## Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

# Clinical Trial Results Synopsis

| Study Design Description | | |
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| Study Sponsor: | Bayer Healthcare AG | |
| Study Number: | BAY 68-4986/12679 | NCT00568945 |
| Study Phase: | IIa | |
| Official Study Title: | Study to investigate the effect of the A1 agonist Capadenoson on ventricular heart rate in patients with persistent or permanent atrial fibrillation by administration of Capadenoson in a dose of 4 mg once daily for five days | |
| Therapeutic Area: | CV Risk Management | |
| Test Product | | |
| Name of Test Product: | Capadenoson (BAY 68-4986) | |
| Name of Active Ingredient: | Capadenoson | |
| Dose and Mode of Administration: | Capadenoson extrudate granulate, 4 mg sachet dispersed in 190 mL of water administered once-daily for 5 consecutive days | |
| Reference Therapy/Placebo | | |
| Reference Therapy: | Beloc-Zok (metoprolol succinate) 23,75 mg tablets | |
| Dose and Mode of Administration: | 23.75, 47.5 and 95 mg individual oral dosing to reach significant HR-lowering effect for 7 consecutive days at a stable dose after previous dose titration | |
| Duration of Treatment: | once daily administration for 5 consecutive days | |
| Studied period: | Date of first subjects' first visit: | 23 Jan 2008 |
| | Date of last subjects' last visit: | 16 Dec 2008 |

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| Study Center(s): | 1 investigational site in Germany |
| Methodology: | •Single-center<br>•Sequential<br>•Non-randomized<br>•Non-blinded<br>•Controlled |
| Indication/<br>Main Inclusion Criteria: | Male and/or female white patients with persistent or permanent atrial fibrillation present for at least 6 months, receiving rate control therapy.<br>Female patients to be included only if their non-childbearing potential was proven. |
| Study Objectives: | Overall:<br>Efficacy of Capadenoson in rate control therapy.<br><br>Primary:<br>To investigate the effect of Capadenoson 4 mg granulate once-daily for 5 days on heart rate control in patients with atrial fibrillation in comparison to baseline. The reduction in heart rate was to be assessed in a 24 hour long-term ECG as well as registered during an exercise tolerance test.<br>Secondary:<br>To investigate safety and tolerability of this treatment with Capadenoson. In addition, the pharmacokinetic profile of Capadenoson was assessed and plasma concentrations pre-administration (at trough) of metoprolol were determined. |
| Evaluation Criteria: | Efficacy (Primary):<br>Reduction of heart rate in 24h Holter ECG<br><br>Efficacy (Secondary):<br>Reduction of heart rate during exercise tolerance test<br><br>Safety:<br>The subjective tolerability of the test product was evaluated by questioning the patients about any adverse events.<br>The objective tolerability during study course was evaluated based on the following parameters: Heart rate, blood pressure systolic, diastolic and mean in supine position, and the ECG intervals as well as on evaluation of hematological and clinical chemical laboratory in plasma and urine. |

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| | Pharmacokinetics:<br>The plasma concentrations of capadenoson were determined after first and last administration and on the interim days (pre-administration) and evaluated using non-compartmental methods. Plasma concentrations of metoprolol were determined pre-administration on Days 04d, 05d, and 06d and after at least 3 days of wash-out.<br><br>Other: |
| Statistical Methods: | Efficacy (Primary) - if applicable:<br>The heart rate during the 24 hours 12–lead Holter ECG and in addition before, during, and after exercise tolerance testing (with stationary bicycle) based on a standard bicycle protocol was evaluated and the respective measurements after Capadenoson were compared to the baseline measurements without any treatment.<br><br>Efficacy (Secondary) - if applicable:<br><br>Safety:<br>Descriptive summary statistical methods were used for quantitative data (arithmetic mean, standard deviation, median, minimum and maximum) for the original data as well as for the difference to baseline. Frequency tables were provided for qualitative data.<br><br>Pharmacokinetics - if applicable:<br>The concentration vs time data of metoprolol and Capadenoson and derived pharmacokinetic parameters of Capadenoson were summarized by descriptive statistics (arithmetic and geometric mean with standard deviation and %CV, median and range).<br><br>Other - if applicable: |
| Number of Subjects: | 21 patients (17 men, 4 women) were treated according to protocol and were valid for safety, pharmacokinetic and pharmacodynamic analyses. |

Study Results

Results Summary — Subject Disposition and Baseline

The 21 patients (17 men, 4 women) treated fulfilled the inclusion criteria of persistent or permanent atrial fibrillation.

| Results Summary — Efficacy |
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| In conclusion, the results of this study did not show any clinically relevant heart rate-lowering effect at steady state of capadenoson in this study population. In comparison, the standard metoprolol treatment in patients with atrial fibrillation was effective in this indication, showing that rate control therapy was an adequate treatment for the study population. |
| Results Summary — Safety |
| The once daily Capadenoson treatment with 4 mg for 5 days was safe and well tolerated without moderate or severe nervous system disorders in 21 patients. There were no drop outs due to adverse effects. |
| Results Summary — Pharmacokinetics |
| Steady-state conditions for metoprolol were reached on the day of pharmacodynamic measurements. Steady-state conditions for Capadenoson were reached on the day of pharmacodynamic evaluation and the peak-trough fluctuation of plasma-concentration was low. At baseline measurement metoprolol concentrations were below limit of quantification. |
| Results Summary — Other |
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| Conclusion(s) |
| 5 days od 4 mg capadenoson treatments were safe and well tolerated in 21 patients with persistent atrial fibrillation without moderate or severe adverse events.The pharmacodynamic measurements of this study did not result in a clinically relevant HR-lowering effect of Capadenoson at steady state. Standard metoprolol treatment in these Afib patients showed an adequate treatment effect of rate control therapy.<br>Pharmacokinetic results for Capadenoson in this study were in the expected range based on previous experience in humans and metoprolol data were also consistent with its known pharmacokinetic characteristics. |

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| Publication(s): | not applicable |
| Date Created or Date Last Updated: | 01. Feb 2010 |