0.4        ;CL4
0.56 FIX   ;Q5
0.5        ;V4
0.59 FIX   ;V5


$SIGMA
0.2 FIX   ;     CEXP ONENTIAL component
0.15 FIX  ;     CADD ITIVE COMPONENT
0.25      ;     SNADD ITIVE COMPONENT


$EST METH0 MAXEVAL=999 PRINT=1 POSTHOC NOABORT MSF=100.MSF

$COVARIANCE


$TABLE ID TIME CMT AMT DV V1 V2 V3 CL Q2 Q3 V4 V5 CL4 Q5 WT BSA
AGE PID
STDY ETA(1) ETA(2) ETA(3) ETA(4) ETA(4) ETA(5) ETA(6) ETA(7)
ETA(8) ETA(9)
ETA(10) Y NOPRINT ONEHEADER FILE=cptsnped_8_wt7b.fit
```

APPENDIX 2 TO PHARMACOMETRICS REPORT

EDR files used in the analysis (Feb 13, 2004 submission):

Path \\cdsesub1\n20571\s_021\2004-02-13\crt\datasets

Folder: CPTAIV_0020_452: Filenames:	pk_9871.xpt
Folder: CPTAIV_0020_453: Filenames:	pk_jude.xpt
Folder: M_6475_056: Filenames:	pk_9571.xpt
Folder: X44OE_ONC_0020_207: Filenames:	pk_9571.xpt
Folder: X44OE_ONC_0020_222: Filenames:	pk_9761.xpt
Folder: X98_6475_178: Filenames:	pk_6957.xpt

EDR files used in the analysis (March 31, 2004 submission):

Path \\cdsesub1\n20571\s_021\2004-03-31\crt\datasets

Folder: 6957:	filenames:	ae.xpt, Demo.xpt, Vitals.xpt, Lab.xpt
Folder: 9571:	filenames:	ae.xpt, Demo.xpt, Vitals.xpt, Lab.xpt
Folder: 9761:	filenames:	ae.xpt, Demo.xpt, Vitals.xpt, Lab.xpt
Folder: 9802:	filenames:	ae.xpt, Demo.xpt, Vitals.xpt, Lab.xpt
Folder: 9871:	filenames:	ae.xpt, Demo.xpt, Vitals.xpt, Lab.xpt
Folder: jude:	filenames:	ae.xpt, Demo.xpt, Vitals.xpt, Lab.xpt

D. Pediatric Written Request

The following table summarizes the elements of the Written Request and information from the studies submitted by the applicant.

Elements of Written Request	H6957	P9571	P9871	St. Jude	P9761	D9802
Phase 1	Yes	Yes	Yes	Yes	No	No
Phase 2	No	No	No	No	Yes	Yes
Sample sizes (N=18-25 for phase 1 and N>=14 for phase 2 studies)	16	33	9	22	170	21
Indication(s) (solid tumors or rhabdomyo-sarcoma)	Pediatric solid tumors	Pediatric solid tumors	Pediatric solid tumors	Pediatric solid tumors	Pediatric solid tumors	Previously untreated metastatic rhabdomyo-sarcoma
Age groups (Infants>1 mo - adolescents) 1 mo - < 2 y 2 y - < 12 y 12 y - < 16 y > 16 y	 - 10 (62.5%) 2 (12.5%) 4 (25.0%)	 2 (6.1%) 18 (54.5%) 5 (15.2%) 8 (24.2%)	 - 2 (22.2%) 3 (33.3%) 4 (44.4%)	 1 (4.5%) 9 (40.9%) 7 (31.8%) 5 (22.7%)	 4 (2.4%) 99 (58.2%) 37 (21.8%) 30 (17.6%)	 3 (14.3%) 4 (19.0%) 7 (33.3%) 7 (33.3%)
Endpoints: -MTD -PK parameters (CL, V) -efficacy (response rates)	 Yes Yes -	 Yes Yes -	 Yes Yes -	 Yes Yes -	 - Yes Yes	 - Yes Yes
Drug information IV regimen	125, 160, 200 mg/m^2 weekly x4 q6wks	30, 39, 50, 65 mg/m^2 daily x5 q3wks	30, 50, 100, 130 mg/m^2 daily x5 q3wks	20, 24, 29 mg/m^2 daily x5, x2 q3wks	50 mg/m^2 daily x5 q3wks	20 mg/m^2 daily x5 x2 q3wks
Evaluation of safety concerns -diarrhea, neutropenia -PK interaction with anticonvulsants	 Yes -	 Yes -	 Yes Yes	 Yes Yes	 Yes Yes	 Yes Yes
Statistical information -descriptive	 Yes	 Yes	 Yes	 Yes	 Yes	 Yes

H. E. CPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-571	**Brand Name**	Camptosar
OCPB Division (I, II, III)	DPE-I	**Generic Name**	Irinotecan HCL
Medical Division	HFD-150	**Drug Class**	Topoisomerase I inhibitor
OCPB Reviewer	Roshni Ramchandani	**Indication(s)**	(Pediatric Exclusivity Determination)
OCPB Team Leader	Atiqur Rahman	**Dosage Form**	IV Injection
		Dosing Regimen	-
Date of Submission	Dec 22, 2003	**Route of Administration**	Intravenous
Estimated Due Date of OCPB Review	May 17, 2004	**Sponsor**	Pfizer Pharmaceuticals Group
PDUFA Due Date	June 26, 2004	**Priority Classification**	P
Division Due Date	June 4, 2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			3 Publications cited. 1 study report previously submitted.
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	4		**4 phase 1 studies (safety and PK) using different regimens:** • 90 min infusion weekly x4 q6wks (n=16) • 60 min infusion daily x5 q3wks (n=33) • 60 min infusion daily x5 q3wks (n=9) • 60 min infusion daily x5 for 2 wks q3wks (n=22)

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	2		2 phase 2 studies (tumor response rates, safety, PK) using 2 different regimens: • 50 mg/m^2 as 60 min infusion daily x5 q3wks (n=170) • 20 mg/m^2 as 60 min infusion daily x5 for 2 wks q3wks (n=21)
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
Solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**6**		

Filability and QBR comments		
	"X" if yes	*Comments*
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. Raw PK data (concentration, time) provided in appendix of study reports (PDF). Requesting data to be sent in XPT format.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	Roshni Ramchandani	
Secondary reviewer Signature and Date	Atiqur Rahman	

CC: NDA 20-571, HFD-850 (Electronic Entry), HFD-150 (Atkins),
HFD-860 (Rahman, Mehta, Sahajwalla), CDR (Biopharm)

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

/s/

Roshni Ramchandani
6/17/04 12:23:25 PM
BIOPHARMACEUTICS

Brian Booth
6/17/04 04:29:26 PM
BIOPHARMACEUTICS

Jogarao Gobburu
6/18/04 01:32:14 PM
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