ACE trial
A pharmacokinetic evaluation of the addition of Aprepitant to the Cisplatin – Etoposide (CE) treatment of patients with solid tumours (ACE)

17/05/2010

GENERAL INFORMATION	
Title	A pharmacokinetic evaluation of the addition of Aprepitant to the Cisplatin – Etoposide (CE) treatment of patients with solid tumours (ACE)
Trial number	UMCN-AKF 07.02
Clinical phase	IV
Sponsor	Dept. of Clinical Pharmacy, Radboud University Medical Centre , The Netherlands
Co-ordinating Investigator	D.M. Burger, PharmD, PhD, Radboud University Medical Centre , The Netherlands
Project Manager	A. Colbers, RUNMC , The Netherlands
Investigator (medical)	C. van Herpen, MD, PhD, RUNMC, The Netherlands A. Timmer, MD, PhD, RUNMC, The Netherlands A. Reyners, MD, PhD, UMCG, The Netherlands
Trial Centre	Departments of Medical Oncology & Pulmonary diseases, RUNMC, The Netherlands Dept. of Medical Oncology, University Medical Center Groningen, The Netherlands
Experimental design	Open-label, randomized, sequential, 2-period, single-centre, phase-IV, multiple-dose trial
Objective(s)	Primary objective: - To study the pharmacokinetics of etoposide with and without the addition of aprepitant in patients with solid tumours treated with the standard CE regimen. Secondary objective: - To study the efficacy and safety of the addition of aprepitant to the anti-emetic regimen in patients with solid tumours treated with the standard CE regimen.
Trial subjects	20 subjects were planned to be included Inclusion criteria: 1. Subject is at least 18 years of age on the day of the first dosing. 2. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations. 3. Subject has an indication for treatment with CE regimen 4. Subject is expected to receive at least 2 cycles of CE regimen 5. Subject is able to swallow capsules Exclusion criteria: 1. Documented history of sensitivity/idiosyncrasy to aprepitant capsules or excipients. 2. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion. 3. History of or current abuse of drugs, alcohol or solvents. 4. Inability to understand the nature and extent of the trial and the procedures required. 5. Participation in a drug trial within 30 days prior to the first dose. 6. Febrile illness within 3 days before the first dose 7. Concomitant use of agents that are known to interfere with aprepitant pharmacokinetics (see appendix A) 8. Abnormal liver or renal function, as indicated by serum liver enzymes >5 times ULN, total bilirubin > 1.5 times ULN (see appendix B) or creatinine clearance <60 mL/ min 9. Receiving concurrent radiotherapy.

TREATMENTS	
Control treatment: standard CE regimen	Etoposide 100mg/m^2 iv Day 1-3 of each cycle Cisplatin 80 mg/m^2 iv Day 1 of each cycle One cycle lasted 21 days Anti-emetic regimen consists of: Ondansetron 8mg iv on Day 1 of each cycle, followed by 8mg po on Days 2 & 3 Dexamethasone 20mg iv on Day 1 of each cycle, followed by 8mg po on Days 2-3 and 2x3mg po on days 4-5 of each cycle. Rescue anti-emetic medication contains diazepam, metoclopramide and ondansetron
Investigational Treatment: aprepitant + standard BEP regimen	Etoposide 100mg/m^2 iv Day 1-3 of each cycle Cisplatin 80 mg/m^2 iv Day 1 of each cycle One cycle lasted 21 days Anti-emetic regimen consists of: Aprepitant 125mg po on Day 1 of each cycle, followed by 80mg po on Days 2 & 3 of each cycle Ondansetron 8mg iv on Day 1 of each cycle Dexamethasone 10mg iv on Day 1 of each cycle, followed by 6mg po on Days 2 & 3 of each cycle and 2x3mg po on days 4-5 of each cycle. Rescue anti-emetic medication contains diazepam, metoclopramide and ondansetron
ASSESSMENTS	
Pharmacokinetics	Blood samples (5 mL) were taken just before start of etoposide infusion (t=0h), at t=0.5h, at t=1h (end of infusion) at t= 4, 6, 8, and 24 hours after dosing (7 samples) on Day 1 (to evaluate potential inhibition by aprepitant) and at the same time points + 32 hours after dosing on Day 3 (8 samples; to evaluate potential induction by aprepitant) of each cycle of CE.
Safety • Medical history, physical examination	At inclusion screening
• Laboratory safety	Biochemistry and haematology evaluation at screening, and at Day 1, 2, 3, 4 and 8 and Day 15 (haematology only) of each cycle.
• Adverse events	Subjects will be asked about occurrence of adverse events on Day 1, 2, 3, 5, 8 and 15 of each cycle.
Efficacy	Nausea and emetic episodes were recorded on a 1-10mm NRS scale on Days 1- 5 and 8; use of rescue anti-emetic treatment was recorded in the CRF.
Confinement	From Study Day 1-4 (standard for CE regimen; Tuesday – Friday)
ANALYTICAL AND STATISTICAL METHODS	
Bioanalysis	Plasma concentrations of etoposide were measured in all available samples by means of validated HPLC methods with tandem mass spectrometric detection
Pharmacokinetics	Determination of pharmacokinetic parameters (AUC_{0-24}, C_{max}, t_{max}, C_{24h} and $t_{½}$) by non-compartmental analysis. Descriptive statistics for the etoposide plasma concentrations at each sampling time (not done).
Safety and demographics	Tabulation and descriptive statistics (not done) for subject characteristics. Tabulation of adverse events, and biochemistry and haematology data (not done).
Efficacy	Tabulation of nausea and emetogenic periods; data on rescue anti-emetic treatment (not done)

RESULTS

IRB/IEC Approval Date:	04-Dec-2007
Clinical Trials Database Posting Date:	24-Dec-2007
Protocol version 1 dated	17-08-2007
Amendment 1 dated	27-08-2008
Amendment 2 dated	30-06-2009
Number of Patients Planned:	20
Number of Patients Enrolled:	3
Date of First Patient Enrolled	19-Aug-2008
Last patient last assessment	22-Sep-2010

Due to a very low recruitment rate the study was terminated per 01-01-2010. Therefore, this description of the data has been written and no formal analysis of the data has been performed.

Subject 01

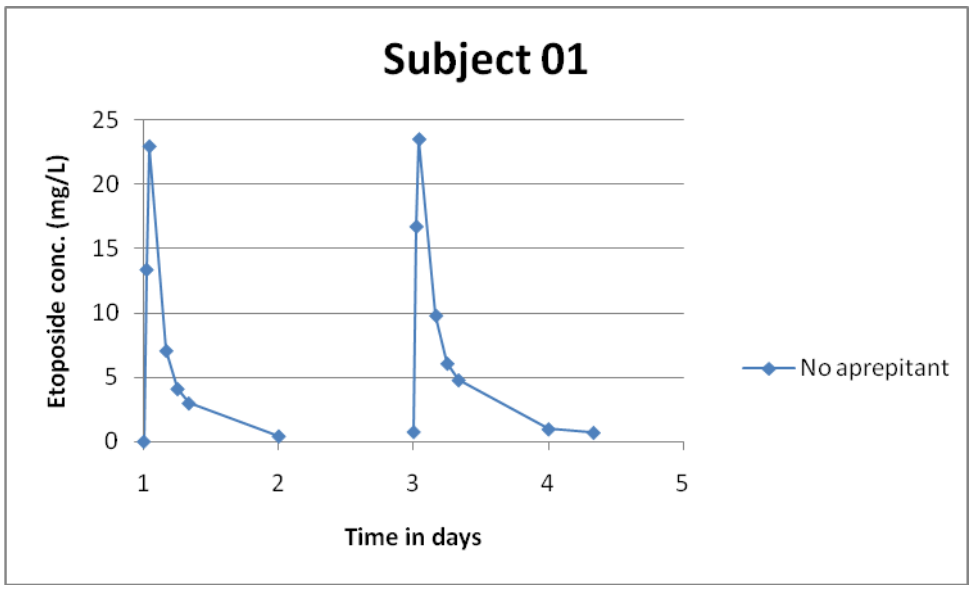
Treatment sequence:	reference – test
DOB :	30/03/1951
Age at inclusion:	57 years
Gender:	female
Body weight (kg):	unk
BSA (m^2):	1.8 m^2
Etoposide dose (mg):	180 mg

Dates:

Inclusion date:	19/08/2008
Date first treatment:	20/08/2008
Date second treatment:	nap; drop out
Date drop out:	18/09/2008

Results

Subject dropped out after the first period due to worsening of WHO performance status.



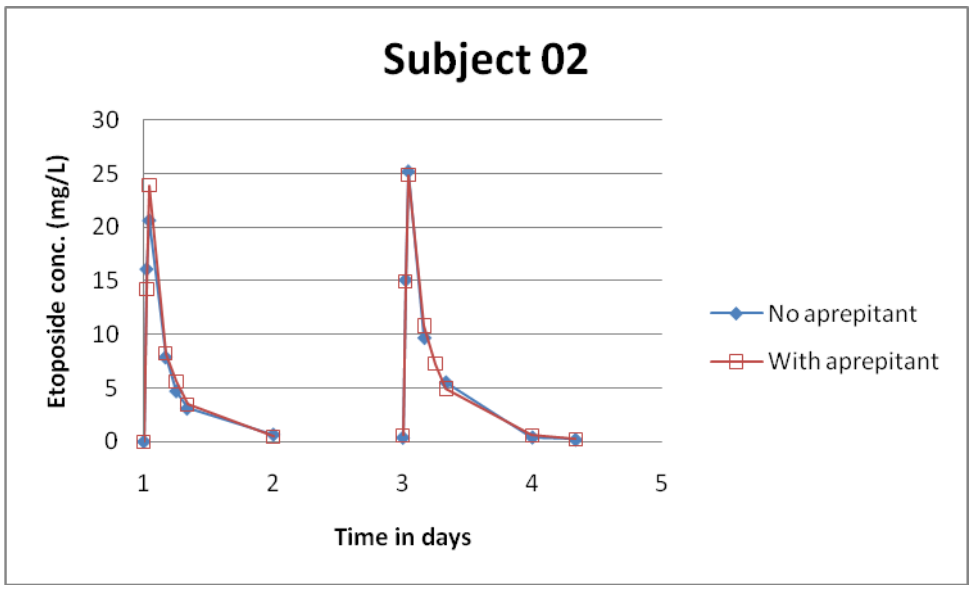
Subject 02

Treatment sequence:	reference – test
DOB :	14/12/1955
Age at inclusion:	53 years
Gender:	female
Body weight (kg)	81.2 kg (first period); 83.4 kg (second period)
BSA (m^2)	1.92 m^2 (first period); 1.94 m^2 (second period)
Etoposide dose (mg)	190 mg

Dates:

Inclusion date:	30/03/2009
Date first treatment:	09/04/2009
Date second treatment:	29/04/2009

Results



Subject 03

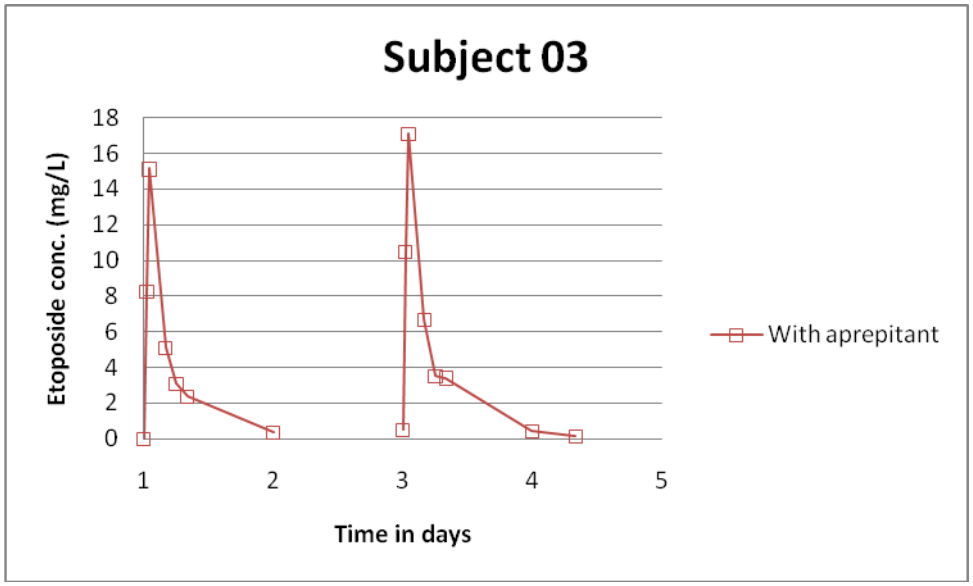
Treatment sequence:	test - reference
DOB :	02/12/1943
Age at inclusion:	65 years
Gender:	male
Body weight (kg):	unk
BSA (m^2):	2.1 m^2
Etoposide dose (mg):	210 mg

Dates:

Inclusion date:	14/09/2009
Date first treatment:	15/09/2009
Date second treatment:	nap, drop out

Results

Subject developed a ECG abnormality consistent with a myocard infarction on 22-09-2009 and was admitted to the cardiology dept of the hospital.



Etoposide PK parameters

Subject		Day	AUC_{0-24h} (mg*h/L)	C_{max} (mg/L)	T_{max} (h)	C_{24h} (mg/L)	C_{trough} (mg/L)	$T_{1/2}$ (h)
01	Without aprepitant	1	91.4	22.9	1	0.415	0	5.5
		3	125.7	23.5	1	0.962	0.747	8.0
02	Without aprepitant	1	97.8	20.6	1	0.654	0	6.6
		3	123.3	25.2	1	0.396	0.582	4.7
	With aprepitant	1	103.7	23.9	1	0.472	0	5.2
		3	126.3	24.8	1	0.555	0.38	5.2
03	With aprepitant	1	65.4	15.1	1	0.329	0	5.6
		3	82.5	17.1	1	0.429	0.479	5.1

Ratio's

Subject		Day	AUC_{0-24h} (mg*h/L)	C_{max} (mg/L)	T_{max} (h)	C_{24h} (mg/L)	$T_{1/2}$ (h)
01	Without aprepitant	3/1	1.37	1.02	1.00	2.32	1.44
02	Without aprepitant	3/1	1.26	1.22	1.00	0.61	0.72
	With aprepitant	3/1	1.22	1.04	1.00	1.18	0.99
03	With aprepitant	3/1	1.26	1.13	1.00	1.30	0.91
02	With / Without aprepitant	1	1.06	1.16	1.00	0.72	0.79
	With / Without aprepitant	3	1.02	0.99	1.00	1.40	1.09

Discussion

C_{max} and t_{max} values were in line with the data reported by Mummaneni et al (1). T_{max} values correspond with the end of infusion of etoposide.
AUC_{0-24h} on Day 1 corresponded with the AUC_{0-inf} (Day 1) reported by Mummaneni et al (1).

The AUC_{0-24h} on Day 3 however was higher compared to the AUC on Day 1, both with and without aprepitant. A higher AUC was expected because the concentration at the moment of start of infusion was not <LOQ, but 0.747 mg/L (subject 1); 0.582 mg/L (subject 2 no aprepitant); 0.38 mg/L (subject 2 with aprepitant) and 0.479 mg/L (subject 3). This attributed to approximately 7-14% increase of AUC. C_{max} was somewhat higher on Day 3 as well, probably because of the baseline concentration.

In the single subject having both treatments (subject no. 2) no change in etoposide AUC_{0-24h} was observed after addition of aprepitant to the therapy on Day 1 and Day 3.

Reference List

(1) Mummaneni V, Kaul S, Igwemezie LN, Newell DR, Porter D, Thomas H, et al. Bioequivalence assessment of etoposide phosphate and etoposide using pharmacodynamic and traditional pharmacokinetic parameters. J Pharmacokinet Biopharm 1996 Aug;24(4):313-25.