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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:				
Name of active ingredient: Cilobradine		**Page:**	**Number:**	
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Report date: 12 April 2005	**Number:** U05-1420	**Study period (dates):** 15 Jan 2004–26 May 2004		

Title of study:	Pharmacodynamic effects, safety and tolerability of 2 mg and 5 mg cilobradine, administered *p.o.* once daily over 14 days to healthy male and female volunteers in a randomised, placebo-controlled, double blind study, with an open-label uncontrolled intra-individual comparison to 400 mg moxifloxacin single dose in a subset of volunteers.
Investigator:	[redacted]
Study centre:	[redacted], Germany
Publication (reference):	None
Clinical phase:	I
Objectives:	Incidence of visual phenomena, heart rate at rest, safety (with particular emphasis on QT analysis of ECGs), and pharmacokinetic parameters
Methodology:	Controlled, randomised, double-blind, parallel group study (three groups)
Number of subjects: **Planned:** **Actual:**	Screened: 189 Entered: 125 Randomised: 100 (50 cilobradine 2 mg, 25 cilobradine 5 mg, 25 placebo, followed by uncontrolled intra-individual comparison treatment with moxifloxacin: 32 subjects) **Dropouts/Withdrawals:** Four subjects prematurely left the study. Subject 60 had SAEs; Subjects 65, 104 and 116 withdrew consent.
Diagnosis and main criteria for inclusion:	Healthy male and female (post-menopausal or who had a hysterectomy only) volunteers, aged ≥21 and ≤55 years, resting HR ≥60 bpm, BMI range: ≥18.5 and <30 kg/m^2
Test product: **Dose:** **Mode of admin.:**	Cilobradine, film-coated tablets 2 mg cilobradine (one 2 mg cilobradine tablet plus one placebo tablet matching 2 mg cilobradine plus one placebo tablet matching 1 mg cilobradine) or 5 mg cilobradine (two 2 mg cilobradine tablets plus one 1 mg cilobradine tablet) over 14 days Oral administration after an overnight fast with 150 mL water
Batch no.:	1 mg tablets: B030709 2 mg tablets: B030710
Duration of treatment:	14 days

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Reference therapy 1:	Placebo, film-coated tablets
Dose:	Placebo tablets (two placebo tablets matching 2 mg cilobradine plus one placebo tablet matching 1 mg cilobradine)
Mode of admin.:	Oral administration after an overnight fast with 150 mL water
Batch no.:	1 mg tablets: B030716 2 mg tablets: B030714
Duration of treatment:	14 days
Reference therapy 2:	Moxifloxacin, film-coated tablets
Dose:	400 mg
Mode of admin.:	Oral administration after an overnight fast with 150 mL water
Batch no.:	XB 8471 = BXB8471 (Bayer)
Duration of treatment:	One day
Criteria for evaluation:	
Pharmacodynamics:	Cilobradine: Pulse (=heart) rate at rest, incidence of visual phenomena
Pharmacokinetics:	Individual cilobradine plasma concentration time profiles after first dose and at steady state and the derived pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-24}, $C_{max,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, and at steady state $t_{1/2}$, MRT_{po}, CL/F and V_z/F
Safety:	Adverse events (incl. visual phenomena), physical examination, vital signs (BP, HR), 12-lead ECG, laboratory parameters in serum/plasma and urine and global tolerability
Statistical methods:	Descriptive statistics and confidence intervals of changes to baseline, analysis of variance (ANOVA) and covariance (ANCOVA); frequencies of events and confidence intervals for proportion of subjects with events.

SUMMARY – CONCLUSIONS:

Pharmacodynamic results:

The pharmacodynamic effect, *i.e.* the decrease in pulse rate, exerted by cilobradine was dose-dependent. The maximum changes from baseline were 10.6 bpm for the 2 mg dose and 16.2 bpm for the 5 mg dose, both observed after the final dose on Day 14, compared to 4.5 bpm in the placebo cohort. In particular after the 5 mg dose, cilobradine caused bradycardia in several subjects. As seen in previous studies, visual phenomena such as slow motion images, flickering lights and blurred vision were associated with cilobradine treatment. Altogether, 40 of the 100 subjects exposed to study drug reported visual phenomena, which occurred in a dose-dependent fashion (84% under cilobradine 5 mg, 36% under cilobradine 2 mg and 4% under placebo).

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	Thus, multiple doses of cilobradine (2 and 5 mg) led to a clear dose-dependent decrease in pulse rate in healthy male and female subjects, as could be expected from the pharmacological action of this compound. In particular, after a 5 mg dose, excessive pharmacodynamic effects (bradycardia) were observed in several subjects.
Safety results:	Dependent on the heart rate, the mean and individual uncorrected QT intervals showed a dose-dependent prolongation, which generally did not exceed 500 ms in any individual, with one exception only. A significant prolongation of 8.2 ms in baseline-adjusted mean QTcB interval *vs.* placebo was observed for the 5 mg cilobradine treatment 24 h after the last dosing. Baseline-adjusted QTcF, QTcI and QTcN intervals were significantly prolonged after repeated doses of 2 and 5 mg cilobradine at cilobradine t_{max}, at the time of the observed maximum pharmacodynamic effects on Day 14 and 24 h after the last dosing. The mean increases in QTcF, QTcI and QTcN over baseline were up to 12.2 ms for cilobradine 2 mg and up to 26.9 ms for cilobradine 5 mg. In the moxifloxacin arm of the study, the subjects showed a significant prolongation of QTcB and QTcF intervals 24 h after dosing compared with placebo. When compared to all placebo-treated subjects moxifloxacin led to an average increase of 11.4 ms (QTcB) and 6.9 ms (QTcF) over baseline. The occurrence of treatment-emergent AEs was dose dependent, *i.e.* 88% of the subjects during cilobradine 5 mg treatment reported any AE, followed by 64% of the subjects in the 2 mg cilobradine cohort compared to 48% during placebo administration. There were SAEs (injuries related to an accident) in one subject who received 2 mg cilobradine (without relationship to active drug). Most of the AEs were associated with eye disorders (visual phenomena), which exclusively occurred during active treatment with cilobradine, except for one event during placebo administration. Vital signs profiles during this study, except for pulse rate, were similar between the two cilobradine cohorts and placebo. No individual value was considered by the investigator to be clinically significant. There were sporadic and transient increases in liver transaminases that did not constitute any AE. Such elevations were observed during placebo and active treatments. None of the elevated liver parameters was considered by the investigator to be clinically significant. Overall, there was no treatment or dose-related effect on any clinical laboratory parameter in this study. Global tolerability was described as “good” in the majority of subjects who received placebo or cilobradine 2 mg, while the assessment fell to below 50% in the cilobradine 5 mg cohort, but was “satisfactory” still.

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Pharmacokinetic results	Cilobradine was rapidly absorbed. The maximum plasma concentrations were reached within about 1 h. The maximum plasma concentrations as well as the AUC showed no relevant deviation from dose proportionality in the dose range tested after the first dose administered and at steady state (Day 14). The maximum plasma levels on Day 1 and 14 were about 4–5 ng/mL per mg dose administered. The AUC values were about 20 ng h/mL per mg dose administered. The C_{max} and AUC values on Day 1 and 14 were not relevantly different, thus almost no accumulation of the drug occurred after once daily administration. The volume of distribution (V_z/F) was >300 L, indicating widespread tissues distribution. The clearance (CL/F) after oral administration was about 800–900 mL/min. The calculated half-life depended on the time point of the last quantifiable plasma concentration. Thus, on Day 1 the half-life was shorter compared to Day 14 and shorter in the 2 mg dose group compared to the 5 mg dose group. Most of the area under the curve was within the first 24 h (>90% of the total area). The half-life calculated on Day 1 seemed to be the dominant one (4–5 h), the longer half-life of about 20 h on Day 14 was the terminal one indicating deep compartments. The accumulation ratio estimated from C_{max} and AUC values on Day 1 and 14 was in the range of one, indicating no relevant accumulation of the drug. The linearity factor between Day 1 and Day 14 was about 0.8–0.9 ($AUC_{t,ss}/AUC_{0-\infty}$).
Conclusion:	Inferred from the ΔQTc data in this study, the potential of cilobradine for a QTc prolongation was significantly increased for the two dose levels of 2 and 5 mg compared with placebo. The global tolerability of cilobradine was “good” in the majority of subjects who received cilobradine 2 mg and “satifactory” in the majority of subjects who received 5 mg. This was caused by a higher number of adverse events during treatment with 5 mg, whereby most of the AEs were associated with eye disorders (visual phenomena), a finding that has been previously described with this class of compound.
Conclusions:	Cilobradine was rapidly absorbed and showed a good distribution into tissue. The maximum plasma levels and the exposure (AUC) revealed no relevant deviation from dose proportionality after the first dose and at steady state. The plasma clearance of cilobradine was high. The dominant half-life was about 4–5 h. No relevant accumulation between Day 1 and Day 14 was observed. The pharmacokinetic profile of cilobradine in the current study showed no relevant difference from previous clinical trials performed.