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A Phase 1 Pharmacokinetic Optimal Dosing Study of Intraventricular Topotecan for Children with Neoplastic Meningitis: A Pediatric Brain Tumor Consortium Study

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Abstract

Purpose—We performed a phase 1 pharmacokinetic optimal dosing study of intraventricular topotecan (IT), administered daily $\times 5$, to determine whether the maximum tolerated dose of IT topotecan was also the pharmacokinetic optimal dose.

Patients and Methods—Patients received topotecan administered through an intraventricular access device (0.1 or 0.2 mg/dose), daily $\times 5$ every other week $\times 2$ (Induction); every 3 weeks $\times 2$ (Consolidation); then every 4 weeks for up to 11 courses (Maintenance). Ventricular CSF pharmacokinetic studies were performed on day 1, week 1 of induction, and in a subset of patients after a single intralumbar topotecan dose on day 1, week 3.

Results—Nineteen patients were enrolled. All were evaluable for toxicity and 18 were assessable for pharmacokinetics. Arachnoiditis requiring corticosteroid therapy occurred in 1/3 patients at the 0.1 mg dose level and 2 of the initial 3 patients enrolled at the 0.2 mg dose level. All subsequent patients were therefore treated with concomitant dexamethasone. Pharmacokinetic evaluation after accrual of the first 7 patients revealed that a topotecan lactone concentration > 1 ng/ml for 8 hours was attained in all patients and thus further dose escalation was not pursued. Results of simulation studies showed that at the dose levels evaluated, $>99.9\%$ of patients are expected to achieve CSF topotecan lactone concentrations > 1 ng/mL for at least 8 h.

Conclusion—Intraventricular topotecan, 0.2 mg, administered daily for 5 days with concomitant dexamethasone is well tolerated and was defined to be the pharmacokinetic optimal dose in this trial.

Keywords

topotecan; intraventricular; neoplastic meningitis; leptomeningeal; pharmacokinetic

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Introduction

The meninges, protected by the blood-brain barrier from the cytotoxic effects of systemic anticancer chemotherapy, are a commonly recognized site of tumor recurrence. Leukemia is the most common cancer with a predilection for leptomeningeal dissemination. However, primary central nervous system tumors (CNS) such as medulloblastoma and glioma; and childhood tumors such as neuroblastoma, retinoblastoma and rhabdomyosarcoma, may also disseminate to the leptomeninges. IT chemotherapy has been an effective strategy in the treatment and prevention of leptomeningeal leukemias. However, it has not dramatically impacted the progression free survival for patients with neoplastic meningitis from solid tumors; in part due to the limited number of IT agents. Therefore, the development of new IT agents with novel mechanisms of action is essential.

Topotecan, a topoisomerase I inhibitor, has anticancer activity against a variety of pediatric tumors. Nevertheless, the optimal topotecan exposure for cytotoxic activity has not been clinically defined [1]. *In vitro* studies evaluating different schedules in cell lines derived from childhood medulloblastomas demonstrated that topotecan was not cytotoxic when the concentration was < 1 ng/mL, regardless of exposure duration. Further studies showed that the IC₉₉ for topotecan lactone was 1 ng/mL for an 8-hour exposure [2]. Although one cannot extrapolate directly from *in vitro* models to the clinic, these data suggest the merit of evaluating topotecan CSF lactone concentrations maintained above this threshold. Such a strategy has been used with methotrexate and cytarabine and appears to be associated with greater efficacy and decreased toxicity [3].

The feasibility of IT topotecan has been previously demonstrated [4-7]. In a phase 1 study of IT topotecan administered every 3 to 4 days, a maximum tolerated dose of 0.4 mg was defined. Six of the twenty-three evaluable patients, including 3 of thirteen with CNS or solid tumors, had evidence of benefit manifest as prolonged disease stabilization or response. A subsequent phase 2 trial in the Children's Oncology Group trial did not demonstrate sufficient activity to pursue development of IT topotecan on that schedule in patients with solid or CNS primary tumors, nevertheless; some patients derived benefit including one child with medulloblastoma who had a cytologic CR and another patient with SD [7]. In children with refractory CNS leukemia, the objective response rate (95% CI) was 38% (15% – 65%) with a median EFS time (95% CI) of 8.1 (2.2 – 15.1) months [8]. In a phase 2 trial in adults with neoplastic meningitis 21% of adults cleared their CSF of malignant cells with an overall median survival of 15 weeks [6]. These clinical data coupled with the phase 1 experience and the substantial preclinical data demonstrating that the anti-tumor activity of topoisomerase I inhibitors is highly schedule dependent [1], prompted us to re-evaluate the dosing schedule for IT topotecan administration. Our goal was to exceed a CSF target concentration, as defined by preclinical studies, for at least 8 hours a day for a minimum of five consecutive days. We also explored CSF expression of matrix metalloproteinases (MMP) and vascular endothelial growth factor (VEGF) as MMPs and VEGF have been correlated with leptomeningeal disease status in some reports [9-13].

PATIENTS AND METHODS

Patient Eligibility

Informed consent was obtained in accordance with federal and institutional guidelines. Patients 3 and < 22 years with neoplastic meningitis from an underlying leukemia/lymphoma (2nd relapse and refractory to conventional therapy, including radiation therapy) or a solid or CNS tumor were eligible if they had a CSF white blood cell (WBC) count > 5/ μ L and blasts. Patients with other tumors had to have tumor cells on cytopathology or MRI evidence of leptomeningeal disease. Recovery from the acute

neurotoxic effects of all prior anticancer therapy was required. Additional eligibility criteria included the willingness to have an intraventricular access device; a performance status 60; and a serum sodium 125 and 150 mmol/L, serum calcium 7 mg/dl, and serum magnesium 0.7 mmol/L. Exclusion criteria included: obstructive hydrocephalus, compartmentalization of CSF flow, dependency on a CSF shunt, uncontrolled infection or other medical illness, or concurrent therapy with XRT, methotrexate ($> 1 \text{ gm/m}^2$), cytarabine ($> 1 \text{ gm/m}^2$), 5-fluorouracil, capecitabine, thioptepa, a nitrosourea, or topotecan.

Dosage and Drug Administration

Patients received IT topotecan daily $\times 5$ every other week $\times 2$ (Induction); every 3 weeks $\times 2$ weeks (Consolidation); then every 4 weeks for up to 11 courses (Maintenance). Lyophilized topotecan was provided in 4 mg vials (GlaxoSmithKline, Philadelphia, PA) that were diluted in 4 ml of sterile water then with preservative-free, pyrogen-free saline to a final volume of 10 ml. Drug was administered through an intraventricular reservoir at a rate of 2.0 ml/min following removal of an isovolumetric amount of CSF. The reservoir was then flushed slowly with 2 ml of CSF or preservative-free normal saline, and pumped 4 to 6 times. In consenting patients, an intralumbar dose was administered on day 1, week 3 for evaluation of pharmacokinetics after intralumbar dosing (Figure 1).

Initially, patients received dexamethasone only if they experienced arachnoiditis. However, after two of three patients at the second dose level experienced arachnoiditis, all subsequent patients were treated with concomitant dexamethasone (0.15 mg/kg po or iv for 5 days).

Based on the results of preclinical cytotoxicity studies³ the optimal dose was defined as a dose producing a ventricular CSF concentration of 1 ng/ml for at least 8 hours. The starting topotecan dose was derived from a pharmacokinetic simulation study of intraventricular topotecan CSF pharmacokinetic data from the initial phase 1 trial [5]. A two compartment model was fit to these data and the median model parameters (K_3 , V_c , K_{cp} and K_{pc}) were estimated. CSF concentrations after various doses were then simulated, and the starting dose of 0.1 mg was chosen with plans to escalate in increments of 0.1 mg to the recommended phase 2 dose of 0.4 mg previously defined using an every 3 to 4 day schedule of administration [5].

Concomitant therapy

Patients could receive chemotherapy to control systemic disease provided if it was not a phase I agent, did not significantly penetrate the CSF, or had known unpredictable CNS side effects.

Off treatment criteria

Criteria for discontinuation of protocol treatment included: unacceptable toxicity as defined in the protocol, progressive disease, development of a medical or psychiatric condition that rendered them incapable of further therapy on protocol, refusal of further therapy or completion of protocol therapy.

Pretreatment and Follow-Up Studies

Pretreatment evaluations included a history and physical examination, complete blood count; electrolytes, liver and renal function tests; and a pregnancy test in females of childbearing age. CSF studies performed included a cell count and differential; protein; glucose and cytological examination of lumbar and ventricular CSF. All patients had a brain MRI with/without contrast within 2 weeks prior to therapy, as well as spine MRI spine for patients with primary CNS tumors and as clinically indicated for leukemia/lymphoma.

A history and physical and neurological exam were performed weekly during induction, and regularly thereafter. CSF was evaluated immediately prior to the first dose, weekly during induction, every 2 weeks during consolidation, monthly during maintenance, and four weeks after the first negative evaluation. Lumbar and ventricular CSF samples were evaluated at the completion of induction and consolidation, and then every 12 weeks.

Criteria for Assessment of Toxicity, Response, and Survival

Adverse events were evaluated according to the NCI Common Toxicity Criteria (Version 3.0). Treatment was stopped if there was grade 3 non-hematologic toxicity considered to be at least possibly related to topotecan with the following exceptions: grade 3 headache prevented after subsequent doses using pre-medication with oral analgesics or grade 3 nausea/vomiting that was well-controlled or prevented after subsequent doses with antiemetics. During the dose escalation phase, patients who experienced arachnoiditis (clinically characterized by fever, nausea and/or vomiting, and headache $\pm$ back pain) were exempted from this criterion. However, after the routine use of dexamethasone, patients with arachnoiditis could not receive further topotecan.

Response was classified as a complete response (CR), stable disease (SD), or progressive disease (PD). A CR required complete clearing of malignant cells from lumbar and ventricular CSF on two consecutive studies 4 weeks apart; complete clearing of disease on 2 consecutive MRI scans 4 weeks apart (if applicable), and a stable or improved physical exam.

PD in leukemia required the presence of blasts and an increase in the number of WBCs in ventricular or lumbar CSF when compared to the lowest (best) CSF WBC count during therapy, with a minimum required CSF WBC count for PD of >10 cells/mm³. For asymptomatic patients with CSF WBC counts > 10 and < 30 /mm³, the increase in the CSF WBC count had to be at least 100% and not attributable to arachnoiditis or infection. In patients with CSF WBC counts > 30 /mm³, the increase in the WBC count had to be 50% and not attributable to arachnoiditis or infection. Patients with CSF blasts and worsening physical or neurologic findings clearly attributable to CNS leukemia were considered to have PD, regardless of the increase in the CSF WBC count. Radiographic PD was defined as an increase of 25% in the size of measurable lesions or new lesions on MRI.

PD in patients with leptomeningeal involvement from solid tumors was defined as the occurrence of new malignant cells in the CSF on two consecutive occasions at least one week apart after at least 3 previous consecutive negative CSF cytologies obtained at least one week apart or an increase 25% in the size of measurable lesions on MRI or new lesions on MRI after a CR; the presence of new lesions of or increasing evidence of leptomeningeal enhancement. Patients were considered to have stable disease (SD) if they did not meet the criteria for either a CR or PD and without worsening of physical findings clearly attributable to disease.

Statistical Considerations

The trial was initially designed to determine whether the MTD (recommended dose) was also the “PK optimal dose (PKOD),” i.e., a dose that maintained topotecan lactone concentrations > 1 ng/mL in the CSF for at least 8 hours after intraventricular dosing. Dose escalation was performed using a standard 3+3 phase 1 design. Once the recommended dose was identified the cohort was to be expanded to 25 patients. If 23 of 25 patients treated at the recommended dose achieved the targeted level then based on the Blyth-Still-Casella approach [15,16], we would be 90% confident that at least 80.4% of future patients would achieve the target level. Patients in the dose escalation phase were prospectively

incorporated into the PKOD evaluation phase. Exploratory analyses including summary statistics, correlations and simple pair-wise tests (Wilcoxon Signed Rank) to detect changes between on-treatment and baseline values were planned for MMP (MMP2, MMP3, MMP9 and TIMP1) and VEGF levels.

Safety monitoring and stopping rules for toxicity were in place for the PK optimality phase. If at any time more than 33% of the patients experienced unacceptable toxicity, accrual would be suspended pending Data Safety Monitoring Board review. Since the PK data demonstrated that the goal of exceeding a threshold concentration of 0.1 ng/ml for at least 8 hours was achieved in all patients at the 0.1 and 0.2 mg doses levels, the protocol was amended to halt further dose escalation and enroll all subsequent patients at the 0.2 mg, to avoid the potential for increased toxicity associated with higher doses. Due to slow accrual concerns, exploring 0.2 mg dose as the potential PKOD was felt to be the more efficient approach with a higher likelihood of success.

Pharmacokinetic and Biologic Studies

Ventricular CSF pharmacokinetic studies were performed after the first intraventricular topotecan dose (day 1, week 1) and after an intralumbar dose in consenting patients (day 1, week 3). Samples were obtained prior to and at 0.25, 0.5, 1, 3, and 6-8 hours after drug administration. Samples were centrifuged for 2 min at 7000 x g and 200 μ L was added to 800 μ L of -20°C methanol. The mixture was processed as previously described, and samples were stored at -70°C until analysis using a previously described HPLC method [14].

Topotecan lactone CSF concentration-time data were analyzed using two approaches. First, a two-compartment model, with a central CSF compartment and a peripheral compartment, was fit to the CSF topotecan lactone data using maximum likelihood estimation as implemented in ADAPT II (Supplemental figure 1) [17]. First-order rate constants were used to describe the equilibrium between the CSF and peripheral compartments and the elimination from the peripheral compartment. Estimated parameters included the volume of the central CSF compartment (V_l), equilibrium rate constants (k_{12} , k_{21}), and the elimination rate constant (k_e). The time that the topotecan CSF lactone concentration exceeded 1 ng/ml was estimated from simulations using individual parameter estimates. Second, all CSF concentration-time data after intraventricular administration were analyzed simultaneously using the same structural model and nonlinear mixed-effects modeling with NONMEM Version 7 (Icon Development Solutions, Ellicott City, MD). Inter-individual variability terms with an assumed log-normal distribution were added to each structural parameter. A proportional error model was used with residuals assumed to have a normal distribution. The suitability of the model was assessed by inspection of residual plots and posterior predictive check. A Monte Carlo simulation of 1000 patients per dose level was performed with the final model by simulating the concentration versus time curves after doses of 0.10, 0.15, and 0.20 mg and calculating the CSF topotecan lactone concentration at 8, 16, and 24 h.

VEGF, TIMP-1, MMP-9, MMP-2 and MMP-3 concentrations were measured in duplicate using Quantikine Immunoassay kits (R&D Systems, Minneapolis, MN) according to manufacturer's instructions. CSF was diluted with the diluent provided and concentrations were calculated using a standard curve obtained using the kit standards. The presence or absence of the activated forms of MMP-2 and MMP-9 were detected by gelatin zymography [18].

RESULTS

PBTC-019 was opened for enrollment between October 2006 and August 2010. Nineteen patients, all eligible, were enrolled including 3 at the 0.1 mg dose level and 16 at the 0.2 mg dose level. The study was closed short of the intended accrual for determining the PKOD due to slow accrual and the fact that investigational drug supply was no longer available. All patients were evaluable for toxicity and 18 were evaluable for the pharmacokinetic evaluation. Patient characteristics are shown in Table I.

Toxicity

Intraventricular topotecan administered daily for 5 consecutive days at doses of 0.1 or 0.2 mg was well tolerated (Table II). At the 0.1 mg dose level one of three patients experienced grade 2 arachnoiditis. At the 0.2 mg dose level the first 3 patients experienced arachnoiditis [(grade 2 (n=1) and grade 3 (n=2)] that was readily reversible with corticosteroids and did not recur in the one patient who went on to receive subsequent doses. Thus, all subsequent patients enrolled on this trial were treated with concomitant dexamethasone. One patient at the 0.2 mg dose level experienced a dose-limiting headache temporally associated with the first dose and did not receive further IT topotecan. No other dose limiting toxicities occurred.

Three patients were removed from protocol therapy for adverse events or complications including: a CSF leak at the Ommaya reservoir surgical site, an Ommaya reservoir infection and concomitant bone marrow relapse, and the development of hydrocephalus requiring a VP shunt. Three patients discontinued protocol therapy: one to receive radiation therapy per the recommendation of the treating physician, one who was noncompliant with protocol therapy, and one who withdrew consent.

Antitumor Activity

No complete anti-tumor responses were observed. One medulloblastoma patient completed all courses of therapy (54 weeks) with SD. One patient with germinoma had SD for 34 weeks and a patient with medulloblastoma had SD for 24 weeks and withdrew because the family had difficulty meeting protocol requirements. The remaining patients were removed from protocol therapy for progressive disease.

Pharmacokinetics

Pharmacokinetic data from ventricular CSF were available for 18 patients [0.1 mg (n=3); 0.2 mg (n=15)] after intraventricular dosing, six of whom also consented to sampling after an intralumbar dose. The median (range) pharmacokinetic parameters after the day 1 dose included: volume of distribution, 0.021 L/m² (0.0021 to 0.168 L/m²), k_e , 1.00 hr⁻¹ (0.013 to 5.27 hr⁻¹), C_{max} , 7590 ng/ml (1134 to 21,380 ng/ml), and estimated time above 1 ng/ml, 24 hr (10.9 to >24 hr). The topotecan concentration versus time data from the six patients receiving intralumbar topotecan were variable with median (range) time to maximum concentration and maximum concentration of 4.5 hr (0.43 to 6.3 hr) and 56.7 ng/ml (2.7 to 867.3 ng/ml), respectively. However, all patients had topotecan lactone concentrations in excess of 1 ng/ml for > 8 hours after lumbar dosing.

Once enrollment was complete, all intraventricular data were reanalyzed with a population approach using NONMEM, which enhances parameter estimation, particularly for experimental designs with sparse sampling. A two-compartment pharmacokinetic model for topotecan lactone adequately fit the intraventricular CSF concentration-time data with little bias (Supplemental figure 2). The model parameters are presented in Table III. BSA was

assessed as a covariate based on visual inspection of plots of BSA versus each model parameter. No relationships were, which supports the current method of flat dosing.

Based on the individual model predictions, all patients had CSF topotecan lactone concentrations above 1 ng/mL at 8 h. Monte-Carlo simulations were used to further examine the relationship between topotecan dose and time the CSF topotecan lactone concentrations were above 1 ng/mL as shown in Figure 2. At the dose levels evaluated, >99.9% of patients are expected to achieve CSF topotecan lactone concentrations > 1 ng/mL for at least 8 h (Table IV). At a dose of 0.2 mg, 38% of patients are predicted to maintain CSF concentrations > 1 ng/mL for at least 24 h.

Correlative Biology Studies

Baseline and at least 1 on treatment value were available from 12 and 11 patients for MMP and VEGF analyses, respectively. No association was detected between MMP and VEGF levels and PFS.

DISCUSSION

This study demonstrates that IT dosing of topotecan daily for 5 days with concomitant corticosteroid therapy to prevent arachnoiditis is feasible and achieves cytotoxic concentrations in ventricular CSF. Both the 0.1 and 0.2 mg doses produce CSF topotecan concentrations exceeding the 1 ng/mL for 8 hr threshold associated with cytotoxicity preclinically; which may be advantageous for increasing cytotoxicity [2]. Whether shorter or longer durations of exposure to topotecan lactone concentrations exceeding the 1 ng/mL threshold would be superior to the 5 day schedule is unknown.

The primary goal of the study was to use pharmacokinetic modeling and simulation to determine the likelihood that an intraventricular dose of 0.2 mg topotecan would achieve a CSF topotecan lactone concentration exceeding 1 ng/mL for at least 8 h. Data from the eighteen patients were sufficient to estimate the structural model parameters with good precision (13 – 23% standard error) and estimate inter-individual variability terms with adequate precision (27 – 38% standard error). Model simulations showed that essentially 100% of patients are expected to achieve the cytotoxic threshold with an intraventricular dose of 0.2 mg. Furthermore, almost twice as many patients at the 0.2 mg dose level were predicted to maintain a CSF concentration exceeding 1 ng/mL for 24 h compared versus the 0.1 mg dose level.

Another objective of the pharmacokinetic studies was to evaluate the ventricular CSF topotecan concentrations after intralumbar administration. Six patients consented to participate in these optional pharmacokinetic studies, and wide interpatient variability was observed in their topotecan lactone CSF concentration-time data. Nonetheless, the observed ventricular topotecan lactone concentration was > 1 ng/mL for 8 hours in all six. Thus intralumbar administration can achieve cytotoxic ventricular drug exposures, although the duration of that exposure is shorter than after intraventricular administration.

Despite attaining cytotoxic exposures in CSF, topotecan did not result in objective responses. Three patients (2 with medulloblastoma, 1 with germinoma) had SD for 24 weeks. Because there were eight different tumor types represented among the eighteen patients, we are unable to make definitive conclusions regarding anti-tumor activity. In the absence of objective responses, we were not able to detect correlation between MMP or VEGF expression in CSF and disease status. The use of concomitant dexamethasone may also decrease the usefulness of MMPs as a disease marker, because such treatment decreases CSF MMP9 concentrations in infectious meningitis [19,20].

Leptomeningeal metastases from solid tumors remain extremely difficult to treat, and the patients in this study were heavily pretreated. Thus the absence of objective responses isn't surprising, particularly given the extent of disease and heterogeneity of tumor types enrolled on this trial. Nonetheless, this study demonstrates the feasibility of achieving prolonged cytotoxic exposure to topotecan in the CSF, and provides a potential treatment option for patients with recurrent or refractory CSN leukemia. Similar to other trials, intraventricular topotecan was overall well tolerated [4-7].

In the future, IT topotecan may provide an option for patients at high risk of leptomeningeal dissemination if predictive biomarkers for CSF metastases are available. Those subsets of patients designated to be at high risk of leptomeningeal dissemination could then receive "preventative" IT therapy with topotecan either alone or in combination with other intraventricular or systemic therapies that penetrate the blood-brain barrier.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Schema for intraventricular topotecan administration.

Figure 2.

The relationship between TPT dose (0.1, 0.15, and 0.2 mg) and time the CSF topotecan lactone concentrations are above 1 ng/mL was determined using Monte-Carlo simulations. Time above 1 ng/mL (noted by vertical dashed line) was calculated for each simulated patient.

Table I

Patient Characteristics

Characteristic	Dose Level	
	0.1 mg (n=3)	0.2 mg (n=16)
Age (years)		
Median (range)	7.8 (3.6 -8.3)	11.4 (3.2 -20)
Sex		
Males	2	9
Females	1	7
Ethnicity		
Hispanic or Latino	0	1
Non-Hispanic	3	14
Unknown	0	1
Race		
Black	0	2
Unknown	0	2
White, non-Hispanic	3	12
Diagnosis		
Acute Leukemia	0	2
ATRT	0	2
Ependymoma	0	3
Germinoma	0	2
Glioblastoma multiforme	0	1
Medulloblastoma	3	4
Pilocytic astrocytoma	0	1
Pineoblastoma	0	1

Table II
Adverse events with attribution of possibly, probably or definitely related to IT topotecan

Event	Grade			
	1	2	3	4
Albumin	-	1	-	-
Alopecia	-	1	-	-
Anorexia	1	-	-	-
Arachnoiditis	-	2	2	-
Diarrhea	1	-	-	-
Electrolytes [^]	15	1	1	-
Diarrhea	1	-	-	-
Fatigue	5	-	-	-
Fever	2	-	-	-
Headache	1	2	-	1
Hepatic [#]	1	1	1	-
Infection/Febrile Neutropenia	-	-	1	-
Nausea	2	-	1	-
Vision-blurred	1	-	-	-
Vomiting	5	1	-	-

* More than 1 event may have occurred in the same patient;

[^] Includes Na, K, Phos. Mg and/or glucose;

[#] Includes ALT, AST and/or bilirubin

Table III
Pharmacokinetic model parameters from population analysis

Parameter	Value	SE (%CV)	Inter-individual variability (%CV)	SE (%CV)
V_1 (L)	0.0184	22.9	75.5	32.5
k_{12} (hr^{-1})	1.98	12.9	33.6	35.3
k_{21} (hr^{-1})	0.0607	23.2	81.5	27.2
k_e (hr^{-1})	0.288	16.2	35.2	37.7
Residual error (%CV)	25.8	20.6	-	-

Table IV
Estimated time above 1 ng/mL threshold

Dose	<u>% patients above threshold</u>		
	8 h	16 h	24 h
0.1 mg	100	76	21
0.15 mg	100	84	31
0.2 mg	100	88	38