Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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Report date: 15 April 2005	**Number:** U05-1437	**Study period (dates):** January 2004 – April 2004		

Title of study:	The effect of cytochrome P 450 3A4 inhibition by itraconazole on the single oral dose pharmacokinetics of cilobradine (an open-label, randomised, single-dose, two-way crossover study)
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	Data from this study have not been published to date
Clinical phase:	I
Objectives:	To investigate the effect of cytochrome P 450 3A4 inhibition by itraconazole on the single dose pharmacokinetics of cilobradine
Methodology:	Open-label, randomised, two-way crossover design
No. of subjects:	
planned:	entered: 25
actual:	enrolled: 25 Treatment arm A: pre study Pre-treatment itraconazole for 8 days followed by a single dose of cilobradine (1 mg oral) and Cilobradine 1 mg oral as a single application (n=4, crossover) entered: 4 treated: 4 analysed (for primary endpoint): 4 Treatment arm B: main study Pre-treatment itraconazole for 8 days followed by a single dose of cilobradine (2 mg oral) and Cilobradine 2 mg oral as a single application (crossover) entered: 21 treated: 21 analysed (for primary endpoint): 21
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥21 and ≤55 years, resting heart rate >55 bpm, BMI range: ≥18.5 and <30 kg/m^2

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Test product:	Cilobradine plus itraconazole (Sempera®)
dose:	Cilobradine: 2 mg in main study, 1 mg in pre-study; Itraconazole: single dose of 400 mg on day -5 and 200 mg qd on days -4 to 3
mode of admin.:	p.o.
batch no.:	B030709 (Cilobradine)
Duration of treatment:	Cilobradine: 1 day for each treatment. Itraconazole: 8 days
Reference therapy:	Cilobradine alone
dose:	Cilobradine: 2 mg in main study, 1 mg in pre-study
mode of admin.:	p.o.
batch no.:	B030709 (Cilobradine)
Criteria for evaluation:	
Efficacy:	Primary endpoints: $AUC_{0-\infty}$, C_{max} (cilobradine) Secondary endpoints: AUC_{0-tz}, t_{max}, λz, $t_{1/2}$, MRTpo, CL/F, Vz/F, fe_{0-tz}, $CLR_{,0-tz}$ (cilobradine)
Safety:	Physical examination, vital signs (BP, PR), ECG with special emphasis on QT measurement, laboratory tests, adverse events and tolerability
Statistical methods:	Descriptive statistical analysis, frequencies of occurrence of events. Confidence intervals for relative bioavailability (with : without itraconazole), 90% and 95% 2-sided

SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics

The plasma concentration profile of cilobradine without itraconazole co-medication was in agreement with previous studies (503.203 [U04-1469]). The mean maximum plasma concentration was about 4-5 ng/mL per mg dose administered. The time to reach the maximum plasma concentration was 1.48 h (median). The area under the curve was about 20-25 ng.h/mL per mg dose administered. The volume of distribution and the clearance were high, indicating a high tissue distribution and a high extraction ratio drug. The calculated terminal half-life depended on the time point of the last quantifiable plasma concentration and was about 9 h. With itraconazole co-medication the maximum plasma concentration increased by 2.4-fold. The time to reach the maximum plasma concentration was not affected by itraconazole co-medication. The area under the curve increased by 4-5-fold. The total as well as the renal clearance

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	was reduced. Nevertheless the amount of cilobradine excreted in urine as parent compound increased with itraconazole, as more parent compound is systemically available. The decreased clearance lead to a longer half-life of about 15 h. Thus co-medication of a potent CYP 3A4 inhibitor like itraconazole has an influence on the pharmacokinetics of cilobradine leading to higher plasma levels. The itraconazole plasma concentrations were in the range of 300-400 ng/mL on the day of cilobradine administration, thus a sufficient exposure to itraconazole and a sufficient inhibition of CYP 3A4 can be assumed.
Safety results:	Overall seven AEs were reported, all in the main study. AEs occurred in five of the 25 subjects. Five AEs were assessed as study drug related, all of these were visual phenomena. In three subjects, the visual phenomena occurred on the combination of 2 mg cilobradine and itraconazole, in one subject they occurred on 2 mg cilobradine alone. The severity of the visual AEs was mild except for subject [redacted] who experienced moderate visual disturbance following 2 mg of cilobradine and pre-treatment with itraconazole. The duration of the visual AEs ranged between few seconds up to 60 minutes, with the exception of subject [redacted], who experienced slow motion images in the evenings for periods longer than 4 hours. All visual AEs were transient in nature and resolved completely, without therapy. The occurrence of visual phenomena in three (out of 21) subjects on the combination of 2 mg cilobradine and itraconazole, the consistent time pattern of these phenomena (all of them starting during the second evening after cilobradine administration, after about 36 hours) and the persistence for at least one more evening, seems to indicate that visual phenomena as typical for cilobradine after higher doses or multiple doses do already occur after single doses of 2 mg cilobradine in combination with itraconazole. This is also consistent with the pharmacokinetic results of this trial, which show increased maximum concentrations and increased half life of cilobradine combination with itraconazole. Safety measures for laboratory values, vital signs and ECG did not reveal clinically relevant adverse events related to study drug administration. The decrease in pulse rate versus baseline as observed in the main study showed a maximum 4h after cilobradine application and was comparable between the cilobradine only group (-11.6 bpm) and the cilobradine + itraconazole group (-10.9 bpm).

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	Neither the pre-study nor the main study had the primary aim to detect a dose dependent safety profile (1 mg versus 2 mg of cilobradine) nor an influence of itraconazole pre-treatment of the cilobradine safety profile. Also the study was not powered for the evaluation of ECG effects including QT interval. Slight increases of on-treatment peak values of QT were found with itraconazole co-treatment, as compared with pure cilobradine treatment. Also, the changes of QTcF relative to baseline were slightly higher with itraconazole co-treatment.
Conclusions:	The maximum plasma concentration of cilobradine increased by 2-fold, the exposure by about 4-5-fold with co-medication of itraconazole, whereas the time to reach the maximum plasma concentration was independent of itraconazole co-medication. The half-life increased with itraconazole co-medication. The total clearance and the volume of distribution after oral administration decreased, because beside the elimination also the first pass effect was inhibited and thus increased the oral bioavailability. The renal clearance also decreased with itraconazole, but the total amount of cilobradine excreted as parent compound increased. It can be concluded that co-medication of potent CYP 3A4 inhibitors like itraconazole with cilobradine lead to a significant increase in cilobradine plasma concentration and exposure. In general, the trial medication was well tolerated and safe. The study was not powered to establish any differences in the frequency and extent of adverse events or other safety measures. However, the occurrence of visual phenomena in three (out of 21) subjects on the combination of 2 mg cilobradine and itraconazole, the consistent time pattern of these phenomena and the persistence for at least one more evening, seems to indicate that visual phenomena do already occur after single doses of 2 mg cilobradine in combination with itraconazole. This is also consistent with the pharmacokinetic results of this trial, which show increased maximum concentrations and increased half life of cilobradine combination with itraconazole.