CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-981

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	20-981/N-000
BRAND NAME:	Hycamtin
GENERIC NAME:	Topotecan Hydrochloride
DOSAGE FORM/ STRENGTH:	0.25 mg and 1 mg capsules for Oral Administration
INDICATION:	Relapsed Small Cell Lung Cancer
SUBMISSION DATES:	11-Apr-, 10-Jul-, 02-Aug-, 09-Aug-, and 14-Aug-2007
SUBMISSION TYPE:	NDA-Original, 1P
APPLICANT:	GlaxoSmithKline
DDOP:	Division of Drug Oncology Products
OCPB DIVISION:	Division of Clinical Pharmacology 5
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1. EXECUTIVE SUMMARY

The Applicant seeks approval for the use of Oral Hycamtin (Topotecan Hydrochloride) Capsules for the treatment of patients with relapsed small cell lung cancer (SCLC) in accordance with Section 505(b)(1) of 21CFR 314.50.

In support of the use of Oral Hycamtin in the SCLC indication, the Applicant submitted a pivotal Phase 3 study **(Study 478)** comparing the overall survival of topotecan plus best supportive care (BSC) to BSC in 141 SCLC patients. In this study, patients were randomized (1:1) to receive either oral topotecan 2.3 mg/m^2 once daily plus BSC for 5 consecutive days every 21 days or BSC alone. The results demonstrated that oral topotecan was associated with a statistically significant improvement in overall survival compared to BSC (p=0.0104). Median survival was 25.9 weeks for oral topotecan and 13.9 weeks for BSC.

The two supportive clinical **Studies 065** and **396** compared oral topotecan to intravenous (IV) topotecan in patients with relapsed SCLC. In both studies, topotecan was administered either orally at a dosage of 2.3 mg/m^2 once daily for 5 days or intravenously (IV) at a dosage of 1.5 mg/m^2 once daily over 30 minutes for 5 days. The overall response rate (complete plus partial responses) was the primary clinical endpoint in both studies.

In Study 065, the overall response rate was 23% for oral topotecan and 15% for IV topotecan.

In Study 396, the overall response rate was 18% for the oral route and 22% for IV topotecan.

Based on an absolute bioavailability value of 40% for oral topotecan, the oral dose that matches the AUC of IV topotecan should be 3.91 mg/m^2. The highest dose studied in the Phase 1, dose-escalation Study 049 was 2.7 mg/m^2. The maximum tolerated dose (MTD) of 2.3 mg/m^2 determined in Study 049 was used in the clinical Studies 476, 065, and 396.

Exposure ($AUC_{0-\infty}$) of topotecan lactone, the pharmacologically active moiety, was about 10% and 20% higher in patients with mild (creatinine clearance (CrCL)=50-80 mL/min) and moderate (CrCl=30-49 mL/min) renal impairment, respectively, than in patients with normal renal function (CrCl > 80 mL/min) ($p < 0.05$). Based on this data, no dosing adjustment is needed in patients with mild renal impairment when treated with oral topotecan. However, oral topotecan dose should be reduced to 1.8 mg/m^2 when given to patients with moderate renal impairment. Insufficient data are available in patients with severe renal impairment (CrCL < 30 mL/min) to provide a dosage recommendation for Hycamtin.

1.1 RECOMMENDATION

The Supplemental NDA 20-981/N-000 submitted for the use of Oral Hycamtin Capsules for the treatment of patients with relapsed small cell lung cancer is acceptable from the clinical pharmacology perspective. The Applicant should incorporate the Clinical Pharmacology labeling recommendations as outlined in Section 3 of this review.

Please forward the above Recommendation, the general Comment below and the clinical pharmacology recommendation outlined on pp. 38 of this review to the Applicant.

1.2 PHASE 4 COMMITMENTS

[None]

GENERAL COMMENT

Please provide information on the potential of oral topotecan to prolong QT/QTc interval (see ICH E14).

1.3 SUMMARY OF CLINICAL PHARMACOLOGY

Topotecan hydrochloride, a semisynthetic analog of camptothecin, is an inhibitor of topoisomerase I. Topoisomerase I is a cellular enzyme involved in maintaining the topographic structure of DNA during translation, transcription, and mitosis.

The FDA approved **Hycamtin for Injection** as a single agent on 28-May-1996 under NDA 20-671 for the treatment of patients with *metastatic carcinoma of the ovary* after failure of initial or subsequent chemotherapy and on 30-Nov-1998 (NDA 20-671/S-004) for the treatment of patients with small cell lung cancer (SCLC) sensitive disease after failure of first-line chemotherapy. The approved dose is 1.5 mg/m^2 given intravenously over 30 minutes once daily for 5 consecutive days of every 21 days.

The Applicant developed a new oral dosage form of Hycamtin. The proposed indication of **Oral Hycamtin** is for the treatment of patients with relapsed SCLC. The proposed dosage is 2.3 mg/m^2 given orally once daily for 5 consecutive days every 21 days. Oral Hycamtin is to be marketed as 0.25 mg and 1 mg hard gelatin capsules for oral administration.

It is noted that based on an absolute bioavailability of 40% for oral topotecan, the oral topotecan dose that matches the AUC of the approved IV dose should be 3.91 mg/m^2. However, because of the toxicity observed, the highest dose administered in the Phase 1, dose-escalation Study 049 was 2.7 mg/m^2. The maximum tolerated dose (MTD) of 2.3 mg/m^2 determined in Study 049 was used in the clinical Studies 476, 065, and 396.

In the original NDA for Hycamtin for Injection, topotecan was found to undergo a pH-dependent reversible hydrolysis of the E-ring lactone, yielding a dihydroxycarboxylic acid (topotecan carboxylate). Only the lactone form of the drug, which is the predominant form in an acidic environment, is pharmacologically active. Under physiological conditions (pH 7.4), hydrolysis of the lactone ring of topotecan to the inactive hydroxy acid is favored. Topotecan is 35% bound to human plasma proteins. Topotecan is primarily cleared renally, with a minor component metabolized to the N-desmethyl metabolite. Topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide were detected in the urine. Mean total topotecan recovery was approximately 68.7% (50.8% urinary and 17.9% fecal) in 4 cancer patients over 9 days. Topotecan is not a substrate, inhibitor, or inducer of any CYP450 enzyme(s).

The key clinical pharmacology findings for the current NDA 20-981 for Oral Hycamtin are summarized below:

- Topotecan is rapidly absorbed following oral administration with a peak plasma concentration reached in a median T_{max} of 1 to 2 hours after dosing in the fasted state.
- The absolute bioavailability (F) of oral topotecan (as total or lactone) was about 40%. This relatively low value for F is primary due to the effect of the gut efflux transporters, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).
- Bioequivalence was demonstrated between the to-be-marketed 1.0 mg capsule and the clinical 1.0 mg capsule.

- Following a high-fat meal, the extent of exposure was similar in the fed and fasted state, while T_{max} was delayed from 1.5 to 3.0 hours (topotecan lactone) and from 3 to 4 hours (total topotecan). The label will indicate that oral Hycamtin may administered without regard to food.

- The terminal half-life (t½) averaged 4.0 hours for both total topotecan and topotecan lactone.

- The mean C_{max} and AUC of topotecan lactone increased in proportional to dose at 1.2-2.7 mg/m^2 once daily oral Doses.

- No accumulation of topotecan with once daily oral dosing was noted.

- The urinary excretion of total topotecan over 9 days averaged 20.4±7.5% of the oral dose compared to 50.8±2.8% of the intravenous dose.

- A cross-study analysis of data collected from 217 patients with advanced solid tumors in the studies submitted in this NDA indicated that age or gender has no effect on the exposure [$AUC_{0-\infty}$ and C_{max}] of oral topotecan.

- A cross-study analysis of data collected from 217 patients with advanced solid tumors indicated that exposure ($AUC_{0-\infty}$) of topotecan lactone, the pharmacologically active moiety, was 10% and 20% higher in patients with mild (creatinine clearance (CrCL=50-80 mL/min) and moderate renal (CrCL=30-49 mL/min) impairment, respectively, than in patients with normal renal function (CrCL > 80 mL/min) ($p < 0.05$). Based on this analysis, no dosing adjustment is needed in patients with mild renal impairment when treated with oral topotecan. However, oral topotecan daily dose should be reduced to 1.8 mg/m^2 when given to patients with moderate renal impairment. Insufficient data are available in patients with severe renal impairment (CrCL < 30 mL/min) to provide a dosage recommendation for Hycamtin.

- The effect of hepatic impairment on the PK of **Oral Hycamtin** has not been evaluated. Patients with SCLC who participated in oral topotecan clinical studies had serum bilirubin of ≤ 2 mg/dL. In a population PK analysis by Leger et al. 2004, no liver function test (e.g., serum bilirubin, ALT, AST) was found to significantly affect the PK of total topotecan. No dosage adjustment appears to be required for patients with impaired hepatic function (serum bilirubin of ≤ 2 mg/dL) when treated with oral topotecan.

- Topotecan is a substrate for both efflux transporters, P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2).

- Co-administration of the BCRP (ABCG2) and P-gp (ABCB1) inhibitor, elacridar at doses of 100 to 1000 mg simultaneously with, or one hour before oral topotecan (2.0 mg/m^2) increased the absolute bioavailability of topotecan lactone and total topotecan by 2.5-fold in 15 patients with advanced solid tumors.

- Co-administration of oral cyclosporin A (15 mg/kg), an inhibitor of ABCB1 (P-gp) four hours before oral topotecan (2.0 mg/m^2) increased the dose-normalized AUC_{0-24} of topotecan lactone and total topotecan by 2.0-fold compared to oral topotecan alone (2.3 mg/m^2) in 7-10 patients with advanced solid tumors.

- The exposure for both total topotecan and topotecan lactone was generally unchanged when oral topotecan (2.3 mg/m^2 once daily for 5 days) was co-administered with rantidine (150 mg twice daily for 4 days) in 13 patients with advanced solid tumors.

- There was a trend towards an increased exposure (Dose-normalized AUC and C_{max}) for both total topotecan and topotecan lactone when cisplatin (75 mg/m^2 single IV dose) was administered before oral topotecan (0.75-2.3 mg/m^2 once daily doses) on Day 1 (C→ T, N=22) as compared to its administration after oral topotecan on Day 5 (T→C, N=38). However, the increase in exposure was small and did not reach statistical significance.

- Significant correlations were observed between the percent of decrease of leukocytes and AUC_{0-t} on Day 1 and AUC_{0-t} per course for topotecan lactone following oral topotecan dosing ($p < 0.05$) (published data).

2 QUESTION BASED REVIEW

Refer to the NDA 20-671 (Hycamtin for Injection), submitted on 21-Dec-1995 for the following un-highlighted questions.

2.1 General Attributes of the Drug

2.1.1 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?

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

For the mechanism of action, refer to the original NDA for Hycamtin for Injection (NDA 20-671, Submission of 21-Dec-1995). The current NDA 20-981 proposes to use Oral Hycamtin for the treatment of patients with relapsed small cell lung cancer (SCLC). It is estimated that 35,000 new cases of SCLC are diagnosed annually in the US, with an associated mortality of 27,000. The median survival of untreated patients is generally 2-4 months. Eventually > 90% of patients will relapse. The prognosis is particularly poor for **"resistant" disease patients** (who relapse **≤ 90 days from the end of prior therapy) compared with "sensitive" disease** patients (who relapse > 90 days from prior therapy). The median survival of patients with sensitive disease is generally about 25 weeks and that of resistant disease patients 16-21 weeks. The current therapy for the treatment of relapsed SCLC sensitive disease in the US is Hycamtin for Injection, which administered intravenously for 5 consecutive days every 21 days. It is the only single-agent therapy approved for this indication.

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

The proposed dosage of Oral Hycamtin is 2.3 mg/m^2 administered once daily for 5 consecutive days every 21 days.

2.2 *General Clinical Pharmacology*

2.2.1 What are the design features of the clinical studies used to support dosing or claims?

The Applicant conducted single- and repeated dose pharmacokinetics (PK) Phase 1 Studies 048 and 049 for oral topotecan in patients with advanced solid tumors. The potential for drug-drug interactions of oral topotecan with ranitidine, cyclosporin A, and elacridar were examined in the Phase 1 Studies 118, 507, and BCR1001, respectively. The sequence-dependent effects of oral topotecan in combination with cisplatin were investigated in Phase 1 Study 101.

The bioequivalence of the commercial 1 mg capsule formulation of oral topotecan relative to the Phase 3 clinical 1 mg capsule formulation and the effect of food were investigated in Study 692. All of these Phase 1 studies were conducted in patients with advanced solid tumors. In a Phase 2 study, the PK of oral topotecan at 2.3 mg/m^2/day in 30 patients with NSCLC (Study 204) was assessed. A list of the submitted clinical pharmacology studies in support of this NDA is provided in Table 1.

TABLE 1. Clinical Pharmacology Studies in Support of this NDA

Study Number	Study Objectives	N	Dosage Regimen; Route; Duration
048	Oral bioavailability	17	A single oral topotecan 2.3 mg/m^2 dose in fasted state on Day 1 or Day 2 crossed over with a single IV topotecan 1.5 mg/m^2 dose on Day 1 or Day 2 during Cycle 1.
049	MTD and PK	92	**Topotecan at the following dosing regimens:** **21-day twice daily regimen:** 0.15, 0.3, 0.4, 0.5, and 0.6 mg/m^2 BID for 21 days every 28 days; **10-day twice daily regimen:** 0.5, 0.6, 0.7, and 0.8 mg/m^2 BID for 10 days every 21 days; **10-day once daily regimen:** 0.6, 1,4, 1.6 mg/m^2/day for 10 days every 21 days; **5-day once daily regimen:** 1.2, 1.8, 2.3, 2.7 mg/m^2/day for 5 days every 21 days.
101	PK, and sequence dependence with cisplatin	C→T 22 T→C 38	**Part 1: C→T;** Single-dose Cisplatin 75 mg/m^2 as a 3-hour infusion on Day 1 followed immediately by escalating doses of oral topotecan (0.75-2.0 mg/m^2/day for 5 days every 21 days) in Cycle 1 or **T→C;** Escalating doses of oral topotecan (0.75-2.0 mg/m^2/day for 5 days every 21 days) followed by a single-dose cisplatin 75 mg/m^2 as a 3-hour infusion on Day 5 every 21 days in Cycle 2.

118	PK in presence or absence of ranitidine	18	**Topotecan** 2.3 mg/m^2 day for 5 days every 21 days without ranitidine (Regimen A) or with **oral Ranitidine** 50 mg twice daily for 4 days prior to topotecan (Regimen B); crossover between Regimens A and B during Courses 1 and 2.
507	PK in presence or absence of cyclosporin A	14	**Topotecan** 2.3 mg/m^2/day for 5 days every 21 days without cyclosporin A (Regimen A) or **topotecan** 2.0 mg/m^2/day for 5 days every 21 days with **cyclosporin A** 15 mg/kg IV over four hours before topotecan; (Regimen B); crossover between Regimens A and B during Courses 1 and 2.
BCR 10001	PK and sequence dependence with elacridar	Part I 24 Part II 15	**Part I: Topotecan** 2.0 mg on Days 1 Day 8 with **elacridar** simultaneously on Day 1 and elacridar 1 hour prior to topotecan on Day 8 (Sequence A) or oral elacridar 1 hour prior to topotecan on Day 1 and simultaneously on Day 8 (Sequence B) at doses of 100, 300, 500, 700, or 1,000 mg on Day 1 and Day 8. **Part II: Topotecan** 1.0, 1.5, 2.0, 2.5 mg; once daily for 5 days and simultaneous elacridar 100 mg; once daily for 5 days.
692	Bioequivalence of commercial formulation (Process 3) vs. clinical formulation (Process 1); and Food effect	78 BE 26 Food effect	**Bioequivalence (BE): Topotecan** 4 mg current formulation (Regimen A); PO; or 4 mg test formulation (Regimen B); PO; on Day 1 or Day 8. **Food Effect:** Subjects fasted on Day 1 and fed on Day 8, given topotecan 4 mg Regimen B on both days; PO.
204	PK in SCLC patients (Phase 2 study)	30	**Topotecan** 2.3 mg/m^2 for 5 consecutive days every 21 days. Subjects treated until disease progression, unacceptable toxicity, or consent withdrawn.

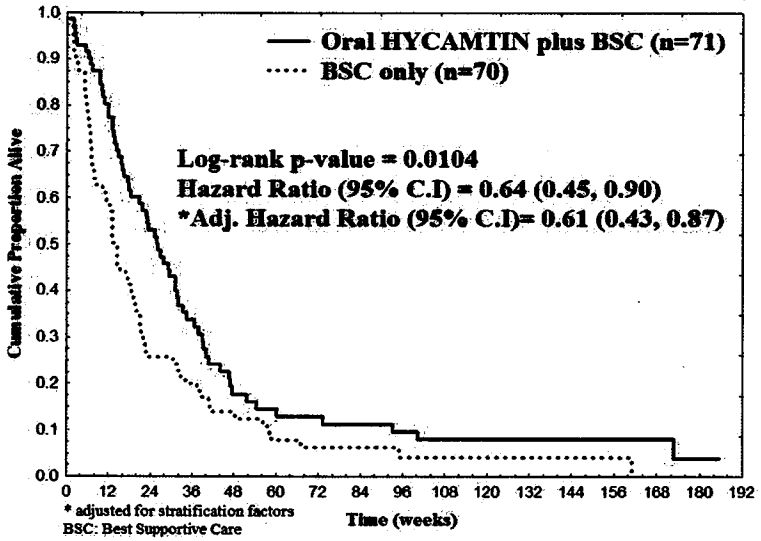
The Applicant also submitted a mass balance/excretion study of oral versus IV topotecan (Study 230). This study was previously submitted and reviewed under NDA 20-671 (SE1-014) on 15-Dec-2005.

In support of the efficacy claim in the relapsed SCLC indication, the Applicant submitted a pivotal Phase 3 study (Study 478) and two supportive Phase 2 and 3 studies (Studies 065 and 396, respectively). A summary of these studies is as follows:

Pivotal Study:

Study 478 compared Oral topotecan to Best Supportive Care (BSC) in patients with relapsed SCLC. This was an open-label, multi-center, randomized, **Phase 3** study in 141 patients. Patients were randomized (1:1) to receive either topotecan 2.3 mg/m^2 orally once daily plus BSC for 5 consecutive days (N=71) every 21 days or BSC alone (N=70). Patients were instructed to take topotecan capsules once daily dose with a glass of water on an empty stomach, preferably in the morning and at least thirty minutes before a meal. The primary clinical endpoint of the study was overall survival, defined as the time from randomization until death. According to the Applicant, this study demonstrated that oral topotecan was associated with statistically significant improvement in overall survival relative to BSC (p=0.0104). Median survival was 25.9 weeks for oral topotecan and 13.9 weeks for BSC. The hazard ratio was 0.64 (95% CI: 0.45, 0.90), indicating a 36% reduction in risk of death by adding oral topotecan to BSC.

FIGURE 1. Plot of Kaplan-Meier Estimates for Overall Survival (Applicant)



Supportive Studies:

Study 065 compared oral topotecan to intravenous (IV) topotecan in patients with relapsed SCLC sensitive disease. This was an open-label, randomized, **Phase 2** study in 106 patients. Patients were randomized (1:1) to receive either oral topotecan capsules (2.3 mg/m^2 once daily for 5 days (N=52) or IV topotecan as a 1.5 mg/m^2 once daily 30-minute infusion for 5 days (N=54); both treatments were repeated every 21 days. Patients were instructed to take topotecan capsules once daily dose with a glass of water on an empty stomach, preferably in the morning and at least thirty minutes before a meal. The primary clinical endpoints were response rate, time-to-response rate, and time-to-progression. According the Applicant, the overall response rate (complete plus partial responses) was 23% (95% CI: 11.6, 34.5) for oral topotecan and **15%** (95% CI: 5.3, 24.3) for IV topotecan. The hazard ratio was 0.9 (95% CI: 0.6, 1.35) indicating a 10% reduction in risk of progression for oral topotecan relative to IV topotecan. It is noted that the overall response rate of IV Hycamtin was lower than that previously observed (**24%**) in 107 patients with SCLC when compared to the cyclophosphamide/docetaxel/vincristine arm.

Study 396 compared oral topotecan versus IV topotecan in patients with SCLC who had relapsed > 90 days after completion of one prior regimen of chemotherapy. This was an open-label, multi-center, randomized, **Phase 3** study in 304 patients. Patients were randomized to receive either oral topotecan 2.3 mg/m^2 once daily for 5 days (N=153) or IV topotecan as a 1.5 mg/m^2 once daily 30-minute infusion for 5 days (N=151); both treatments were repeated every 21 days. Patients were instructed to take all the capsules for that day with a glass of water on an empty stomach, preferably in the morning and at least 30 minutes before a meal. The primary endpoint, response rate, was compared between oral and IV topotecan treatment arms. According to the Applicant, the overall response rates were 18% (28/153) for oral and 22% (33/151) for IV patients. The 95% confidence interval for the difference in the rate of response (oral- IV) (95% CI= -12.5, 5.4).

Based on an oral bioavailability value of 40% for topotecan, the oral dose that matches the AUC of IV Hycamtin should be 3.91 mg/m^2. The highest dose studied in the Phase 1, dose-escalation Study 049 was 2.7 mg/m^2. The MTD determined in this study was 2.3 mg/m^2 given once daily for 5 days which was used in the above clinical studies (478, 065, and 396).

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

TABLE 2. Primary Endpoint(s) in the Pivotal and Supportive Clinical Studies

Study	Primary Endpoint(s)	Definition
478	Overall Survival	Defined as the time from randomization until death.
065	Response Rate, Response Duration, and Time to Progression.	**Response Rate:** the percentage of patients achieving either a complete or partial response (CR or PR). **Complete Response (CR):** Complete disappearance of all known measurable and evaluable disease determined by two measurements not less than 4 weeks apart. **Partial Response (PR):** A greater than 50% decrease in the sum of the products of the greatest length and perpendicular width of the largest measurement of all measurable lesions for at least 4 weeks with no simultaneous increase in size of a known lesion (> 25%) or appearance of new lesions or increase in evaluable disease during this period. **Response Duration:** the time from the initial documented response to the first documented sign of progression. **Time to Progression:** the time from the first dose of study medication to the time of first documented sign of progression.
396	Response Rate	Response Rate: The percentage of patients achieving either a complete or partial response (CR or PR as defined above).

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

The following active moieties were measured in human plasma using a reverse-phase high performance liquid chromatography separation with [redacted] (HPLC-[redacted] with excitation at [redacted]nm and emission at [redacted] nm: b(4)

- Topotecan lactone, N-desmethyl topotecan lactone, total topotecan and total N-desmethyl topotecan (lactone plus carboxylate form) in Study 048.
- Topotecan lactone and its ring-opened carboxylate in Study 049.
- Total topotecan and topotecan lactone in Studies 692, 118, 507, and BCR10001.
- Total topotecan in Study 204.

The assay methods used in these studies were adequately validated according the FDA guidance on the bio-analytical methodology (see Section 2.6 of this review).

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The exposure-response relationships for efficacy could not be assessed as there were no PK sampling performed during the pivotal Phase 3 Study 478 or the supportive Studies 065 and 396 in SCLC patients. In the Phase 2 Study 204, although plasma data were collected, there were no patients with a complete or partial response to treatment following oral dosing of 2.3 mg/m^2 topotecan once daily for 5 days.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The toxicity of topotecan after the oral route is comparable to that after the intravenous route [*Gerrits et al., Five days of once daily oral topotecan, a phase 1 and pharmacologic study in adults. Eur J Cancer 34:1030-1035, 1998*].

Following oral topotecan dosing to 55 patients with advanced solid tumors, significant correlations were observed between AUC_{0-t} on Day 1, and also *AUC_{0-t} per course for topotecan lactone and the percent decrease of leukocytes ($p < 0.05$) [*Gerrits et al., A comparison of clinical pharmacodynamics of different administration schedules of oral topotecan (Hycamtin). Clin Cancer Res 5:69-75, 1999*]. The AUC_{0-t} day 1 and AUC_{0-t} per course were fitted to the observed % decrease in leukocytes using a sigmoidal E_{max} model

*(The AUC_{0-t} per course was calculated by multiplying the AUC(t) day 1 with the number of doses per course)

2.2.4.3 Does this drug prolong the QT or QTc interval?

No information is available regarding whether topotecan causes a QTc prolongation either for the IV or oral formulations (see General Comment).

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

The selection of the 2.3 mg/m^2/day for 5 days dosage that was used in the pivotal and supportive studies was based on the MTD (maximum tolerated dose) determined in the Phase 1, dose-escalation **Study 049**. This dosage was associated with lowest incidence of diarrhea compared to the other dosing regimens (once or twice daily). In Study 049, oral topotecan was administered to 92 patients with advanced solid tumors at the following four dosing regimens: (1) twice daily for 21 days every 28 days (N=31), (2) twice daily for 10 days every 21 days (N=18), (3) once daily for 10 days every 21 days (N=20), and (4) once daily for 5 days every 21 days (N=23). The starting oral dose for all dosing regimens was 0.15 mg/ m^2. For each regimen, the dose was escalated until the MTD was determined. The MTD was 0.7 mg/m^2/day and 0.5 mg/m^2/day for the twice daily dosing regimen for 10 days and 21 days

dosing, respectively. For the once daily dosing regimen, the MTD was 2.3 mg/m^2/day for the 5 days dosing and 1.4 mg/m^2/day for the and 10 days.

During the first course of therapy, diarrhea rather than hematological toxicity was dose-limiting with the 21-day and 10-day dosing regimens. The twice-daily dosing regimens for 10 and 21 days, and the once daily dosing regimen for 10 days were associated with higher severe (grade 3-4) diarrhea than the once daily for 5 days regimen (32%, 28%, and 25% versus 4.3%, respectively). This toxicity may be related to the intestinal damage caused by unabsorbed topotecan. During the first course of therapy, hematological toxicity was comparable among the four dosing regimens, except that for neutropenia and leucopenia which were relatively high after the once daily 5-day dosing regimen. As the incidence of severe diarrhea was the lowest after the once daily for 5 days doing regimen than after the other dosing regimens, the MTD of 2.3 mg/m^2/day determined for the once daily for 5 days dosing regimen was selected for further efficacy/safety testing.

The percent of patients with Grade 3 or hematologic or non-hematologic toxicities are summarized in Figures 2 and 3.

FIGURE 2. Proportion of Patients with Grade 3 or 4 Hematological Toxicity *vs* Dosing Regimen

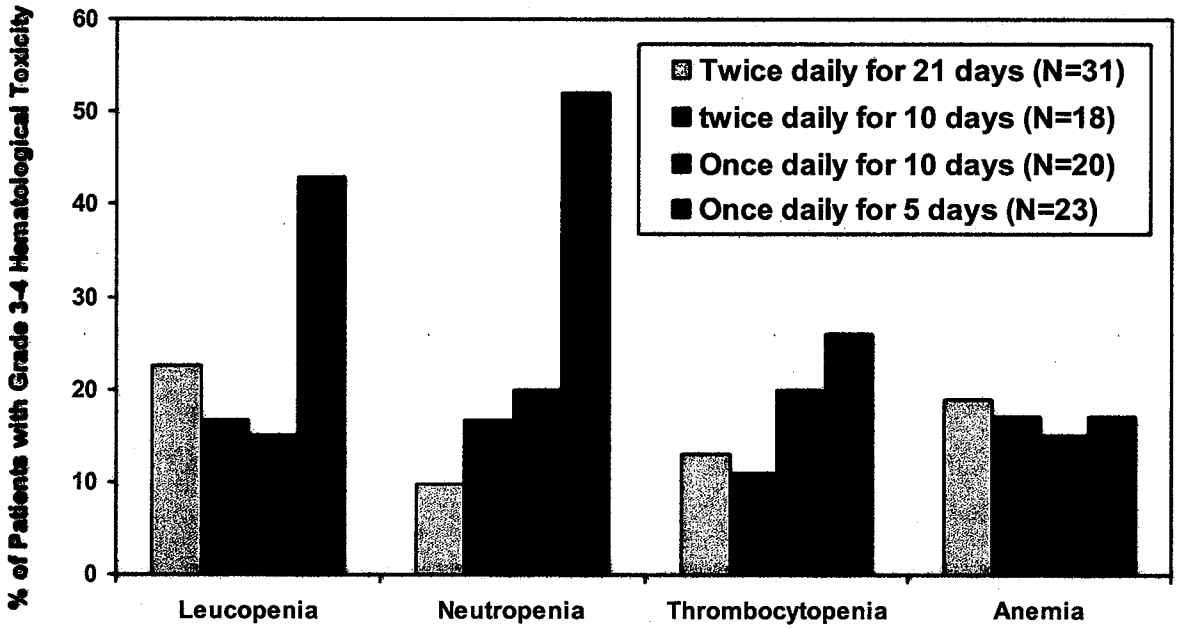
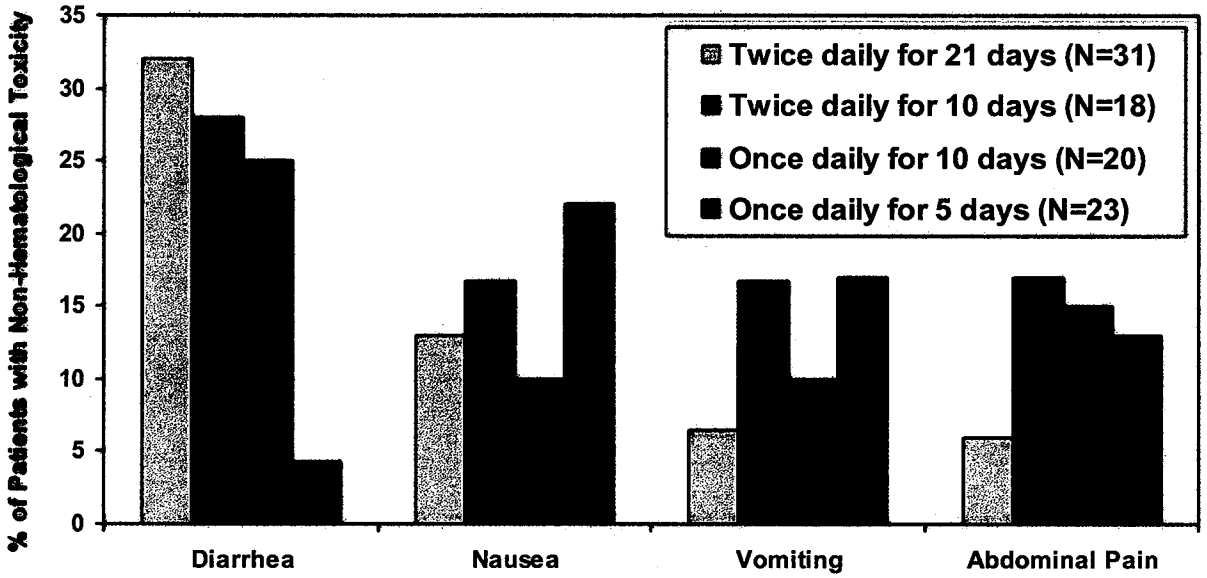


FIGURE 3. Proportion of Patients with Grade 3 or 4 Non-Hematological Toxicity *vs* Dosing Regimen



2.2.5 *Pharmacokinetics (PK) characteristics of the drug and its metabolite(s)*

2.2.5.1 What are the single-dose and multiple-dose PK parameters?

Single-Dose Pharmacokinetics:

The single-dose PK of total topotecan and topotecan lactone were determined in 17 patients with advanced solid tumors (Study 048) following a 1.5 mg/m^2 intravenous (IV) dose over 30-minutes, and an oral 2.3 mg/m^2 dose in the fasted state. The results are shown in Figures 4 and 5 and Table 3.

FIGURE 4. Mean Concentration-Time Profiles to Total Topotecan Following Single-Dose Oral and IV Administrations of Topotecan to 17 Patients with Advanced Solid Tumors

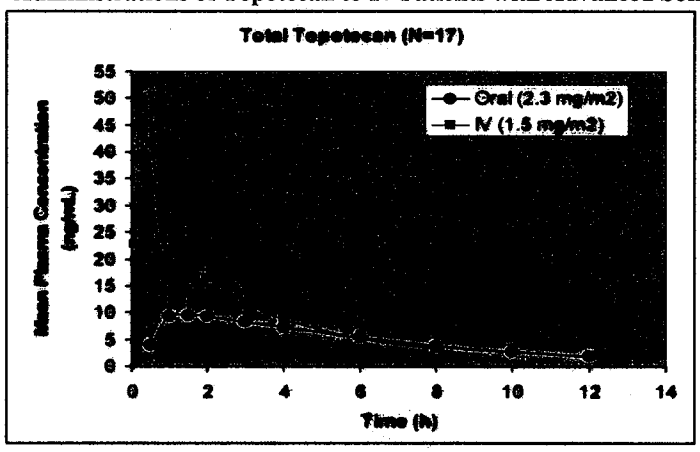


FIGURE 5. Mean Concentration-Time Profiles to Topotecan Lactone Following Single-Dose Oral and IV Administrations of Topotecan to 17 Patients with Advanced Solid Tumors

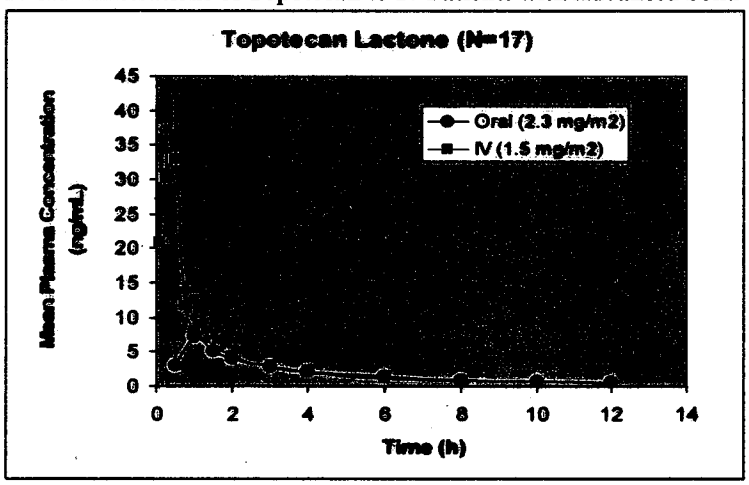


TABLE 3. Mean±SD (CV%) PK Parameters Following a Single-Dose Administration of Topotecan to Patients with Advanced Solid Tumors (Study 048)

PK Parameter	Single-Dose Topotecan (N=17)	
	Oral (2.3 mg/m^2)	IV (1.5 mg/m^2)
Total Topotecan		
C_{max} (ng/mL)	11.5±5.4 (46%)	42.7±8.6 (20%)
*T_{max} (h)	1.5 (0.5 - 6.0)	0.5 (0.25 - 0.5)
$AUC_{0-\infty}$ (ng·h/mL)	72.5±29.4 (40%)	106±25.7 (24%)
t½ (h)	4.1±1.1 (27%)	2.6±0.34 (13%)
CL (L/h)	--	14.5±3.9 (27%)
V_{ss} (L)	--	46.9±9.0 (19%)
F_{abs} (%)	43.9 ±11.6%	--
AUC_{0-t} Ratio of N-des-methyl/parent (N=13)	5.4±3.4%	3.2±2.1%
Topotecan Lactone		
C_{max} (ng/mL)	7.4±3.8 (51%)	34.7±7.5 (22%)
*T_{max} (h)	1.0 (0.5 - 4.0)	0.5 (0.25 - 0.5)
$AUC_{0-\infty}$ (ng·h/mL)	24.6±9.25 (37%)	39.8±9.8 (27%)
t½ (h)	4.0±1.2 (30%)	2.6±0.30 (11%)
CL (L/h)	--	38.5±8.9 (23%)
V_{ss} (L)	--	79.3±19.2 (24%)
F_{abs} (%)	42.3±10.8%	--
AUC_{0-t} Ratio of N-des-methyl/parent (N=13)	6.1±4.8%	2.5±2.2%

*Median (range)

The absolute bioavailability of oral topotecan averaged 44±12% when measured as total topotecan and 42±11% when measured as topotecan lactone in plasma samples.

The single-dose PK of topotecan were also assessed in the Phase 2 **Study 204** on Day 1 of Course 1 following 2.3 mg/m^2 and 1.3 mg/m^2 oral topotecan doses in patients with SCLC.

The PK parameters were only determined for total topotecan. The results are shown in the Table below.

TABLE 4. Mean±SD (CV%) PK Parameters for Total Topotecan Following a Single-Dose Oral Administration of Topotecan to Patients with SCLC (Study 204)

PK Parameter	2.3 mg/m^2 (N=30)	1.3 mg/m^2 (N=4)
C_{max} (ng/mL)	10.9±5.6 (51%)	16.7±6.1 (36%)
*T_{max} (h)	2.0 (0.5 - 4.0)	1.25 (1.0 - 1.5)
$AUC_{0-\infty}$ (ng·h/mL)	61.8±31.0 (50%)	85.0±25.4 (30%)
t½ (h)	3.9±0.57 (15%)	3.6±0.86 (24%)

*Median (range)

The PK of total topotecan determined in this study in SCLC patients are comparable to those determined in patients with solid advanced tumors (Study 048).

Multiple-Dose Pharmacokinetics:

The multiple-dose pharmacokinetics of topotecan were determined in the Phase 1 Study 049 in patients with advanced solid tumors following oral administration of 1.2-2.7 mg/m^2 once daily for 5 consecutive days.

TABLE 5. Mean±SD PK Parameters Following Once Daily for 5 Days to Patients with Advanced Solid Tumors (Study 049)

PK Parameter	Topotecan Dose							
	1.2 mg/m^2 (N=3)		1.8 mg/m^2 (N=3)		2.3 mg/m^2 (N=6)		2.7 mg/m^2 (N=4)	
	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
	Topotecan Lactone							
C_{max} (ng/mL)	5.8±4.0	3.3±1.3	9.0±6.0	5.7±3.9	8.5±2.5	8.9±4.5	10.1±5.6	11.8±7.6
*T_{max} (h)	0.75 (0.75-1)	1.5 (0.7-1.5)	0.75 (0.7-0.8)	2.5 (0.7-4.5)	0.72 (0.5-1)	1.0 (0.5-2.5)	1.3 (0.6-4.5)	1.0 (0.7-4.5)
AUC_{0-t} (ng·h/mL)	14.5±4.0	14.3±3.5	16.7±3.4	19.8±2.8	21.0±6.6	24.4±9.8	30.9±13.0	37.7±11.0
	Open-Ring Carboxylic Acid							
C_{max} (ng/mL)	4.3±1.9	3.7±0.95	6.2±2.1	5.6±2.3	5.6±1.5	7.3±3.3	8.6±4.3	9.7±4.6
*T_{max} (h)	1.5 (2.5-3.5)	2.5 (2.5-3.5)	1.5 (0.7-1.5)	2.5 (2.5-3.5)	1.5 (1.5-2.5)	1.5 (1.5-3.5)	2.5 (2.5-4.5)	2.0 (1.5-8.7)
AUC_{0-t} (ng·h/mL)	25.9±4.7	27.6±8.9	28.8±7.2	37.3±10.6	29.0±9.3	37.4±17.1	50.3±22.7	70.5±33.3

*Median (range)

No accumulation was noted for both topotecan lactone (pharmacologically active) and the open-ring carboxylic acid form (pharmacologically inactive) upon once daily dosing of oral

topotecan. The accumulation ratio (calculated as the $AUC_{0\text{-}t,Day\ 4}/AUC_{0\text{-}t,Day\ 1}$) ranged from 0.98-1.2 for topotecan lactone and 1.1-1.4 for carboxylic acid form.

2.2.5.2 How does the PK of the drug and its major active metabolites in Healthy volunteers compare to that in patients?

Topotecan is a cytotoxic agent and has never been administered to healthy volunteers.

2.2.5.3 What are the characteristics of drug absorption?

Topotecan was rapidly absorbed following oral administration with a peak plasma concentration (C_{max}) reached in a median T_{max} of 1-2 hours after dosing in the fasted state.

The absolute bioavailability (F) of oral topotecan compared to an IV dosing was about 40%. This relatively low value for F is primary due to the effect of the gut efflux transporters, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Topotecan is soluble and chemically stable under physiologic conditions, and there is no significant first-pass metabolism.

2.2.5.4 What are the characteristics of drug distribution?

The mean steady state volume of distribution was 46.9±9.0 L and 79.3±19.2 L for total topotecan and topotecan lactone, respectively, following a single 1.5 mg/m^2 IV dose (**Study 048**). Topotecan is about 35% bound to human plasma proteins (NDA 20-671).

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

The mass balance **Study 230** was previously submitted and reviewed under NDA 20-671 (SE1-014, 15-Dec-2005). Following oral administration, the overall recovery of total topotecan plus its total N-desmethyl metabolite in urine and feces was 56.8±10% of administered oral dose in 4 patients with advanced solid tumors. The fecal excretion of total topotecan over 9 days averaged 33±6.5% of the oral dose with 20.4±7.5% excreted in urine (Table 6). The urinary and fecal excretion of N-desmethyl topotecan averaged 2.0±0.7% and 1.5±0.6% of the administered oral topotecan dose, respectively, over 9 days.

TABLE 6. Mean±SD cumulative urinary and fecal excretion of topotecan and N-desmethyl topotecan over 9 days after IV and oral administration of topotecan

Route	Total Topotecan (N=4)			Total N-Desmethyl Topotecan N=4)	
	Urinary Excretion (%)	Fecal Excretion (%)	CLR (L/h)	Urinary Excretion (%)	Fecal Excretion (%)
Oral (2.3 mg/m^2)	**20.4±7.5%**	**33.05±6.5%**	14.2±5.5	2.01±0.73%	1.47±0.64%
IV (1.5 mg/m^2)	50.8±2.8	17.9±3.1%	13.6±5.4	3.1±0.99%	1.7±0.51%

TABLE 7. Overall Recovery (% of Administered Dose) in urine and feces over 9 days

	Oral (2.3 mg/m^2/day)				
Patient #	**002**	**006**	**009**	**010**	**Mean±SD**
Total topotecan	49.2	51.4	46.4	66.8	53.5±9.1%
Total desmethyl topotecan	4.1	1.8	2.7	4.9	3.4±1.4%
Overall total	53.3	53.2	49.1	71.7	**56.8±10%**
Patient #	IV (1.5 mg/m^2/day)				
	001	**004**	**007**	**011**	**Mean±SD**
Total topotecan	68.1	68.2	71.3	67.3	68.7±1.5%
Total desmethyl topotecan	3.2	4.2	5.1	6.6	4.7± 1.5%
Overall total	71.3	72.4	76.4	73.9	73.5±2.2%

2.2.5.6 What are the characteristics of drug metabolism?

2.2.5.7 What are the characteristics of drug excretion?

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

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

Mean AUC_{0-t} and C_{max} for topotecan lactone increased in proportion to dose following 1.2-2.7 mg/m^2 once daily oral doses of topotecan.

FIGURE 6. Mean AUC_{0-t} vs Dose for Topotecan Lactone

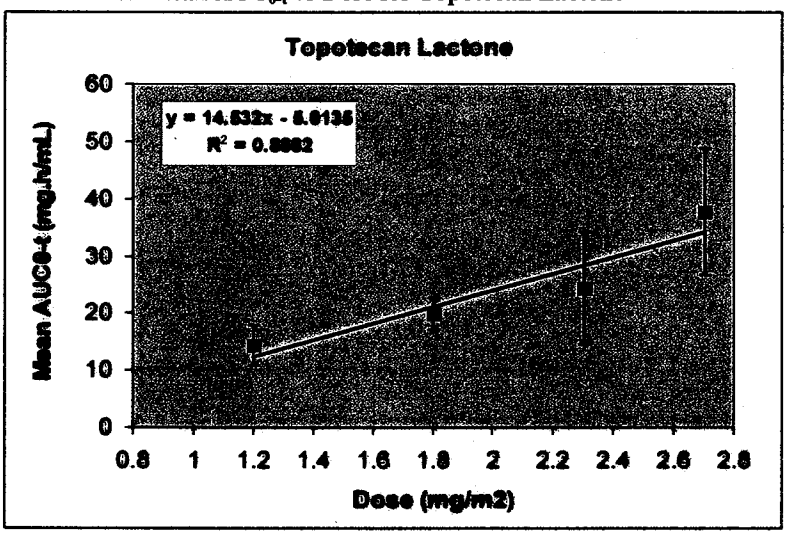
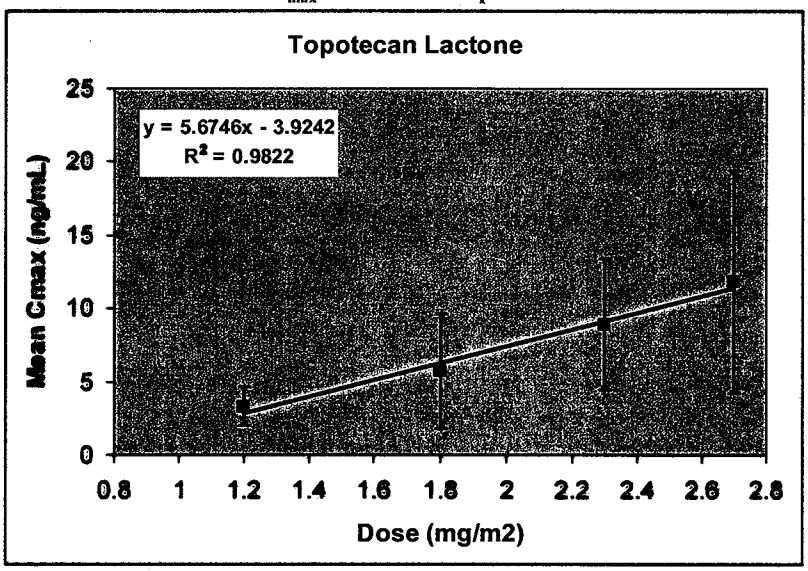


FIGURE 7. Mean C_{max} vs Dose for Topotecan Lactone



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

The inter-patient variability in systemic exposure was extremely high. The dose-normalized AUC for total topotecan varied 7.6-fold after oral administration compared to 4.8-fold after IV administration of topotecan [*Leger et al., Factors affecting pharmacokinetic variability of oral topotecan: a population analysis. Br J Cancer 90:343-347, 2004*]. The creatinine clearance and performance status were the only two covariates that explained the high inter-patient variability in total topotecan plasma clearance. The intra-patient variability was 43% after oral administration compared to 22.5% after IV administration.

2.3 *Intrinsic Factors*

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

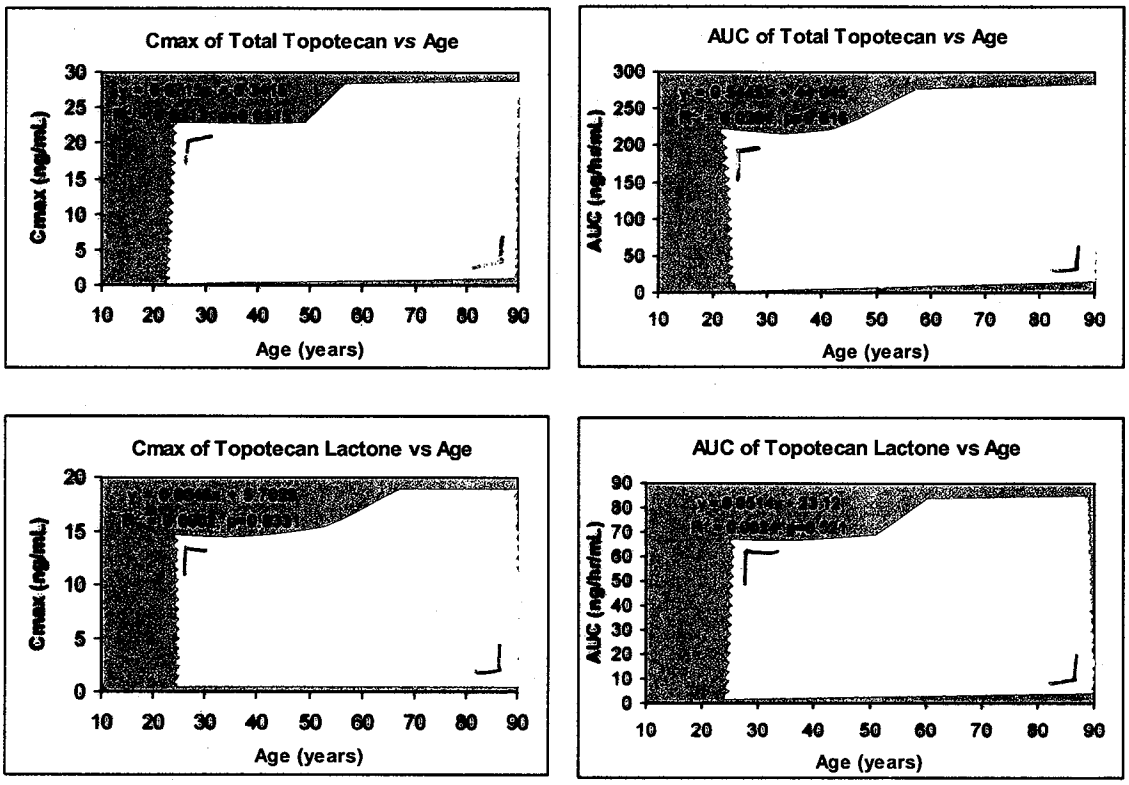
2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?

2.3.2.1 Age

A cross-study analysis of data collected from 217 patients with advanced solid tumors in the studies submitted in this NDA indicated that age has no effect on the exposure [$AUC_{0-\infty}$ and C_{max}] of topotecan lactone following a single 2.3 mg/m^2 oral topotecan dose. However,

exposure of topotecan lactone was significantly related to age ($p < 0.05$). Patients had a medium (range) age of 58 (28-84) years.

FIGURE 8. Effect of Age on the Exposure to Oral Topotecan



b(4)

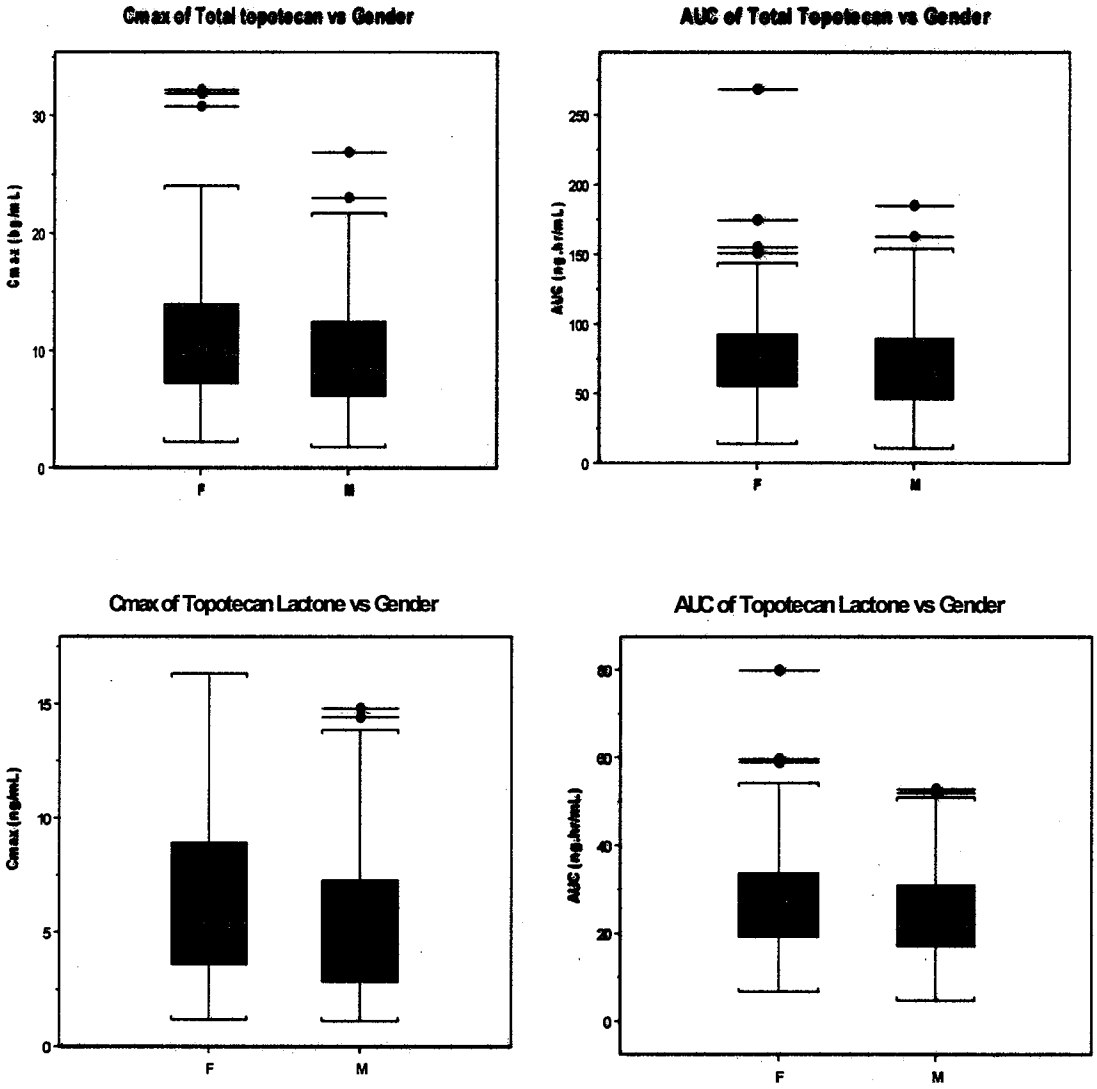
2.3.2.2 Gender

A cross-study analysis of data collected from 217 patients with advanced solid tumors in the studies submitted in this NDA indicated exposure of total topotecan and topotecan lactone was comparable between males and females following a single 2.3 mg/m^2 oral topotecan dose.

TABLE 8. Mean±SD PK parameters by Gender

PK Parameter	Males (N=98)	Females (N=119)
	Total Topotecan	
C_{max} (ng/mL)	9.7±5.1	11.1±5.5
AUC (ng.h/mL)	71.0±33.4	78.9±36.2
	Topotecan Lactone	
C_{max} (ng/mL)	5.5±3.5	6.3±3.3
AUC (ng.h/mL)	23.8± 10.6	27.6±11.9

FIGURE 9. Effect of Gender on the Exposure to Oral topotecan



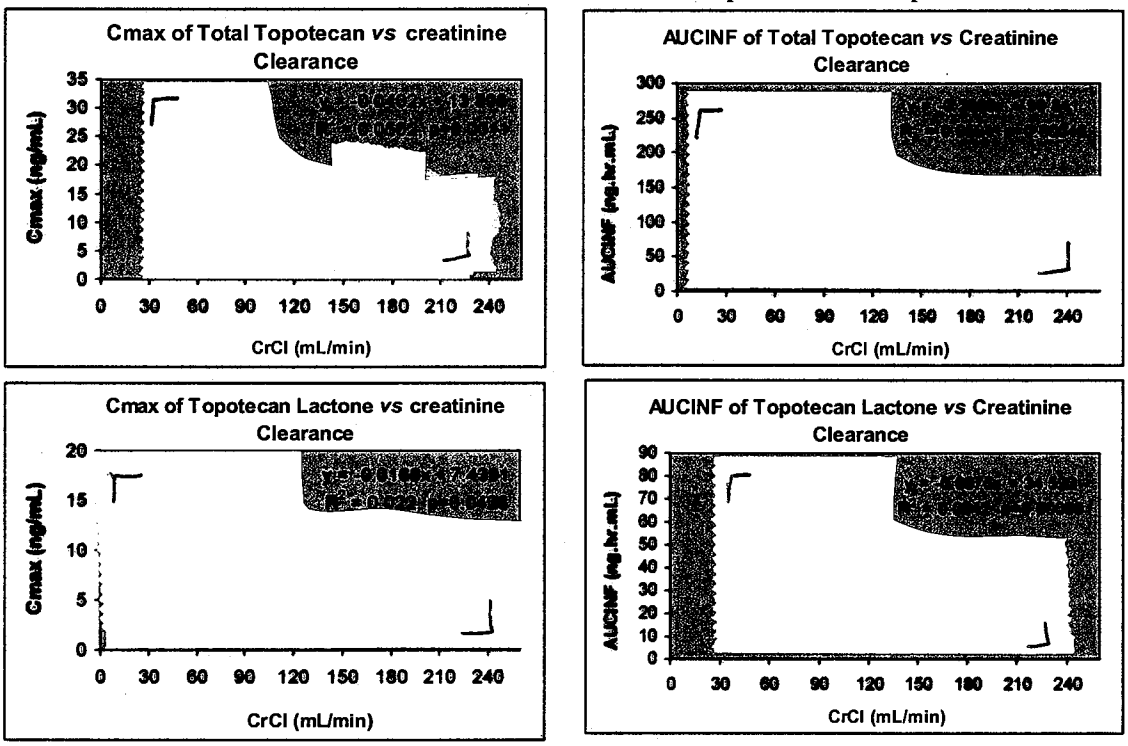
2.3.2.3 Race

The effect of race on the PK of topotecan has not been studied. More than 90% (198/217) of patients in the cross-study analysis were Caucasians.

2.3.2.4 Renal Impairment

A cross-study analysis of data collected from 217 patients with advanced solid tumors in the studies submitted in this NDA indicated a significant correlation between creatinine clearance and exposure [$AUC_{0-\infty}$ and C_{max}] of both total topotecan and topotecan lactone ($p < 0.05$). Patients had a median (range) creatinine clearance value of 82.5 mL/min (31.7-230 mL/min).

FIGURE 10. Effect of Creatinine Clearance on the Exposure to Oral topotecan



b(4)

According to the FDA published Guidance for Industry on the Renal Impairment Studies, patients were categorized into three groups: Normal with CrCl > 80 mL/min (N=119), Mild with CrCl=50-80 mL/min (N=74), and Moderate with CrCl=30-49 mL/min (N=24). A summary of PK parameters per group is shown below:

TABLE 9. Mean±SD PK parameters by Renal Group

PK Parameter	Normal (N=119)	Mild (N=74)	Moderate (N=24)
*CrCl (mL/min)	95.6 (80-230)	67.2 (50.1-79.2)	45.9 (31.7-49.8)
	Total Topotecan		
C_{max} (ng/mL)	9.5±4.9	11.7±5.8	11.4±5.3
AUC (ng.h/mL)	67.5±28.2	86.5±41.8	80.5±34.5
	Topotecan Lactone		
C_{max} (ng/mL)	5.5±3.4	6.3±3.3	7.0±3.7
AUC (ng.h/mL)	23.9±9.8	28.7±13.5	29.6±11.6

*Median (range)

C_{max} of total topotecan was 23% and 20% higher in patients with mild and moderate renal impairment, respectively, than in patients with normal renal function (p=0.003 and 0.051, respectively).

C_{max} of topotecan lactone was 15% and 27% higher in patients with mild and moderate renal impairment, respectively, than in patients with normal renal function (p=0.001 and 0.062, respectively).

AUC of total topotecan was 28% and 20% higher in patients with mild and moderate renal impairment, respectively, than in patients with normal renal function (p=0.0001 and 0.031, respectively).

AUC of topotecan lactone was 20% and 24% higher in patients with mild and moderate renal impairment, respectively, than in patients with normal renal function (p=0.005 and 0.022, respectively).

The AUC values estimated from the relationship between CrCl and AUC for topotecan lactone (Y = 34.522 - 0.0795 * X) were 25.2, 27.9, and 30.05 ng.h/mL for the normal, mild, and moderate groups, respectively. Thus, patients with mild renal impairment had only 10% higher AUC than the normal group. Patients with moderate renal impairment had 20% higher AUC than the normal group. Based on this analysis, no dosage adjustment is needed in patients with mild renal impairment when treated with oral topotecan. However, the oral topotecan dose should be reduced to 1.8 mg/m^2 when given to patients with moderate renal impairment.

Insufficient data are available in patients with severe renal impairment (CrCl < 30 mL/min) to provide a dosage recommendation for oral topotecan.

The effect of hemodialysis on topotecan disposition was characterized in one patient with severe renal insufficiency receiving hemodialysis [*Herrington et al., Effect of hemodialysis on topotecan disposition in a patient with severe renal dysfunction. Cancer Chemother Pharmacol 47:89-93, 2001*]. The topotecan lactone clearance determined after administration of topotecan alone and with hemodialysis was 5.3 L/h/m^2 versus 20.1 L/h/m^2 respectively. The topotecan terminal half-life off dialysis was 13.6 hours, compared with an apparent half-life determined during hemodialysis of 3.0 hours. These results demonstrated that topotecan plasma clearance while on hemodialysis increased about 4-fold. The authors suggest that hemodialysis may be an effective process to clear topotecan from the body in case of overdose.

2.3.2.5 Hepatic Impairment

The effect of hepatic impairment on the PK of **Oral Hycamtin** has not been evaluated. Patients with SCLC who participated in oral topotecan clinical studies had serum bilirubin of ≤ 2 mg/dL. In a population PK model described by Leger et al. 2004 involving oral topotecan administered at doses of 0.15-2.7 mg/m^2/day to 118 cancer patients, no liver function test (e.g., serum bilirubin, ALT, AST) was found to significantly affect the PK of total topotecan [*Leger et al., Factors affecting pharmacokinetic variability of oral topotecan: a population analysis. Br J Cancer 90:343-347, 2004*]. No dosage adjustment appears to be required for patients with impaired hepatic function when treated with oral topotecan.

2.3.2.6 Pediatric Patients

No studies are planned in pediatric patients with SCLC due to the rare incidence of the disease in this age group.

2.4 ***Extrinsic Factors***

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Topotecan is a substrate for P-glycoprotein (ABCB1) efflux transporter [*Hendricks et al., Effect of P-glycoprotein expression on the accumulation and cytotoxicity of topotecan, a New Camptothecin Analogue. Cancer Res 52:2268-2278, 1992*].

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Topotecan is also a substrate for breast cancer resistance protein (BCRP or ABCG2) [*Ma et al., Reduced cellular accumulation of topotecan: a novel mechanism of resistance in a human ovarian cancer cell line. Br J Cancer 77:1645-1652, 1998*].

BCRP is known to confer multi-drug resistance to cancer cells against chemotherapeutic agents such as SN-38 (an active metabolite of irinotecan), mitoxantrone, and topotecan. In a study by Imai et al., three variants of *BCRP cDNAs* **were identified: G34A, C421A, and 944–**949 deletion [*Imai et al., C421A Polymorphism in the Human Breast Cancer Resistance Protein Gene Is Associated with Low Expression of Q141K Protein and Low-Level Drug Resistance. Molecular Cancer Therap 1:611-616, 2002*]. G34A and C421A variants were **polymorphic, and the 944–949 deletion was a splicing** variant. C421A was associated with markedly decreased protein expression and low-level drug resistance compared with wild type BCRP-transfected cells. G34A showed similar or somewhat lower protein expression and drug resistance compared with wild-type *BCRP*-transfected cells. The C421A polymorphism was found to be very frequent in the Japanese population and may be associated with decreased protein expression and low-level drug resistance; 46% of the normal Japanese population carries the C421A allele and, in particular, 7% were homozygous. The authors suggest that screening for the C421A polymorphism in cancer patients before chemotherapy may be useful for the prevention of serious side effects of some anticancer drugs.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The label specifies that Oral Hycamtin is to be administered as a single agent for the treatment of patients with small cell lung cancer.

2.4.2.7 Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The potential for drug-drug interactions of oral topotecan was investigated with ranitidine, cyclosporin A, elacridar, the and cytotoxic agent, cisplatin.

Ranitidine:

The effect of ranitidine on the PK of topotecan was examined in **Study 118** on Day 1 of each of Courses 1 and 2. This was a randomized, open-label, two-period, crossover, Phase 1 study in 18 patients with advanced solid tumors. Patients were treated with oral topotecan (2.3 mg/m^2/day) for 5 days every 21 days either in the absence of ranitidine or the presence of ranitidine. Ranitidine was given as a 150 mg twice daily for four days prior to the administration of topotecan. A summary of the results is shown in the Table 10.

TABLE 10. Mean±SD (CV%) PK Parameters Following a Single 2.3 mg/m^2 Oral Topotecan Dose in Presence and Absence of Ranitidine (150 mg Twice Daily Oral Doses) in **13 Patients with Advanced Solid Tumors

PK Parameter	Topotecan + Ranitidine	Topotecan Alone
	Total Topotecan	
C_{max} (ng/mL)	12.9±3.7 (28%)	12.2±2.9 (24%)
*T_{max} (h)	1.5 **(0.5 – 1.5)**	**1.5 (1.0 -3.0)**
AUC_{0-t} (ng·h/mL)	56.0±16.4 (29%)	59.3±17.7 (29%)
t½ (h)	4.6±1.9 (41%)	4.3±1.2 (28%)
	Topotecan Lactone	
C_{max} (ng/mL)	8.7±2.7 (31%)	8.4±2.0 (24%)
*T_{max} **(h)**	**1.0 (0.5 – 1.5)**	**1.0 (0.5 -1.5)**
AUC_{0-t} (ng·h/mL)	22.0±5.3 (24%)	24.2±6.9 (28%)
t½ (h)	4.6±1.5 (32%)	4.1±1.1 (27%)

* Median (range)

** A total of 18 patients enrolled, as a result of sample loss during shipment, PK data were not available for 1 patient in the absence of ranitidine and 4 subjects in the presence of ranitidine (Total N=13).

Ranitidine, a histamine-2 blocker which reduces the amount of acid in the stomach, is commonly administered with topotecan as a palliative treatment during chemotherapy. Topotecan undergoes reversible pH-dependent hydrolysis of its lactone moiety. At pH ≤ 4, the lactone is extensively present, whereas at the physiological pH, the inactive ring-opened form predominates. The results of this study demonstrated that ranitidine did not have an effect on the PK of oral topotecan.

Cyclosporin A:

The effect of cyclosporin A, a potent of P-gp inhibitor, on the PK of oral topotecan was examined in Study 507. Study 507 was a randomized, open-label, two-period, crossover, Phase 1 study in 14 patients with advanced solid tumors. Patients received either Regimen A (2.3 mg/m^2 oral topotecan once daily for 5 days) or Regimen B (2.0 mg/m^2 oral topotecan plus 15 mg/kg oral cyclosporin A 4 hours before topotecan once daily for 5 days). Patients were crossed over between Regimens A and B during Courses 1 and 2.
Of the 14 patients enrolled in the study, 7-10 patients were evaluable for PK determination. One patient did not have PK data for either regimen because no samples were collected for the one cycle in which the patient received therapy. Two patients withdrew after the first period for insufficient therapeutic effect. Some patients had missing data for at least one regimen and were excluded from the PK analysis. The PK of total topotecan and topotecan lactone were determined on Day 5 of each of Courses 1 and 2. The results of this study are shown in Table 11.

TABLE 11. Mean±SD (CV%) PK Parameters on Day 5 Following Once Daily Oral Topotecan Alone or with Oral Cyclosporin A (15 mg/kg) on Day 5 of each of Courses 1 and 2 in 7-10 Patients

PK Parameter	Topotecan Alone (2.3 mg/m^2)	Topotecan + Cyclosporin A (2.0 mg/m^2+0.15 mg/kg)
Total Topotecan		
C_{max} (ng/mL) **(N=10)**	11.5±4.8 (42%)	11.0±8.5 (77%)
C_{max}/Dose (ng/mL/1 mg)	3.2±1.6 (49%)	3.0±2.7 (80%)
T_{max} (h) **(N=10)**	2.0 (0.5-4.0)	4.0 (1.0-12)
AUC_{0-24} (ng·h/mL) **(N=7)**	63.5±34.9 (55%)	124.8±130.2 (104%)
AUC_{0-24}/Dose (ng·h/mL/1 mg)	18.0±10.1 (55%)	42.6±49.7 (117%)
Topotecan Lactone		
C_{max} (ng/mL) **(N=9)**	5.6±2.8 (51%)	5.1±3.5 (70%)
C_{max}/Dose (ng/mL/1 mg)	1.5±0.94 (60%)	1.5±1.0 (64%)
*T_{max} (h) **(N=10)**	**2.2 (1.0 – 6.0)**	**2.0 (1.25 – 4.0)**
AUC_{0-24} (ng·h/mL) **(N=8)**	24.6±9.7 (39%)	39.8±27.1 (68%)
AUC_{0-24}/Dose (ng·h/mL/1 mg)	6.5±2.9 (45%)	12.6±10.4 (82%)

*Median (range)

Co-administration of cyclosporine A four hours before oral topotecan increased the exposure (dose-normalized steady state AUC_{0-24}) and variability in exposure by 2-fold for both total topotecan and topotecan lactone. Dose-normalized C_{max} of both total topotecan and topotecan lactone was not affected by co-administration of cyclosporine A.

Elacridar:

The effect of elacridar, a potent inhibitor of both P-gp and BCRP in gut wall, on the bioavailability of oral topotecan was investigated in **Study BCR1001**. Study BCR1001 was

an open-label, randomized, parallel-group, two-part, Phase 1 study in a total of 39 patients with advanced solid tumors. The study was carried in two parts.

In **Part I** of the study, 24 patients were randomized to receive orally 100, 300, 500, 700, or 1000 mg of elacridar on Days 1 and 8 co-administered either simultaneously with or one hour (sequential) before 2.0 mg oral topotecan. Both groups (Simultaneously or sequential) were treated with 2.0 mg topotecan intravenously (IV) on Day 15 and subsequently with 1.5 mg/m^2 IV on Days 16 to 19. Of the 24 patients in Part I, four went off study before its completion. Two of these patients had progressive disease and another patient had a course delay >2 weeks because of fever. No lactone samples were collected from three patients and no total topotecan samples were collected from the fourth patient.

In **Part II** of the study, 15 patients received oral topotecan at doses of 1.0, 1.5 mg, 2.0, and 2.5 mg given once daily for 5 days every 21 days, co-administered simultaneously with 100 mg oral elacridar (Study design is shown below).

The primary objectives of the first part of the study were to determine the minimal dose of elacridar required for maximal oral bioavailability of topotecan and to determine the appropriate schedule of co-administration of oral topotecan and elacridar. The primary objective of the second part of the study was to estimate the maximum tolerated dose (MTD) of oral topotecan when co-administered with the previously determined schedule and dose of elacridar. The results of this study are shown in Tables 12-15.

TABLE 12. Part I: Mean±SD PK Parameters for Total Topotecan Following a Single 2.0 mg Oral Topotecan dose on Days 1 and 8 of Cycle 1

Elacridar Dose	**100 mg**	**300 mg**	**500 mg**	**700 mg**	**1000 mg**
N	**4**	**4**	**4**	**3**	**4**
Simultaneously					
C_{max} (ng/mL)	12.9±4.9	12.0±2.0	12.6±4.4	14.9±11.7	14.0±2.2
*T_{max} (h)	2.0 (1.9-4.0)	3.0 (2.0-4.0)	1.3 (0.62-4.0)	2.0 (0.5-2.0)	1.8 (1.5-4.0)
$AUC_{0-\infty}$ (ng.h/mL)	88.6±21.9	74.6±22.1	78.0±9.4	102±38.6	91.0±20.6
F_{ab} (%)	102±7.1%	100±24%	108±23%	88±16%	110±10%
t½ (hr)	4.1±0.27	3.7±0.55	4.6±0.50	5.8±2.4	4.3±0.43
Sequential					
C_{max} (ng/mL)	16.5±3.6	11.4±1.6	13.8±5.0	11.5±7.6	15.1±1.8
*T_{max} (h)	1.3 (0.6-2.3)	2.0 (1.9-4.0)	1.7 (1.0-3.9)	4.0 (0.95-4.2)	1.75 (1.5-2.0)
$AUC_{0-\infty}$ (ng.h/mL)	92.8±21.4	74.2±10.6	82.6±14.9	81.3±32.1	90.2±20.5
F_{ab} (%)	108±19%	102±15%	110±14%	81±10%	110±14%
t½ (hr)	4.5±0.76	4.0±0.33	4.1±0.4	4.9±1.2	4.6±0.62

*Median (range)

TABLE 13. Part I: Mean±SD PK Parameters for Topotecan Lactone Following a Single 2.0 mg Oral Topotecan dose on Days 1 and 8 of Cycle 1

Elacridar Dose	100 mg	300 mg	500 mg	700 mg	1000 mg
N	3	4	3	3	3
Simultaneously					
C_{max} (ng/mL)	7.4±3.7	5.8±1.6	11.3±5.8	9.4±10.8	7.7±3.2
*T_{max} (h)	2.0 (1.9-4.0)	1.8 (1.5-2.0)	0.8 (0.3-0.8)	2.0 (0.5-2.0)	2.0 (0.98-4.0)
$AUC_{0-\infty}$ (ng.h/mL)	30.2±0.12	24.1±5.3	27.8±0.79	30.9±13.5	31.3±5.1
F_{ab} (%)	101±8.7%	93±15.5%	111±22.5%	90±14.5%	112±17.9%
t½ (h)	2.7±0.28	2.9±1.1	3.9±1.6	5.5±2.4	3.8±1.0
Sequential					
C_{max} (ng/mL)	11.1±2.1	5.9±0.71	9.4±3.6	6.5±6.2	9.7±0.64
*T_{max} (h)	1.2 (0.58-1.6)	1.5 (1.1-2.0)	0.76 (0.75-1.5)	2.0 (0.95-4.2)	1.5 (1.0-1.5)
$AUC_{0-\infty}$ (ng.h/mL)	32.5±6.3	25.4±4.5	30.6±6.2	25.6±10.8	29.3±4.8
F_{ab} (%)	112±13.9%	98±13.7%	111±6.5%	75.4±9.5%	106±24.1%
t½ (h)	3.3±0.70	3.4±0.76	2.9±0.39	5.2±2.7	3.5±1.3

*Median (range)

TABLE 14. Part II: Mean±SD PK Parameters for Total Topotecan Following Once Daily doses and a Single 100 mg Oral Elacridar Dose on Day 1 of Cycles 1 and 2

Topotecan Dose	1.0 mg	1.5 mg	2.0 mg	2.5 mg
N	3	3	6	3
Cycle 1				
C_{max} (ng/mL)	4.6±1.1	8.3±2.4	9.2±4.8	14.5±3.6
*T_{max} (h)	4.0 (2.0-4.0)	1.9 (1.5-2.1)	2.0 (2.0-4.0)	4.0 (2.0-4.2)
$AUC_{0-\infty}$ (ng.h/mL)	41.5±15.6	50.8±13.8	60.7±36.9	107±55.1
t½ (h)	4.5±1.4	3.7±1.2	3.1±1.0	4.5±0.5
Cycle 2				
C_{max} (ng/mL)	&4.3	9.3±3.8	11.0±6.4	&11.2
*T_{max} (h)	&4.0	2.0 (2.0-2.23)	4.0 (2.0-6.0)	&2.0
$AUC_{0-\infty}$ (ng.h/mL)	&28.1	61.7±25.1	77.9±41.4	&65.4
t½ (h)	&2.6	4.1±0.81	4.3±0.61	&4.9

*Median (range) &N=1

TABLE 15. Part II: Mean±SD PK Parameters for Topotecan Lactone Following Once Daily doses and a Single 100 mg Oral Elacridar Dose on Day 1 of Cycles 1 and 2

Topotecan Dose	1.0 mg	1.5 mg	2.0 mg	2.5 mg
N	3	3	6	3
Cycle 1				
C_{max} (ng/mL)	1.5±0.24	4.9±1.7	5.4±3.1	9.0±3.5
*T_{max} (h)	4.0 (1.5-6.0)	2.0 (0.97-2.1)	1.75 (1.0-2.0)	2.0 (2.0-2.2)
$AUC_{0-\infty}$ (ng.h/mL)	10.3±3.1	17.0±2.4	24.1±37.9	37.8±18.0
t½ (h)	3.9±1.7	5.3±4.3	4.6±2.8	3.3±1.5
Cycle 2				
C_{max} (ng/mL)	&1.5	5.3±2.2	5.0±2.1	&7.1
*T_{max} (h)	&2.0	1.6 (1.5-2.0)	2.0 (1.0-4.1)	&1.5
$AUC_{0-\infty}$ (ng.h/mL)	&7.4	22.7±7.26	29.1±14.6	&32.4
t½ (h)	&2.4	5.3±4.2	4.4±2.4	&6.8

*Median (range) &N=1

The results in the above Tables revealed a complete oral bioavailability (F_{abs}) of topotecan for all treatment arms of elacridar (100-1000 mg doses) for both schedules (simultaneous or sequential). Co-administration of elacridar simultaneously with topotecan or 1 hour before topotecan increased the absolute bioavailability of oral topotecan by 2.5-fold. The mean absolute bioavailability of oral topotecan alone is 42±11% in Study 048.

No statistically significant difference in F_{abs} between administrations of elacridar either simultaneously or sequentially was observed for either total topotecan (P = 0.71) or for topotecan lactone (P = 0.55).
Mean dose-normalized $AUC_{0-\infty}$ values for total topotecan and topotecan lactone were comparable to those obtained after oral topotecan alone administration in Study 048. Mean dose-normalized $AUC_{0-\infty}$ ratio of oral topotecan+elacridar/oral topotecan alone was 1.3-fold.

According to the Applicant, elacridar and topotecan in various dosing combinations and schedules (simultaneous or sequential) were generally well-tolerated in all patients during Parts I and II of the study.

During **Part I**, the most commonly reported drug-related adverse events (AEs) were nausea (42%), neutropenia (25%), alopecia (21%), and fatigue (21%). The cohort sizes were too small to draw comparisons across cohorts.

In **Part II** of the study, the most commonly reported drug-related AEs were thrombo-cytopenia (60%), nausea (53%), fatigue (53%), anemia (47%), neutropenia (47%), and alopecia (47%). The cohort sizes were too small to draw comparisons across cohorts.

The lowest elacridar dose of 100 mg with the simultaneous administration of 2.0 mg oral topotecan once daily for 5 days every 21 days was recommended as the effective and safe dosing regimen for the combination.

Cisplatin:

The sequence-dependent effects of oral topotecan administered once daily for five days in combination with a single intravenous (IV) dose of cisplatin were investigated in **Part 1** of **Study 101** in a total of 61 patients with advanced solid tumors. In Part 1 of Study 101, six patients were randomized to receive either Sequence A or Sequence B at each topotecan dose level. Oral topotecan dose was escalated at dose levels of 0.75, 1.0, 1.25, 1.5, 1.75 and 2.0 mg/m^2/day.

	Sequence A	Sequence B
Cycle 1	Cisplatin on Day 1 followed by topotecan on Days 1-5 (C→T)	Topotecan on Days 1-5 followed by cisplatin on Day 5 (T→C)
Cycle 2	Topotecan on Days 1-5 followed by cisplatin on Day 5 (T→C)	Cisplatin on Day 1 followed by topotecan on Days 1-5 (C→T)

For both C→T and T→C regimens, a single 75 mg/m^2 dose of cisplatin was administered intravenously (IV) over three hours. The PK of oral topotecan were determined during **Part 1** of the study on Days 1 and 5 for the first two cycles of treatment to assess the effect of concomitant administration of cisplatin on Day 1 (regimen C→T) or Day 5 (regimen T→C). The results are shown in Tables 16 and 17.

TABLE 16. Mean±SD PK Parameters Following Co-Administration of Oral Topotecan (0.75-2.3 mg/m^2 Once Daily) with a Single Cisplatin 75 mg/m^2 IV Dose On Days 1 and 5 of Cycles 1 and 2

Topotecan Dose	C→T (N=22)		T→C (N=38)	
	Day 1	Day 5	Day 1	Day 5
Total Topotecan				
C_{max} /Dose (ng/mL/2.3 mg/m^2)	11.7±5.1	12.8±7.5	10.5±5.2	10.3±4.7
*T_{max} (h)	1.5 (0.75-6.1)	1.5 (0.5-6.0)	1.5 (0.5-6.0)	1.6 (0.5-6.2)
$AUC_{0-\infty}$/Dose (ng.h/mL/2.3 mg/m^2)	64.1±22.8	87.2±22.4	56.4±22.1	66.8±30.3
t½ (h)	3.5±1.0	4.2±1.5	3.7±1.2	3.7±1.4
Topotecan Lactone				
C_{max} /Dose (ng/mL/2.3 mg/m^2)	7.4±3.9	7.5±5.3	6.5±4.2	5.9±3.1
*T_{max} (h)	1.1 (0.45-6.1)	1.0 (0.5-4.0)	1.0 (0.5-6.0)	1.3 (0.5-6.2)
$AUC_{0-\infty}$/Dose (ng.h/mL/2.3 mg/m^2)	25.4±8.9	29.9±13.0	21.2±7.8	25.6±10.8
t½ (h)	3.2±0.91	3.9±0.98	3.6±1.1	3.7±1.3

*Median (range)

TABLE 17. Number (%) of Patients with Grade 3-4 Hematological Toxicity at each Oral Topotecan Dose Level Given in Combination with 75 mg/m^2 Cisplatin

		Grade 3-4 Hematological Toxicity			
Topotecan Dose (mg/m^2)	**N**	**Leucopenia**	**Neutropenia**	**Thrombocytopenia**	**Anemia**
		C →T			
0.75	6	3 (50%)	4 (67%)	1 (17%)	1 (17%)
1.0	6	4 (67%)	5 (83%)	1 (17%)	0
1.25	11	9 (82%)	10 (91%)	6 (55%)	1 (9%)
1.5	6	1 (17%)	4 (67%)	0	3 (50%)
1.75	6	2 (33%)	5 (83%)	2 (33%)	3 (50%)
		T→ C			
0.75	6	1 (17%)	0	0	0
1.0	6	0	1 (17%)	0	1 (17%)
1.25	6	3 (50%)	2 (33%)	0	0
1.5	3	1 (33%)	1 (33%)	0	0
1.75	6	2 (33%)	2 (33%)	2 (33%)	1 (17%)
2.0	10	5 (50%)	5 (50%)	2 (20%)	2 (20%)
2.3	7	5 (71%)	6 (85%)	2 (28%)	1 (14%)

From Table 15, it is seen that there was a trend for higher exposure in the C→T regimen than that in the T→C regimen for both total topotecan and topotecan lactone. For example, on Day 5, dose-normalized C_{max} and $AUC_{0-\infty}$ for total topotecan were 24% (p=0.042) and 13% (p=0.035) higher, respectively, in the C→T regimen than in the T→C regimen. The corresponding p-values on Day 1 were p=0.190 and p=0.119 for dose-normalized C_{max} and $AUC_{0-\infty}$, respectively. For topotecan lactone, dose-normalized C_{max} and $AUC_{0-\infty}$ were 27% (p=0.071) and 17% (p=0.095) higher, respectively, on Day 5 in the C→T regimen than in the T→C regimen. The corresponding p-values on Day 1 were p=0.234 and p=0.033 for dose-normalized C_{max} and $AUC_{0-\infty}$, respectively.

The incidence of grade 3/4 toxicities was higher in patients receiving C→T Regimen than those receiving T→C Regimen. Grade 3-4 neutropenia occurred in 80% of patients treated with the C→T regimen and in 43% of patients treated with the T→C regimen. Grade 3/4 leucopenia occurred in 63% and 36% of patients in the C→T and T→C regimens, respectively. Grade 3/4 thrombocytopenia and anemia were less common: grade 3/4 thrombocytopenia occurred in 28% and 14% of patients, respectively, and grade 3 anemia occurred only in 14% and 11% of patients in the respective groups.

The incidence of grade 3/4 neutropenia was higher at all oral topotecan doses for the C→T regimen than for the T→C regimen. For the T→C regimen, the incidence of grade 3/4 neutropenia tended to increase with increased oral topotecan dose. It is preferable to administer oral topotecan before cisplatin when the two drugs are to be given in combination.

2.5 *General Biopharmaceutics*

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

According to the Biopharmaceutics Classification System (BCS), topotecan can be classified as a high soluble/low permeable Class 2 compound.

Topotecan is a high solubility compound. Although the solid state forms are different, the pH-dependent solubilities of both synthetic routes A3 and A4 drug substance are equivalent and highly water soluble across a pH range of 1 to 6.2 (see Table below). The solubility of topotecan was the highest in the pH 3.0 medium, averaged 70±1.6 mg/mL.

TABLE 18. Solubility of Routes A3 and A4 Drug Substances

Route	Drug Substance Batch	Solubility			
		pH 1.0 (mg/mL)	pH 3.0 (mg/mL)	pH 4.5 (mg/mL)	pH 6.8 (mg/mL)
A3	9416-TPTC-1	46	71	4.8	0.3
	9418-TPTC-1	43	72	6.0	0.4
	816TC-01	43	68	5.3	0.3
A4	104864-A4-02M	39	69	5.0	0.3
	02TC-001	39	68	5.9	0.4
	02TC-002	40	70	5.7	0.4

The apparent permeability of topotecan was determined *in vitro* at pH 7.4 across the human intestinal epithelial cell Caco-2 cell line. The results are shown in the Table 19.

TABLE 19. Permeability Data for Topotecan

Tissue	Mean P_{app} ± SD (Cm/h) (mucosal-to-serosal)	Number of Tissues
Caco-2	$1.5 \times 10^{-2} \pm 1.0 \times 10^{-3}$	3
Distal	$1.7 \times 10^{-2} \pm 8.0 \times 10^{-3}$	6
Ileum	$1.1 \times 10^{-2} \pm 4.0 \times 10^{-3}$	9

Compared to the highly permeable probe,*Propranolol, which has a permeability value of 0.162 Cm/h, topotecan can be considered a low permeability compound.

*[*Caldwell et al., In vitro permeability of eight–blockers through Caco-2 monolayers utilizing liquid chromatography/electrospray ionization mass spectrometry. J Mass Spectrum 33:607-614, 1998*]

2.5.2 What is the composition of the to-be-marketed formulation?

The early dosage forms used during development were [redacted] ng [redacted] capsules which were manufactured by [redacted] Due to the [redacted] of the [redacted] formulations the hydrogenated vegetable oil formulations were developed. The drug substance was manufactured by several manufacturing processes during the development of the capsule formulation. [redacted] routes of drug substance were used: Routes [redacted] and [redacted] Route [redacted] provided material that was [redacted] form. Route [redacted] produced only a [redacted] form of topotecan drug substance.

b(4)

Manufacturing Process — was developed to accommodate the ' ——— form of drug substance; however, bioequivalence (BE) was not demonstrated relative to the reference Phase — formulation. Further development work led to manufacturing refinements that resulted in Process —/Route —, which was identified as the proposed commercial (to-be-marketed) process, and was demonstrated to be bioequivalent to the Phase — formulation Study 692). A summary of these manufacturing processes for the drug substance is shown in the Table below: b(4)

TABLE 20. Manufacturing Processes Used for Topotecan Capsules

	Manufacturing Process Label

b(4)

The composition of the clinical Phase — and proposed for marketing capsule formulations is shown in Tables 21 and 22. The composition of the prototype capsule formulations (Process —) was the same as that for those proposed for marketing (Process —). b(4)

TABLE 21. Composition of the Phase — Clinical capsule Formulations Manufactured with Process — (— Route —)

Component	Quantity (mg/capsule)		
	0.25 mg Capsules	— mg Capsules	1 mg Capsules
Topotecan Hydrochloride	0.25*		1.0*
Glyceryl Monostearate			
Hydrogenated Vegetable Oil			
Opaque White Hard Gelatin		-	-
Capsule Size —			

Opaque Pink Hard Gelatin				
Capsule Size				
Opaque Yellow Hard Gelatin				
Capsule Size				
Gelatin				
Total Unit Dose				

b(4)

TABLE 22. The Composition of the Proposed to-be-Marketed Formulations Manufactured with Process Route)

Component	Quantity (mg/capsule)	
	0.25 mg Capsules	1 mg Capsules
	Active Component	
Topotecan Hydrochloride	0.25*	1.0*
	Inactive Components	
Glyceryl Monostearate		
Hydrogenated Vegetable Oil		
Opaque White Hard Gelatin		
Capsule Size		
Opaque Pink Hard Gelatin		
Capsule Size		
Gelatin		
Total Unit Dose		

b(4)

2.5.3 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The relative bioavailability of topotecan from the proposed to-be-marketed capsule formulations (1.0 mg) manufactured with Process was compared to the Phase clinical capsule formulations (1.0 mg) manufactured with Process following oral administration of a single flat 4 mg oral dose (**Study 692**). This was a Phase 1, open-label, randomized, multi-center, crossover study in 78 patients with advanced solid tumors. Patients were randomized (1:1) to receive either **Treatment A** (Phase 3 clinical formulation, Process 1/A3) or **Treatment B** (proposed for marketing formulation, Process 3/A4) on both Day 1 (Sequence AB) and Day 8 (Sequence BA) of Course 1 at a flat single 4 mg oral dose (4x1.0

mg capsules) in the fasted state. The results of this study are shown in Figures 10 and 11 and Tables 23-25.

FIGURE 10 . Mean Plasma Concentration-Time Profiles for Total Topotecan Following a Single 4 mg Oral Topotecan Dose (Study 692)

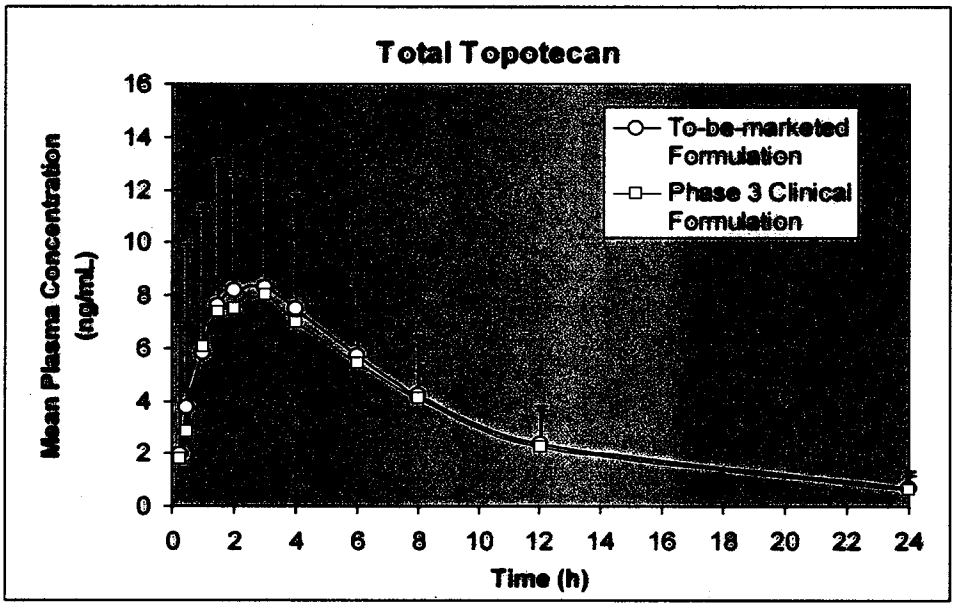


FIGURE 11. Mean Plasma Concentration-Time Profiles for Topotecan Lactone Following a Single 4 mg Oral Topotecan Dose (Study 692)

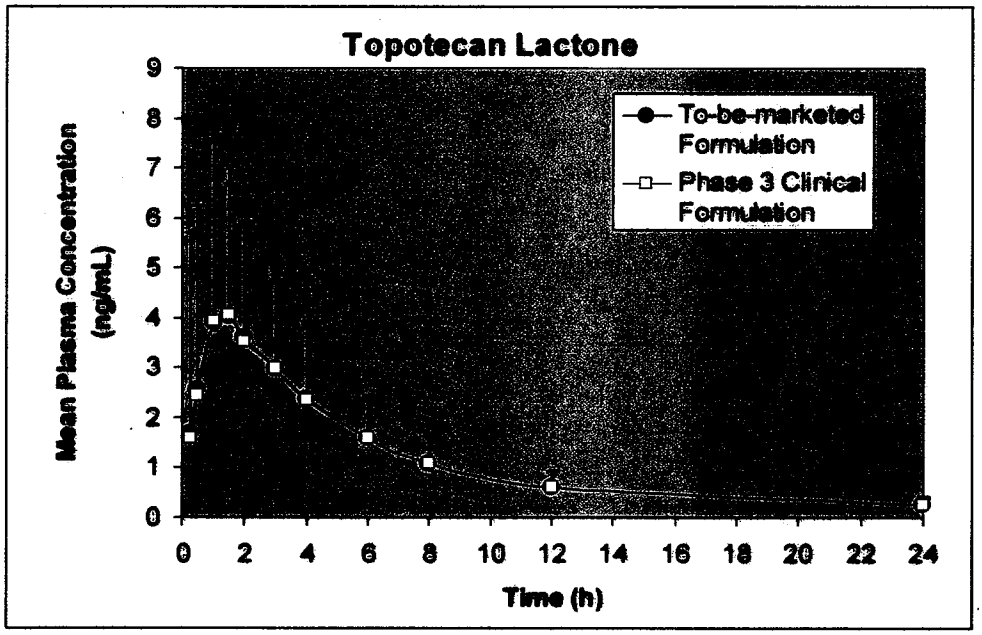


TABLE 23. Mean±SD (CV%) PK Parameters following a Single 4 mg Oral Dose of Topotecan

PK Parameter	@4 mg Single Oral Dose of Topotecan (N=78)	
	To-Be-Marketed Formulation	Phase 3 Clinical Formulation
Total Topotecan		
C_{max} (ng/mL)	10.2±5.9 (58%)	9.6±5.1 (53%)
*T_{max} (h)	2.5 (0.5-8.07)	2.02 (0.5-8.12)
$AUC_{0-\infty}$ (ng·h/mL)	82.1±38.3 (47%)	82.9±59.6 (72%)
t½ (h)	6.1±2.3 (37%)	5.7±1.5 (26%)
Topotecan Lactone		
C_{max} (ng/mL)	5.5±4.03 (73%)	5.4±3.5 (65%)
***T_{max} (h)**	**1.5 (0.5 - 8.03)**	**1.5 (0.5 – 8.07)**
$AUC_{0-\infty}$ (ng·h/mL)	26.7±13.1 (49%)	26.2±13.8 (53%)
t½ (h)	5.0±1.7 (35%)	5.4±2.4 (44%)

*Median (range)
@The 4 mg dose was the closest to the MTD that established for the 5-day QD regimen based on a mean body surface area of 1.85 m^2 (2.3 mg/m^2 once daily for 5 days).

TABLE 24. Statistical Analysis of Primary PK Parameters for Total Topotecan (N=78)

Parameter	Geometric Mean		Mean Ratio (B/A)	90% CI
	*A (Reference)	*B (Test)		
$AUC_{0-\infty}$ (ng.h/mL)	69.6	73.8	1.06	[100-112%]
C_{max} (ng/mL)	8.41	8.92	1.06	[99-114%]

*A and B are the Phase 3 clinical and to-be-marketed 1-mg capsule formulations, respectively

TABLE 25. Statistical Analysis of Primary PK Parameters for Topotecan Lactone (N=78)

Parameter	Geometric Mean		Mean Ratio (B/A)	90% CI
	*A (Reference)	*B (Test)		
$AUC_{0-\infty}$ (ng.h/mL)	22.3	23.1	1.03	[98-111%]
C_{max} (ng/mL)	4.42	4.43	1.00	[91-111%]

*A and B are the Phase 3 clinical and to-be-marketed 1-mg capsule formulations, respectively

In conclusion, bioequivalence was demonstrated between the proposed to-be-marketed 1 mg capsule formulation and the Phase 3 clinical 1 mg capsule formulation, as the 90% CI for log-transformed C_{max} and $AUC_{0-\infty}$ for both total topotecan and topotecan lactone were within the acceptable range of 0.80 to 1.25 and p-value > 0.05. b(4)

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on the absorption of topotecan was examined in the BE **Study 692** in 26 patients with advanced solid tumors. Patients were randomized to receive a single 4 mg oral topotecan dose after either an overnight fast (Day 1 of Course 1) or a high-fat breakfast (Day 1 of Course 2). The high-fat breakfast constituted approximately 50% of the total caloric content of the meal and consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, 8 ounces of whole milk and a cup of coffee or tea) as recommended in the FDA guidance on the effect of food on bioavailability and bioequivalence. The proposed to-be-marketed formulation (1 mg capsule) was used in this sub-study. The results are shown in Tables 26-28.

TABLE 26. Effect of Food on the PK Parameters of Total Topotecan and Topotecan Lactone

PK Parameter	4 mg Single Oral Dose of Topotecan (N=26)	
	Fasted	Fed
Total Topotecan		
C_{max} (ng/mL)	10.0±5.2 (51%)	10.6±5.5 (52%)
T_{max} (h)	2.0 (0.5-4.0)	4.0 (1.0-12)
$AUC_{0-\infty}$ (ng·h/mL)	78.7±38.9 (49%)	86.6±41.7 (48%)
t½ (h)	5.9±2.1 (36%)	5.1±0.88 (17%)
Topotecan Lactone		
C_{max} (ng/mL)	5.5±3.4 (61%)	4.8±2.6 (54%)
T_{max} (h)	**1.5 (0.5 – 6.0)**	**3.0 (1.0 – 8.0)**
$AUC_{0-\infty}$ (ng·h/mL)	24.6±9.8 (40%)	27.8±10.9 (39%)
t½ (h)	5.4±2.1 (38%)	4.9±2.1 (42%)

*Median (range)

TABLE 27. Statistical Analysis of Primary PK Parameters for Total Topotecan (N=26)

Parameter	Geometric Mean		Mean Ratio (Fed/Fasted)	90% CI
	Fasted (Reference)	Fed (Test)		
$AUC_{0-\infty}$ (ng.hr/mL)	68.6	76.3	1.11	[94-118%]
C_{max} (ng/mL)	8.36	9.31	1.11	[96-129%]

TABLE 28. Statistical Analysis of Primary PK Parameters for Topotecan Lactone (N=26)

Parameter	Geometric Mean		Mean Ratio (Fed/Fasted)	90% CI
	Fasted (Reference)	Fed (Test)		
$AUC_{0-\infty}$ (ng.hr/mL)	21.9	24.8	1.13	[80-110%]
C_{max} (ng/mL)	4.23	4.12	0.97	[79-120%]

Following a high-fat breakfast, the extent of absorption (C_{max} and $AUC_{0-\infty}$) was similar in the fed and fasted state; however, the rate of absorption (T_{max}) was delayed from 2 to 4 hours for total topotecan and from 1.5 to 3.0 hours for topotecan lactone.

In the clinical studies, patients were instructed to take topotecan capsules once daily dose with a glass of water on an empty stomach, preferably in the morning and at least thirty minutes before a meal.

As there is no obvious food effect on the exposure of oral topotecan, the label will indicate that oral Hycamtin may be administered without regard to food.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

A dissolution method was developed for oral topotecan 0.25 mg and 1 mg hard gelatin capsules using USP [redacted] For more details on the dissolution method and specifications, please refer to Chemistry Review for this NDA. b(4)

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology studies?

Total topotecan, topotecan lactone, open-ring carboxylate form, and N-desmethyl topotecan were measured in plasma samples.

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

Total (bound+unbound) drug concentrations of total topotecan and topotecan lactone were measured in plasma samples. Topotectan is 35% bound to human plasma proteins.

2.6.3 What bioanalytical methods are used to assess concentrations?

An isocratic reverse-phase high-performance liquid chromatography separation [redacted] at an excitation wavelength of [redacted] nm and emission wavelength of [redacted] nm was used to measure the concentrations of the active moieties in b(4)

human plasma [*Rosing et al., High-performance liquid chromatographic determination of the novel antitumour drug topotecan and topotecan as the total of the lactone plus carboxylate forms, in human plasma. J Chromatog B 668:107-115, 1995*].

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Calibration curves were linear over range of [redacted] ng/mL for total topotecan and toptecan lactone, [redacted] ng/mL for the open-ring carboxylate, and [redacted] ng/mL for total N-desmethyl topotecan and N-desmethyl topotecan lactone. b(4)

2.6.4.2 What are the lower limits of quantification (LLOQ)?

The LLOQ for total topotecan and topotecan lactone was 0.1 ng/mL.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

TABLE 29. Analytical Summary Statistics (showing Between-run Accuracy and Precision of Quality Control (QC) Samples) b(4)

Study Analyte	Between-Run Precision (%CV)	Between-Run Accuracy (%Bias)
Study 048		
Topotecan lactone	[redacted]	[redacted]
Total Topotecan	[redacted]	[redacted]
Study 049	[redacted]	[redacted]
Topotecan lactone	[redacted]	[redacted]
Topotecan Carboxylate	[redacted]	[redacted]
Study 692	[redacted]	[redacted]
Topotecan lactone	[redacted]	[redacted]
Total Topotecan	[redacted]	[redacted]
Study 101	[redacted]	[redacted]
Topotecan lactone	[redacted]	[redacted]
Total Topotecan	[redacted]	[redacted]
Study 118	[redacted]	[redacted]
Topotecan lactone	[redacted]	[redacted]
Total Topotecan	[redacted]	[redacted]
Study 507	[redacted]	[redacted]
Topotecan lactone	[redacted]	[redacted]
Total Topotecan	[redacted]	[redacted]
BCR10001	[redacted]	[redacted]
Topotecan lactone	[redacted]	[redacted]
Total Topotecan	[redacted]	[redacted]
Study 204	[redacted]	[redacted]
Total Topotecan	[redacted]	[redacted]

3. Clinical Pharmacology Labeling Recommendations

*Labeling recommendations were made in Sections 7.0, 8.0 and 12.0 of the proposed PLR labeling for oral Hycamtin[The **Black** statements are the originally prescribing Information for Hycamtin for Injection (NDA 20-671). The **Blue** statements are proposed by Sponsor for Oral Hycamtin. The **Red** ones are our proposed labeling recommendations for Oral Hycamtin.*

2 DOSAGE AND ADMINISTRATION
The recommended dose of Oral HYCAMTIN is 2.3 mg/m2/day once daily for 5 consecutive days repeated every 21 days.

Adjustment of Dose in Special Populations:

Renal Functional Impairment: No dosage adjustment of HYCAMTIN appears to be required for treating patients with mild renal impairment (CrCl=50-80 mL/min.). [redacted]. Insufficient data are available in patients with severe renal impairment (CrCl < 30 mL/min) to provide a dosage recommendation for Oral HYCAMTIN.

7 DRUG INTERACTIONS

[redacted]

7.4 Effects of Topotecan on Drug Metabolizing Enzymes

In vitro inhibition studies using marker substrates known to be metabolized by human P450 (CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A) or dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated in vivo.

20 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

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