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Study No: GF120918/BCR10001
Title: A Phase I, Randomized, Open-Label, Parallel-Cohort, Dose-Finding Study of Elacridar (GF120918) in Combination with 2.0 mg Oral Topotecan in Cancer Patients.
Rationale: The purpose of the current study was to determine the minimum dose of elacridar required for maximal oral bioavailability of topotecan and to select an appropriate schedule of administration. The dose of elacridar previously tested (1000 mg) was the highest dose level tested in the multi-drug resistance (MDR) reversal program and was shown to have effects on systemic P-glycoprotein (P-gp) activity. The goal of the current proposal was to have a localised effect on breast cancer resistance protein (BCRP) and P-gp activity in the gastrointestinal tract, while minimising systemic effects on the transporters. In addition, once the appropriate dose and schedule of elacridar administration was determined, the purpose of the study was to determine a recommended oral dose of topotecan in combination with elacridar for five consecutive days every 21 days.
Phase: I
Study Period: Part 1: 14 June 2002 to 02 June 2003 and Part 2: 21 February 2003 to 04 June 2004
Study Design: The initial part of the study was a randomized, open-label, parallel-cohort study in cancer subjects. The effect of elacridar on oral topotecan bioavailability was studied using a single dose of elacridar at various dose levels in combination with 2.0 mg oral topotecan as compared to data after 2.0 mg intravenous (IV) topotecan. Subjects were randomized to one of five dose levels of elacridar (100, 300, 500, 700, and 1000 mg); with four subjects planned at each dose level. Each subject was studied for the determination of oral topotecan bioavailability on two occasions, one week apart. In addition, subjects were randomised to either simultaneous administration of oral topotecan and elacridar or administration of elacridar 60 minutes prior to oral topotecan administration on Day 1 or Day 8 of the study. Subjects received IV topotecan on Days 15 to 19 (as 2.0 mg on Day 15 and 1.5 mg/m ² on Days 16 to 19). Blood samples for the determination of topotecan plasma concentrations were collected on Days 1, 8, and 15. Blood samples for the determination of elacridar plasma concentrations were collected on Day 1 and Day 8. After completing the first course of IV treatment (Days 15 to 19), and following a 16-day washout, subjects could continue to receive standard IV topotecan therapy (1.5 mg/m ² /d for 5 days every 21 days) until disease progression or toxicity warranted discontinuation of therapy. Once the dose and schedule of elacridar was selected, a dose-escalation of oral topotecan was performed to estimate the maximum tolerated dose (MTD) of oral topotecan, when co-administered with elacridar, in the standard daily x 5 days regimen administered every 21 days.
Centres: Two centres in Netherlands
Indication: Histologically confirmed diagnosis of cancer
Treatment: Patients received a single oral dose of 2.0 mg topotecan on Days 1 and 8 in combination with a single oral dose of one of the following dose levels of elacridar: 100, 300, 500, 700, or 1000 mg. Four patients were randomized to each dose level of elacridar and received that dose on both days. Elacridar was given 60 minutes before oral topotecan on one day and simultaneously with oral topotecan on the other day. IV topotecan 2.0 mg was administered on Day 15, followed by administration of IV topotecan 1.5 mg/m ² on Days 16-19. All infusions of IV topotecan were over 30 minutes. Patients were eligible to continue to receive IV topotecan at 1.5

mg/m² dx5 every 21 days until disease progression or toxicity warranted discontinuation of therapy.

Once the dose and schedule of elacridar was selected, a dose-escalation of oral topotecan was performed to estimate the MTD of oral topotecan when co-administered with elacridar, in the standard daily x 5 days regimen administered every 21 days. The initial dose of topotecan was 1.0 mg, dosed daily x 5 days with 100 mg elacridar. Dose escalations of topotecan were made in ≤ 0.5 mg increments, if tolerated, up to a maximum daily dose of 4.0 mg. De-escalations were not limited in size, but were, at a minimum, a multiple of 0.25 mg since this is the smallest capsule size of topotecan.

Objectives: The primary objective of the study was to determine the minimum dose of elacridar required for maximum oral bioavailability of oral topotecan, the appropriate schedule of co-administration of oral topotecan and elacridar and to determine the dose-limiting toxicities (DLT) and MTD of oral topotecan when co-administered with a fixed dose of elacridar in the standard daily x 5 days regimen administered every 21 days.

Methods: Blood samples for the determination of topotecan plasma concentrations were collected on Days 1, 8, and 15. Blood samples for the determination of elacridar plasma concentrations were collected on Day 1 and Day 8. Plasma samples were obtained by centrifugation of the blood samples and the samples were analysed by a high performance liquid chromatography (HPLC) method. Part I: Pharmacokinetic (PK) parameter values for topotecan (total and lactone) were listed and summarized for each elacridar dose level and schedule of elacridar in Part I. For elacridar in part I, PK parameter values were listed and summarized for each dose level. With the exception of t_{max} , the PK parameters were \log_e -transformed and geometric means were calculated, along with the corresponding 95% confidence intervals (CIs). Estimates of t_{max} and corresponding 95% CIs were obtained using standard non-parametric methods. A repeated-measures, multivariate analysis was performed to examine the effects on oral bioavailability of the within-subject factor (i.e., schedule at 2 levels: simultaneous or 60 minutes pre-dose), the between-subjects factor (i.e., elacridar dose at 5 levels), and the interaction of these two factors.

Part II: Individual subject parameter values, as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, standard deviation and geometric mean of \log -transformed parameters) were reported by cohort. The intra-subject variability of systematic exposure (AUC and C_{max}) to topotecan when co-administered with elacridar and the inter-subject variability of all pertinent PK parameters of systematic exposure to the drugs were derived using per-subject Cycle 1 and 2 data. A mixed effect analysis of variance (ANOVA) model was used for the calculation with subject as a random effect. The model also included factors of treatment dose and cycle as fixed effects. Pharmacokinetic parameters were \log_e -transformed. Standard deviation of logs (SD) was reported. PK parameters derived from the urinary topotecan data were summarized and listed. The effect of urinary pH on the renal elimination of topotecan was evaluated by correlating the apparent renal clearance (CL_r/F) or percentage of dose excreted in the urine ($100 \cdot Ae/dose$) and urinary pH. Correlation coefficients and their associated p values were calculated using Spearman's rank correlation method. All adverse events (AEs) and drug-related AEs were summarized by body system within these tables. A separate table was produced to summarize AEs by toxicity grade. Any deaths and serious adverse events (SAEs) were listed and summarized as appropriate.

Study Population: Subjects ≥ 18 years of age with histologically confirmed diagnosis of cancer who had no previous anti-cancer therapy, surgery or extensive radiotherapy for at least 4 weeks prior to study entry (no previous nitrosourea or mitomycin C therapy for at least 6 weeks prior to study entry), ECOG performance status ≤ 2 , adequate haematological, hepatic, and renal function, and a signed informed consent.

Number of Subjects:	Part 1	Part 2
Planned N	30	

Randomised/Entered N	24	15		
Completed n (%)	19 (79)	7 (47)		
Total Number Subjects Withdrawn N (%)	5 (21)	8 (53)		
Withdrawn due to Adverse Events n (%)	2 (8)	5 (33)		
Withdrawn due to Lack of Consent n (%)	0	1 (7)		
Withdrawn due to Lost to Follow up	0	1 (7)		
Withdrawn for Other Reasons n (%)	3 (13)	1 (7)		
Demographics	Part 1	Part 2		
N (ITT)	24	15		
Females: Males	16:8	5:10		
Mean Age in Years (SD)	55.0 (10.9)	52.7 (14.4)		
Mean Weight in Kg (SD)	74.5 (13.7)	73.8 (14.4)		
White n (%)	24 (100)	15 (100)		
Primary PK Conclusions: Total topotecan and topotecan lactone				
Elacridar Dose (mg)	Geometric Mean (95% CI) [n]			
	Total Topotecan AUC_(0-∞) (ng.h/mL) [n]		Topotecan Lactone AUC_(0-∞) (ng.h/mL) [n]	
	Simultaneous	Sequential (elacridar 60 min before topotecan)	Simultaneous	Sequential (elacridar 60 min before topotecan)
100	102 (91.5-114) [4]	107 (82-140) [4]	101 (81.4-126) [3]	112 (82.9-151) [3]
300	98.4 (67.5-143) [4]	101 (79.0-129) [4]	92.1 (70.4-121) [4]	97.6 (77.2-123) [4]
500	107 (64.4-176) [3]	110 (89.0-135) [4]	95.1, 127 [2]	111 (96.2-129) [3]
700	76.5, 100 ¹ [2]	80.5 (57.4-113) [3]	80.4, 101 [2]	68.7, 82.2 [2]
1000	110 (94.3-129) [4]	109 (88.9-135) [4]	111 (74.9-166) [3]	104 (59.2-184) [3]
1: Observed values, CI= confidence interval				

Elacridar PK		Geometric Mean (95% CI)			
Dose (mg)	Treatment	n	AUC _(0-t) (ng.h/mL)	C _{max} (ng/mL)	t _{max} (h) ¹
100	Simultaneous	4	1168 (252-5404)	81.4 (19.2-345)	6.00 (4.00-7.95)
	Sequential	4	935 (205-4260)	62.9 (13.0-305)	7.18 (7.00-11.02)
300	Simultaneous	4	895 (434-1847)	66.6 (38.2-116)	4.00 (2.03-4.10)
	Sequential	4	975 (579-1642)	81.5 (55.0-121)	6.01 (2.03-7.08)
500	Simultaneous	4	822, 2900 ²	100 (41.7-241)	4.04 (2.07-8.02)
	Sequential	4	1353 (451-4054)	104 (52.6-207)	4.51 (2.03-7.02)
700	Simultaneous	4	1300 (770-2195)	97.8 (55.8-171)	4.13 (4.02-8.40)
	Sequential	4	956 (571-1602)	97.2 (49.6-190)	3.05 (2.50-5.18)
1000	Simultaneous	4	2109 (1771-2511)	140 (114-171)	6.02 (6.02-8.17)
	Sequential	4	2629 (1660-4166)	185 (138-248)	6.03 (3.02-9.08)

1. median (range), n=2, observed values.

Part II						
Total Topotecan Geometric Mean (95% CI) PK on Day 1 of each Cycle						
Dose (mg)	Cycle	n	AUC(0-∞) (ng.h/mL)	C _{max} (ng/mL)	t _{max} (h) ¹	t _{1/2} (h)
1.0	1	3	39.2 (13.6-113)	4.53 (2.35-8.71)	4.03 (2.00-4.03)	4.33 (2.03-9.21)
	2	1	28.1 ³	4.35	4.00	2.65
1.5	1	3	49.7 (26.3-94.1)	8.14 (4.08-16.2)	1.90 (1.50-2.08)	3.65 (1.52-8.79)
	2	3	58.7 (23.0-150)	8.76 (3.19-24.1)	2.00 (2.00-2.23)	4.07 (2.51-6.60)
2.0	1	6	51.0 (24.6-106)	8.04 (4.22-15.3)	2.00 (2.00-4.00)	2.99 (2.14-4.20)
	2	6	70.9 (44.0-114)	9.75 (5.58-17.0)	4.00 (2.00-6.03)	4.35 (3.75-5.05)

2.5	1	3	98.9 (30.4-321)	14.2 (7.19-28.1)	4.00 (2.03-4.25)	4.46 (3.38-5.88)
	2	1	65.4 ²	11.2	2.00	4.17

1. median (range) 2. Observed values 3. n=2

Topotecan Lactone Geometric Mean (95% CI) PK on Day 1 of each Cycle

Dose (mg)	Cycle	n	AUC(0-∞) (ng.h/mL)	Cmax (ng/mL)	tmax (h) ¹	t½ (h)
1.0	1	3	9.91 (4.28-23.0)	1.50 (0.996-2.26)	4.03 (1.50-6.03)	3.69 (1.16-11.7)
	2	1	7.40 ³	1.51	2.00	2.42
1.5	1	3	16.9 (11.8-24.2)	4.71 (1.97-11.2)	2.00 (0.97-2.08)	4.26 (0.599-30.4)
	2	3	21.9 (9.76-49.1)	4.99 (1.81-13.8)	1.57 (1.50-2.00)	4.35 (0.645-29.3)
2.0	1	6	21.9 (13.4-35.8)	4.62 (2.36-9.02)	1.75 (1.00-2.05)	3.84 (1.93-7.65)
	2	6	26.5 (16.4-42.9)	4.62 (2.90-7.35)	2.02 (1.00-4.08)	3.89 (2.23-6.78)
2.5	1	3	35.2 (11.1-112)	8.53 (2.95-24.7)	2.03 (2.00-2.22)	3.06 (1.02-9.21)
	2	1	32.4 ²	7.12	1.50	6.80

1. median (range) 2. observed value 3. n=2

There was no apparent effect of either elacridar dose (100 mg to 1000 mg) or schedule on the apparent oral bioavailability of topotecan. Thus, the lowest elacridar dose (100 mg) and more convenient schedule (simultaneous administration with oral topotecan) was selected for evaluation in Part II of the study

Urinary Results: Median renal elimination during the first 24 hr after oral administration of topotecan with 100 mg of elacridar accounted for 38.5% of the administered dose (range 8.9% to 61.3%). Based on Cycle 1 data significant effect of urinary pH on the renal elimination of topotecan during the 0-12 hr collection interval, with more renal elimination observed with higher urinary pH. Urinary pH during 12-24 hr collection interval did not correlate with apparent renal elimination or renal clearance.

Safety results: An on-therapy was defined as an AE with onset on or after the start date of study medication and up to 30 days after the last dose of medication. An on-therapy SAE was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication. **Urinary Results:** Median renal elimination during the first 24 hr after oral administration of topotecan with 100 mg of elacridar accounted for 38.5% of the administered dose (range 8.9% to 61.3%). Based on Cycle 1 data significant effect of urinary pH on the renal elimination of topotecan during the 0-12 hr collection interval, with more renal elimination observed with higher urinary pH. Urinary pH during 12-24 hr collection interval did not correlate with apparent renal elimination or renal clearance.

Most frequent AE(s) (all grades)	Part 1 Total N =24	Part 2 Total N =15
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Subjects with any non-haematological AEs (%)	n	22 (92)	15 (100)
Nausea		13 (54)	10 (67)
Vomiting		8 (33)	5 (33)
Neutropenia		6 (25)	7 (47)
Fatigue		6 (25)	9 (60)
Anemia		5 (21)	8 (53)
Alopecia		5 (21)	7 (47)
Constipation		4 (17)	8 (53)
Headache		4 (17)	3 (20)
Leukopenia		2 (8)	6 (40)
Thrombocytopenia		2 (8)	9 (60)
Pain		2 (8)	0
Bronchitis		2 (8)	0
Anorexia		2 (8)	6 (40)
Platelet count decreased		2 (8)	0
White blood cell count decreased		2 (8)	0
Abdominal pain		1 (4)	4 (27)
Diarrhea		1 (4)	4 (27)
Dyspnea		0	3 (20)
Dyspepsia		1 (4)	2 (13)
Febrile neutropenia		1 (4)	2 (13)
Malaise		0	2 (13)
Pyrexia		1 (4)	2 (13)
Dehydration		0	2 (13)
Dizziness		0	3 (20)

Influenza	0	2 (13)
Weight decreased	0	2 (13)
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:		
	Part 1 Total N =24	Part 2 Total N =15
Subjects with non-fatal SAEs, n (%) [related]	9 (38) [3]	6 (40) [4]
Febrile neutropenia	1 (4) [1]	2 (13) [2]
Leukopenia	1 (4) [1]	0
Neutropenia	1 (4) [1]	0
Thrombocytopenia	1 (4) [1]	1 (7) [1]
Candidiasis	1 (4) [0]	0
Citrobacter infection	1 (4) [0]	0
Ascites	1 (4) [0]	0
Ileus	1 (4) [0]	0
Ileus paralytic	1 (4) [0]	0
Euthanasia	1 (4) [0]	0
Pain	1 (4) [0]	0
Joint dislocation	1 (4) [0]	0
Chest pain	0	1 (7) [0]
Malaise	0	1 (7) [0]
Medical device complication	0	1 (7) [0]
Dehydration	0	1 (7) [1]
Tumour necrosis	0	1 (7) [0]

Fatal Serious Adverse Events within 30 days from last dose	Part 1 Total N =24	Part 2 Total N =15
Subjects with fatal SAEs, n (%) [related]	2 (8) [0]	1 (7) [1]
Euthanasia	1 (4) [0]	0
Septic shock	1 (4) [0]	0
Ventricular fibrillation	0	1 (7) [1]

Conclusions: Please refer to the publication below.

Publications: Kuppens IELM; et al. A phase I, randomized, open-label, parallel-cohort, dose-finding study of elacridar (GF 120918) in combination with 2.0 mg oral topotecan in cancer patients. Br. J. Clin. Pharmacol. 2004;57(3):360