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 (DK-AH 269 CL)		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 12 January 2005	**Number:** U04-2146	**Study period (dates):** 11 MAR 04 – 19 APR 04		

Title of study:	Metabolism and pharmacokinetics of [^{14}C]-DK-AH 269 CL after administration of single doses of 5 mg [^{14}C]-DK-AH 269 CL intravenously and 10 mg [^{14}C]-DK-AH 269 CL as oral solution in a parallel-group design in 12 healthy male volunteers.
Investigator:	[redacted]
Study center:	[redacted] The Netherlands [redacted]
Publication (reference):	None at time of writing this report
Clinical phase:	I
Objectives:	To investigate absorption, metabolism and excretion of [^{14}C]-DK-AH 269 CL after oral and intravenous administration in healthy volunteers To assess the safety and tolerability of DK-AH 269 CL after oral and intravenous administration to healthy volunteers
Methodology:	Randomised, open label, parallel-group comparison
No. of subjects:	
planned:	Entered: 12
actual:	Enrolled: 12 Oral [^{14}C]-DK-AH 269 CL: entered: 6; treated: 6; analysed: 6 Intravenous [^{14}C]-DK-AH 269 CL: entered: 6; treated: 6; analysed: 6
Diagnosis and main criteria for inclusion:	Healthy male elderly volunteers, between 50 and 65 years of age, with a BMI (Body Mass Index) of 19.9 to 29.9 kg/m^2 inclusive, heart rate (HR) at rest ≥ 55 beats per minute (bpm)
Test product:	[^{14}C]-DK-AH 269 CL
dose:	10 mg (single dose) composed of 7 mg [^{14}C]-radio-labelled and 3 mg unlabelled material
mode of admin.:	Oral solution

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batch no.:	B040309
Duration of treatment:	Single dose
Reference therapy:	[^{14}C]-DK-AH 269 CL
dose:	5 mg (single dose) [^{14}C]-radio-labelled
mode of admin.:	Intravenous infusion (30 minutes)
batch no.:	B040308
Criteria for evaluation:	
Pharmacokinetics:	Cilobradine plasma concentration time profile [^{14}C]-radioactivity concentration time profile in plasma and whole blood; Amount of cilobradine excreted in urine and of [^{14}C]-radioactivity excreted in faeces and urine; Pharmacokinetic parameters of cilobradine after single oral and intravenous dose and pharmacokinetic parameters of [^{14}C] radioactivity determined from radioactivity concentrations in plasma (and whole blood if necessary); Excretion balance based on [^{14}C] radioactivity in urine and faeces; Metabolic profile in plasma, urine and faeces, if feasible (reported separately by the sponsor).
Safety:	Blood pressure, pulse rate, ECG, clinical laboratory parameters, adverse events, physical examination, visual phenomena characterisation.
Statistical methods:	*Pharmacokinetics:* Descriptive statistics of pharmacokinetic parameters and drug concentrations. *Safety:* Frequencies of events, descriptive statistics for quantitative data.

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SUMMARY – CONCLUSIONS:

Pharmacokinetics:

After oral administration cilobradine was rapidly absorbed within 1h. The geometric mean maximum cilobradine plasma concentrations were 42.4 ng/mL. After intravenous administration (30 minutes infusion) the maximum cilobradine plasma concentration (101 ng/mL; gMean) was reached at the end of infusion. The dose normalized exposure ($AUC_{0-\infty,norm}$) was 24.5 after oral and 46.2 ng.h/mL per mg dose after intravenous administration leading to an estimate for absolute oral bioavailability of about 53%. The clearance after intravenous administration was 361 mL/min (gMean). The volume of distribution was high (124 L; gMean) indicating a good distribution into tissue. The renal clearance contributed with 5% after oral and 12 % after intravenous administration, to the overall clearance. The terminal half-life was about 19 h after both administrations.

The dose normalized maximum [^{14}C] radioactivity plasma concentrations were 8.00 ng.eq/mL/mg and 23.5 ng.eq/mL/mg after oral and intravenous administration, respectively (gMean). The maximum [^{14}C] radioactivity in plasma was reached after about 1 h after oral and at the end of infusion after intravenous administration. The dose normalized exposure was slightly less after oral compared to intravenous administration (108 vs. 135 ng.eq.h/mL/mg; gMean). The clearance (154 mL/min vs. 124 mL/min; gMean) and the volume of distribution (387 L vs. 476 L; gMean) were similar after both administrations. The terminal half-life was 29.0 h after oral and 44.5 h after intravenous administration (gMean), as this was longer compared to parent drug, the formation of metabolites with longer half-lives can be assumed. The renal clearance contributed to about 32% and 49%, respectively, to the total clearance. The amount of [^{14}C] radioactivity excreted in faeces was 60.5% of dose after oral and 45.6% of dose after intravenous administration (gMean). Thus the total recovery was 91.6% after oral and 91.6% of the dose after intravenous administration.

The parent compound accounted for only about 22.6% of the [^{14}C] radioactivity in plasma after oral administration and for about 34.2% after intravenous administration (AUC ratios). The excretion into urine was higher for [^{14}C] radioactivity compared to parent compound for both oral and intravenous administration (31.1% vs. 7.24% of the dose resp. 45.2% vs. 12.4% of the dose; gMean). The excretion of [^{14}C] radioactivity in faeces after oral administration was higher compared to intravenous administration (60.5% of the dose vs. 45.6% of the dose; gMean).

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Safety results:

Six out of 12 subjects reported one or more treatment emergent adverse events (AEs). Two out of six subjects (33.3%) reported AEs following an oral dose of cilobradine, and four out of six subjects (66.7%) reported AEs following an intravenous dose of cilobradine. The most frequently reported AEs were somnolence, headache and dizziness. Adverse events were mainly of mild intensity, except for one subject who reported one AE (dizziness) of moderate intensity following an intravenous dose. Dizziness was the only reported treatment emergent AE of moderate intensity, which started approximately 1.5 hours after start of infusion. This AE lasted for 5 minutes.

In total, five out of 12 subjects reported AEs, which were considered to be related to the study medication. One out of six subjects (16.7%) who received oral administration of cilobradine reported one AE which was considered to be related to the study medication. Four out of six subjects (66.7%) who received intravenous administration of cilobradine reported a total of five AEs which were considered to be related to the study drug. The most frequently reported related AE was dizziness.

One AE (exanthema reported by Subject 1 following intravenous injection) required therapy, and the subject recovered completely after 7 days. All other AEs were transient and resolved without sequelae.

There were no serious adverse events (SAEs), no other significant AEs and no AEs leading to treatment discontinuation.

No clinically significant abnormalities for vital signs, standard 12-lead ECG, 2-lead ECG (telemetry), physical examination, visual phenomena examination and clinical laboratory were observed.

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Conclusions:

Pharmacokinetics

After oral administration cilobradine was rapidly absorbed. The mean absorption time as the difference between oral and intravenous mean residence time (MRT) was about 2 h. Cilobradine undergoes a first-pass metabolism after oral administration. The absolute bioavailability was about 53% for the parent compound. Cilobradine as well as the metabolites showed a good distribution into tissue. No relevant distribution into blood cells was observed. Cilobradine revealed a high clearance. The terminal half-life was longer for [^{14}C] radioactivity compared to parent compound indicating the formation of metabolites with longer terminal half-lives. The renal clearance contributed with 5% after oral and 12% after intravenous administration to the overall clearance of cilobradine. For [^{14}C] radioactivity the amount excreted in urine was higher, thus renal clearance contributed to about 32 and 49%, respectively to the overall clearance of [^{14}C] radioactivity. The higher faecal excretion of [^{14}C] radioactivity after oral administration might be due to non-absorbed material. The overall recovery in urine and faeces was above 90% for both oral and intravenous administration.

Safety

An intravenous dose of 5 mg cilobradine and an oral dose of 10 mg cilobradine were safe and well tolerated by healthy, elderly male subjects.

The number of subjects reporting AEs after intravenous administration of cilobradine was greater compared to those receiving cilobradine orally.

There were no serious adverse events during the study.

The most frequently reported AEs were dizziness, headache and somnolence.

No clinically significant abnormalities for vital signs, standard 12-lead ECG, telemetry, physical examination, visual phenomena examination and clinical laboratory were observed.