Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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 hydrochloride		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 09 July 2004	**Number:** U04-1469-02	**Study period (dates):** 05 FEB 03 – 25 NOV 03		**Revision date:** 12 May 2010

Title of study:	Pharmacodynamic effects, safety and tolerability of 0.25 mg, 0.5 mg, 1 mg and 2 mg cilobradine, compared to 190 mg metoprolol succinate and placebo, administered p.o. once daily over 14 days to healthy volunteers in a randomised, placebo-controlled, partly double blind study, with a 4 mg/14 mg and 10 mg/20 mg cilobradine single dose versus placebo substudy (double blind, three-fold cross-over). As per Protocol Amendment No. 5, an additional treatment of a 5 mg cilobradine dose group, compared to 190 mg metoprolol and placebo, was performed. As per Protocol Amendment No. 7, the substudy was not performed
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	Data of this study has not been published
Clinical phase:	I
Objectives:	Pharmacodynamic effects on HR (heart rate) at rest and during exercise and on FFF (flicker fusion frequency). Safety, tolerability and pharmacokinetics of cilobradine.
Methodology:	Controlled, randomised, partly double-blind (cilobradine/placebo doses), parallel group study for the main study.
No. of subjects:	
planned:	Entered and treated: 102 for the main study and 27 for the Amendment No.5
actual:	All: entered/treated: 119 analysed: 110 Placebo: entered/treated: 20 analysed: 20 0.25 mg cilobradine: entered/treated: 12 analysed: 11 0.5 mg cilobradine: entered/treated: 12 analysed: 11 1.0 mg cilobradine: entered/treated: 18 analysed: 17 2.0 mg cilobradine: entered/treated: 16 analysed: 15 5.0 mg cilobradine: entered/treated: 18 analysed: 15 Metoprolol: entered/treated: 23 analysed: 21
Diagnosis and main criteria for Inclusion:	Healthy male and female (postmenopause only) volunteers, age 21-55 years, BMI 19.9-29.9 kg/m^2, HR > 55 beats per min.

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Test product:	Cilobradine solution
dose:	Daily dose: 0.25 mg/4 mL, 0.5 mg/4 mL, 1.0 mg/4 mL, 2.0 mg/4 mL. Amendment No.5: daily dose: 5.0 mg/10 mL.
mode of admin.:	p.o.
batch no.:	0.25 mg cilobradine: B021009 0.5 mg cilobradine: B021011 1.0 mg cilobradine: B021106 2.0 mg cilobradine: B021103 Amendment No.5: 5.0 mg cilobradine: B030701
Duration of treatment:	14 days
Reference therapy:	Placebo solution matching cilobradine, metoprolol
dose:	Daily dose matching 0.25 mg/4mL, 0.5 mg/4mL, 1.0 mg/4mL, 2.0 mg/4 mL, 5.0 mg/10 mL (Amendment No.5) cilobradine. Metoprolol succinate: 2 days with 95 mg per day; 12 days with 190 mg per day.
mode of admin.:	p.o.
batch no.:	Placebo: B021110, B030203 Metoprolol: DH9347A1 Amendment No.5: placebo: B030707, metoprolol: ED9413A2
Criteria for evaluation:	
Efficacy:	Main study: HR at rest and during exercise, FFF. AUC_{0-24}, C_{max}, t_{max}, AUC_{ss}, $C_{max,\ ss}$, $t_{max,ss}$, (and if feasible) $t_{½}$, MRT_{po}, CL/F, V_z/F (after first dose and at steady state), individual cilobradine plasma concentrations after first dose and at steady state.
Safety:	Physical examination, blood pressure; HR (= PR [pulse rate]), ECG (electrocardiogram), laboratory tests, AE (adverse events).
Statistical methods:	Descriptive statistics and confidence intervals of changes to baseline, frequencies of events.

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SUMMARY – CONCLUSIONS:

Efficacy / Clinical pharmacology results:

Pharmacodynamics:

The effect of 2.0 mg cilobradine on heart rate (HR) at rest and after exercise was slightly inferior to the effect of metoprolol succinate at the highest tolerated dose. With 5.0 mg cilobradine, HR reduction was similar to metoprolol succinate at rest, but stronger than the comparator at end of exercise. Figure 1 and 2 present the course of HR at rest and at end of exercise, respectively, in all treatment groups.

The measurement of flicker frequency did not reveal relevant, dose-dependent changes when comparing the various cilobradine doses to placebo and metoprolol.

Pharmacokinetics:

Cilobradine showed a rapid absorption as the maximum plasma concentration (C_{max}) was reached within about 1 h. C_{max} as well as the area under the curve (AUC) showed no relevant deviation from dose proportionality in the dose range tested. The mean values for the highest dose group (5.0 mg) were only slightly higher compared to the lower dose groups. The C_{max} and AUC values on days 1 and 14 are not relevantly different, thus almost no accumulation of the drug occurs. The maximum plasma levels on days 1 and 14 were about 3-5 ng/mL per mg dose administered. The AUC values were approximately 20 ng·h/mL per mg dose administered. Cilobradine was well distributed into tissue and can be assumed as a high clearance drug. The half-life estimated from the 24 h profile on day 1 was about 4-6 h, which might be assumed as the dominant one. The terminal half-life depended on the time of the last quantifiable plasma concentration (half-life: 14 h vs. 70 h). The pharmacokinetic profile of cilobradine showed no relevant difference from previous clinical trials performed.

Metoprolol plasma concentrations showed a high inter-subject variability with maximum plasma values of about 60 ng/mL after once daily dosing of 190 mg metoprolol succinate. The plasma concentrations were stable over about 12 h due to administration of a sustained release formulation. The pharmacokinetic profile of metoprolol in the current study was in agreement with the pharmacokinetic parameters published for metoprolol sustained release formulations.

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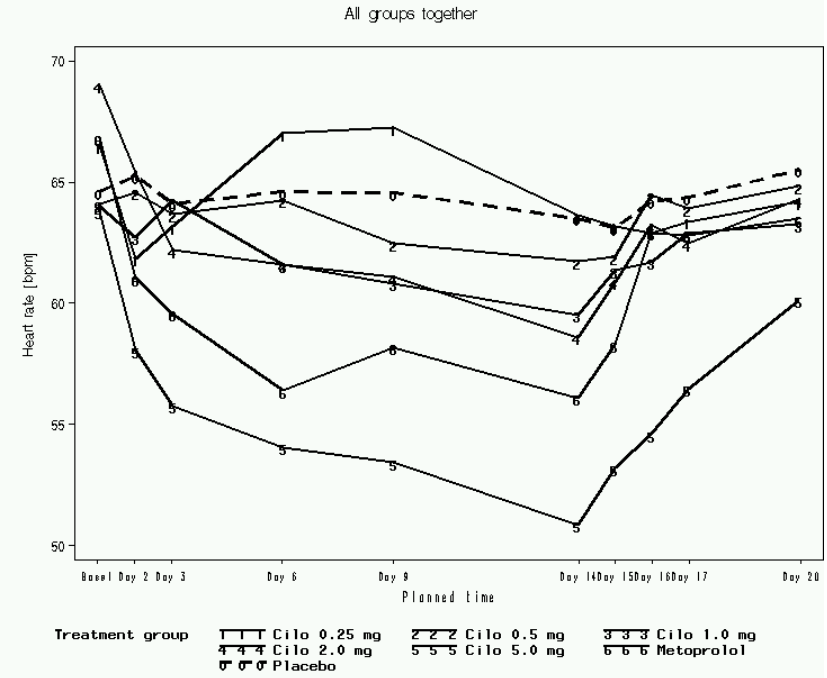
(cont.) Efficacy / Clinical pharmacology results:

Figure 1: Mean heart rate at rest



Source Data: Tables 15.2.2.1: 1 (absolute values) and Figure 15.2.2.1: 3 (trough time-points)

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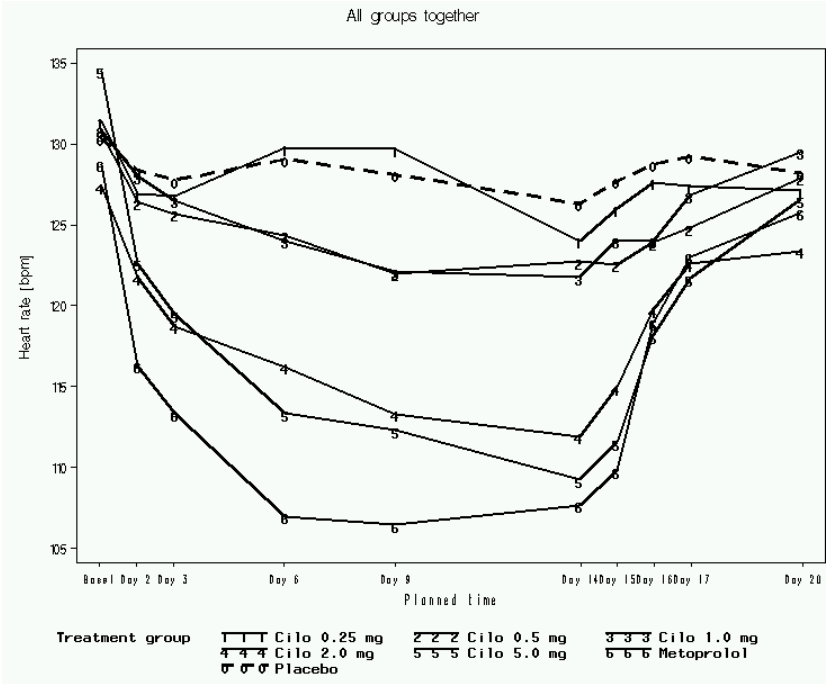
(cont.) Efficacy / Clinical pharmacology results:

Figure.2: Mean heart rate at end of exercise



Source Data: Tables 15.2.2.1: 3 (absolute values) and Figure 15.2.2.1: 4 (trough time points)

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Safety results:

The highest number of subjects with any AE was seen in the system organ classes 'Nervous system disorders' (N = 45, mainly due to 'Headache' N = 41), 'General disorders and administration site conditions' (N = 32, mainly due to 'Fatigue' N = 23), 'Eye disorders' (N = 19, mainly due to 'Visual disturbance' N=17), 'Cardiac disorders' (N = 15) and 'Gastrointestinal disorders' (N = 14). Cardiac AE - which at least partly may reflect the intended pharmacological effect of the study treatment (HR reduction) - occurred more frequently in the 5.0 mg cilobradine and metoprolol groups compared to the other cilobradine groups and placebo. Within the 'Cardiac disorders' system organ class, a causal relationship to study treatment was suspected for the AE 'Bradycardia', 'Extrasystoles', 'Palpitations', 'Tachycardia', 'Ventricular arrhythmia' and 'Ventricular extrasystoles', which were all reported either in the 5.0 mg cilobradine or in the metoprolol treatment group. During treatment with 1.0 mg or 2.0 mg cilobradine a total of three subjects reported visual phenomena (VP). In two subjects (both in the 2.0 mg cilobradine group), the VP were typical for a selective bradycardic agent. During treatment with 5.0 mg cilobradine, a total of fourteen subjects (out of 18 subjects treated) reported at least one episode of VP. All VP except the one in the 1.0 mg cilobradine group were judged drug-related. No VP was serious. Nine VP were classified as 'mild', seven as 'moderate', and one as 'severe'. Overall, two AE were rated 'severe': one VP (related to study drug) and one 'Ventricular bigemini' (unrelated to study drug). Both occurred in the 5.0 mg cilobradine treatment group. In the group of AE rated 'moderate' there was no dose-dependent increase of AE but a threshold effect. With 5.0 mg cilobradine, the frequency of 'moderate' AE was much higher (61.1 %) compared to all other treatment groups (0 % to 20.0 % [placebo]). 'Visual disturbance' and, to a lesser extend, 'Fatigue', account for most of this difference. There was one unrelated and unexpected serious AE (adenocarcinoma) in a subject who had been treated with metoprolol. This AE was discovered as a chance finding during cardiologic work-up (echocardiography) of a non-serious arrhythmia. Within the group of AE assessed as 'possibly drug related', the highest frequency of AE was seen in the 5.0 mg cilobradine group (77.8 %), followed by the metoprolol group (39.1 %). Nine subjects withdrew due to non-serious AE (one in each of the dose groups 0.25 mg, 0.5 mg and 2.0 mg cilobradine, two in the dose groups 1.0 mg and 5.0 mg cilobradine, two with metoprolol and none with placebo). Clinical laboratory values did not reveal dose-dependent changes. Vital signs and ECGs were unremarkable except bradycardia and a minor decrease of systolic and diastolic blood pressure (the latter only in the metoprolol group), and possible prolongation of QTcF in the 5.0 mg cilobradine group when QTcF results were compared to metoprolol (mean of the max. Δ QTcF: 21.3 ms for metoprolol vs. 31.7 ms for 5.0 mg cilobradine).

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Conclusions:

The effect of 2.0 mg cilobradine on heart at rest and after exercise was slightly inferior to the effect of metoprolol succinate at the highest tolerated dose. With 5.0 mg cilobradine, HR reduction was similar to metoprolol succinate at rest, but stronger than the comparator at end of exercise. Pharmacodynamic steady-state was approximately reached. The effect on HR was baseline-dependent: at rest, for each +3.5 bpm of baseline HR, the effect was stronger by -1 bpm. At end of exercise, the effect was stronger by -1 bpm for each +4 bpm at baseline. The measurement of peripheral flicker frequency did not reveal any consistent or relevant, dose-dependent changes when comparing the various cilobradine doses to placebo and metoprolol.

Cilobradine was rapidly absorbed and showed a high distribution into tissue. The apparent clearance was high, indicating that cilobradine is a high extraction ratio drug. No relevant deviation from dose proportionality was observed. Overall, the PK profile of cilobradine in the current study did not relevantly differ from that of previous clinical trials with the same compound. Although metoprolol plasma concentrations showed a high inter-subject variability, the PK profile in the current study was in agreement with the published experience from metoprolol sustained release formulations.

Treatment with cilobradine in the dose range 0.25 mg to 5.0 mg as well as with the comparators placebo and metoprolol, was safe. Tolerability was good to satisfactory in the placebo and 0.25 mg to 2.0 mg cilobradine groups but was not satisfactory in three subjects in the 5.0 mg cilobradine group and in one subject in the metoprolol group. There was one serious AE in the metoprolol group which was not drug-related. Two severe non-serious AE were reported in the 5.0 mg cilobradine group (one drug-related, one not drug-related). The overall frequency of AE was highest in the 5.0 mg cilobradine and in the metoprolol groups. VP which were typical for selective bradycardic agents frequently occurred with 5.0 mg cilobradine (14/18 subjects treated). With 2.0 mg cilobradine, typical VP were reported by two out of 16 subjects treated. AE from the MedDRA System Organ Classes ‘Cardiac disorders’ were more common with 5.0 mg cilobradine (33.3 %) and with metoprolol (17.4 %) compared to the other treatment groups. Overall laboratory analysis was unremarkable and did not reveal dose-dependent changes. There were no clinically relevant changes in vital signs and ECGs apart from expected pharmacological effects (bradycardia with cilobradine and metoprolol, blood pressure reduction with metoprolol). Treatment with 5.0 mg cilobradine seemed to prolong QTcF when compared to placebo and metoprolol.