Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Antistax®				
Name of active ingredient: Red Vine Leaf Extract		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 10 NOV 2006	**Number:** U06-0085	**Study period (dates):** 24. AUG-01. SEP 2004		

Title of study:	An open, uncontrolled trial in healthy volunteers to explore the plasma and urinary pharmacokinetics of a single oral dose of 1,800 mg Red Vine Leaf Extract (Antistax®)
Investigator:	[redacted]
Study center(s):	[redacted] Bulgaria
Publication (reference):	N.A.
Clinical phase:	Phase I
Objectives:	To describe the plasma and urinary pharmacokinetics of quercetin glucuronide and kaempferol glucuronide after the administration of a single peroral dose of 1,800mg Red Vine Leaf Extract (Antistax®). Additionally, the trial evaluated the safety and tolerability of this dose in healthy subjects.
Methodology:	Single-centre, uncontrolled, open, single-dose PK trial in healthy men and women. Subjects were studied on one occasion; all subjects received the same medication; the trial medication was administered once on the morning of Day 1
No. of subjects:	
planned:	entered: 20
actual:	enrolled: 12 (6 men, 6 women) 12 subjects were enrolled and entered the study, all were treated and all are evaluable in terms of the primary and secondary study objectives
Diagnosis and main criteria for inclusion:	consenting healthy male and female volunteers, 18 to 40 years of age, 18-28 kg x m^{-2}
Test product:	Antistax® 360 mg tablet
dose:	1,800 mg (5 tablets)
mode of admin.:	Orally with 240 mL after an overnight fast and rest; the subjects remained fasted until 4:00 h after dosing
batch no.:	Article-N°: 305490 – Batch-N°: 316243
Duration of treatment:	Single dose

Reference therapy:	N.A.
dose:	N.A.
mode of admin.:	N.A.
batch no.:	N.A.
Criteria for evaluation:	
Efficacy:	N.A.
Pharmacokinetics:	Primary: C_{max} and AUC of quercetin glucuronide and kaempferol glucuronide in plasma Secondary: t_{max}, $t_{½}$ and MRT; fractional and cumulative urinary excretion
Safety:	Clinical signs and symptoms, vital functions, adverse events; laboratory safety (haematology, clinical chemistry, urinalysis)
Statistical methods:	Descriptive statistics

SUMMARY – CONCLUSIONS:

Disposition	Twelve healthy caucasian volunteers (six males, six females) were enrolled, treated and completed the trial in accordance with the protocol: 25 to 38 years of age (mean: 31.3 ± 4.2), body weight 70.3 to 85.1 kg (mean: 77.5 ± 6.8), body mass index: 22.19 to 27.98 kg x m^{-2} (mean: 24.82 ± 2.05)
Clinical Pharmacology results:	Concentrations in urine were too low for further evaluation. Plasma concentrations of quercetin-3'-O-ß-D-glucuronide were not sufficiently clearly and consistently expressed to permit in-depth pharmacokinetic evaluation. The time courses of the plasma concentrations of quercetin-3-O-ß-D-glucuronide were well expressed, but showed substantial inter-subject variability both with regard to the height of the concentrations and the timely distribution thereof. The main pharmacokinetic properties were: geometric mean C_{max} of 35.85 ng x mL^{-1} (CV: 0.95) after a median t_{max} of 4:00 h (range: 1:00 to 8:00) with a geometric mean quantifiable $AUC_{(0-t_z)}$ of 123.47 ng x h x mL^{-1} (CV: 0.75). The time courses of the plasma concentrations of kaempferol-3-O-ß-D-glucuronide also showed substantial inter-subject variability with regard to the height of the concentrations, but less for their timely distribution. The main pharmacokinetic properties were: geometric mean C_{max} of 46.82 ng x mL^{-1} (CV: 0.58) after a median t_{max} of 0:45 h (range: 0:30 to 3:00 h) with a geometric mean quantifiable $AUC_{(0-t_z)}$ of 125.40 ng x h x mL^{-1} (CV: 0.56) and a geometric mean extrapolated $AUC_{(0-\infty)}$ of 130.18 ng x h x mL^{-1} (CV: 0.54); the arithmetic mean $t_{½}$ was 1.90 h (CV: 0.47) and the arithmetic mean MRT 3.99 h (CV: 0.46).
Safety results:	Single doses of 1,800 mg Red Vine Leaf Extract (Antistax®) were very well tolerated. No adverse events were reported. There was no evidence or indication of relevant study related individual or average changes in the safety laboratory tests, blood pressure and pulse rate, 12-lead ECG, physical examination and body weight; there was some indication of increased diuresis early after dosing
Conclusions:	The oral administration of Red Vine Leaf Extract (Antistax®) yields quantifiable systemic exposure to pharmacologically relevant flavonoid glucuronides.