
This Summary of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can't be considered as a recommendation. Patients must 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 can 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.

# 2 SYNOPSIS

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| **Investigators:** | A list of participating investigators is displayed in appendix 16.1.4. | |
| **Clinical Trial Centers:** | 1 clinical trial center | |
| **Publication:** | Planned | |
| **Studied Period (Years):**<br><br>Date of First Enrolment:<br><br>Date of Last Completed: | <br><br>02/05/2006<br><br>26/06/2009 | **Phase of Development:**<br>Phase III Trial |
| **Sponsor's Responsible Person:** | [redacted]<br>Berlin-Chemie AG<br>Glienicker Weg 125, 12489 Berlin, Germany<br>[redacted] | |
| **Authors of the Synopsis:** | [redacted] | |
| **Objectives:** | The objective of this clinical trial was to evaluate the clinical efficacy and tolerability of nebivolol in comparison with metoprolol in the treatment of arterial occlusive disease (AOD) and arterial hypertension with a primary efficacy focus on endothelial function (assessed by means of flow-mediated dilation).<br>Further trial objectives were to assess the influence of both treatments on functional leg perfusion, blood pressure, erectile function (in males), on the quality of life and on laboratory markers of cardiovascular risk and coagulation. | |

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| **Methodology:** | Primary efficacy variable:<br>Flow-mediated dilation according to the guidelines of the international brachial artery reactivity task force<br>Secondary efficacy variables:<br>• Treadmill testing<br>• Doppler ultrasound<br>• Sphygmomanometric blood pressure measurement<br>• International index of erectile function (IIEF)<br>• Claudication scale / CLAU-S<br>• Immunoassay (NT-proBNP)<br>• Routine laboratory techniques (hs-CRP, homocysteine, fibrinogen) |
| **No. of Patients:** | |

| | planned | | | realized | | | | |
|---|---|---|---|---|---|---|---|---|
| | total | M | CD | total | M | | CD | |
| | n | n | n | n | n | % | n | % |
| Randomized | 128 | 64 | 64 | 128 | 65 | 101.6 | 63 | 98.4 |
| Evaluable - safety | 128 | 64 | 64 | 128 | 65 | 101.6 | 63 | 98.4 |
| - efficacy | | | | | | | | |
| - ITT | 102 | 51 | 51 | 109 | 52 | 102.0 | 57 | 111.8 |
| - PP | – | – | – | 108 | 52 | – | 56 | – |

M = Medication, CD = Comparator Drug, ITT = Intention To Treat, PP = Per Protocol

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| **Diagnosis / Indication and Main Criteria for Inclusion:** | Diagnosis / Indication: Essential hypertension and intermittent claudication (arterial occlusive disease) Fontaine's stage II<br><br>Main criteria for inclusion:<br>1. Male patients 30 years to 80 years or female postmenopausal patients up to 80 years<br>2. AOD Fontaine's stage IIa or IIb with<br>o a history of typical intermittent claudication (IC) for at least 6 months with documented lesions by duplex sonography or angiography within the last 12 months prior to inclusion<br>o actual proven AOD by objective means such as haemodynamics and non-invasive imaging or angiography<br>o an ankle-brachial pressure index (ABPI) < 0.90 of the worse leg and / or systolic ankle pressure < 70 mmHg<br>o advice on smoking cessation has been given and documented prior to inclusion in the trial; smoking habit is stable for at least 3 months prior to inclusion in the trial.<br>3. Stage I hypertension according to JNC (SBP 140-159 mmHg or DBP 90-99 mmHg) with or without antihypertensive treatment<br>4. Flow-mediated dilation < 8.0 % (criterion changed to < 10 % after amendment no. 4 and screening of 23 patients who were randomized afterwards, canceled after amendment no. 5 and screening of 32 patients who were randomized afterwards)<br><br>Inclusion criteria at baseline were:<br>5. SBP > 140 and < 160 mmHg and DBP < 100 mmHg at visit 2 (baseline)<br>6. SBP ≥ 100 mmHg and no symptoms of hypotension at visit 2 (baseline)<br>7. Heart rate ≥ 50 bpm at visit 2 (baseline) |

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| **Test Product, Dose,**<br>**Mode of Administration, Batch-No.:** | Nebilet®<br>Active ingredient: nebivolol<br>Dose: 5 mg daily<br>Mode of administration: oral<br>Batch-nos.: B0205081, B0207061 |
| **Duration of Treatment for Each Patient:** | 48 weeks treatment period (+ 2 weeks screening period) |
| **Reference Therapy, Dose, Mode of Administration, Batch-No.:** | Beloc-Zok 95 mg<br>Active ingredient: metoprololsuccinat<br>Dose: 95 mg daily<br>Mode of administration: oral<br>Batch-nos.: B0205081, B0207061 |
| **Criteria for Evaluation:**<br>**<u>Efficacy:</u>** | Primary efficacy variable:<br>Absolute change of mean brachial artery diameter increase between baseline and visit 7 (value at visit 7 minus value at visit 2), whereby mean brachial artery diameter increase at each visit is expressed as percentage maximum change in vessel diameter before and after endothelial-dependent flow-mediated dilation (%).<br>Secondary efficacy parameters:<br>• Absolute change of mean brachial artery diameter increase between baseline and visit 7, whereby mean brachial artery diameter increase at each visit is expressed as percentage maximum change in vessel diameter before and after intake of nitrate (%) – this variable was not specified in the study protocol.<br>• Absolute change in ICD between visits 2 and 7<br>• Percent change in ICD between visits 2 and 7<br>• Absolute change in ACD between visits 2 and 7<br>• Percent change in ACD between visits 2 and 7 (not specified in the study protocol)<br>• Proportion of responders regarding ICD at visit 7. Response is hereby defined as an increase of ICD by 50 % or more between visits 2 and 7<br>• Proportion of responders regarding ACD at visit 7. Response is hereby defined as an increase of ACD by 40 % or more between visits 2 and 7 |

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| | • Absolute change in ABPI between visits 2 and 7<br>• Absolute change of systolic and diastolic blood pressure between visits 2 and 4, 5, 6 (not specified in the study protocol) and 7<br>• In males: absolute change of each of the 5 IIEF subscores between visits 2 and 7<br>• Absolute change in each of the 5 dimensions of the CLAU-S between visits 2 and 7<br>• Absolute change of laboratory markers of cardiovascular risk and coagulation (hs-CRP, homocysteine, NT-proBNP, fibrinogen) between visits 2 and 7 |
| **Safety:** | Incidence of adverse events<br>• Incidence and type of adverse events<br>• Time course of laboratory parameters (safety laboratory parameters: hemoglobin (g/dl), hematocrit (%), erythrocytes (/pl), leucocytes (/nl), platelets (/nl), SGOT/ASAT (U/l), SGPT/ALAT (U/l), GGT (U/l), serum creatinine (mg/dl), urea (mg/dl), fasting glucose (mg/dl), HbA1c (%), sodium (mmol/l), potassium (mmol/l), TSH (mU/l))<br>• Number of patients with normal, abnormal and clinically not relevant or abnormal and clinically relevant safety laboratory parameters<br>• Time course of heart rate |
| **Statistical Methods:** | The statistical analysis was performed for two analysis populations: a safety population consisting of all 128 randomized patients who received at least once the double-blind trial medication and an intention to treat (ITT) population including all 109 patients of the safety population for whom the primary efficacy variable is evaluable, i.e. both the values at baseline and at V7 are available. Since ITT and per protocol (PP) populations differ in only one patient, only one population, the ITT population, was used for efficacy analysis.<br>Quantitative data (e.g. age and body weight) were analyzed by statistical parameters such as mean, standard deviation, minimum, median and maximum. Qualitative data (e.g. gender) were presented by absolute and relative frequency distributions.<br>The primary efficacy variable was tested for treatment group differences on a confirmative basis by means of a two-tailed significance test at a significance level of $\alpha = 0.05$.<br>Null hypothesis ($H_0$) and alternative hypothesis ($H_1$) are as follows: |

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| | $H_0$: $\mu_N = \mu_M$<br>$H_1$: $\mu_N \neq \mu_M$<br>where $\mu_N$ = expected mean absolute change for treatment group nebivolol<br>$\mu_M$ = expected mean absolute change for treatment group metoprolol<br>An analysis of covariance (ANCOVA) model was applied, including the baseline value as a covariate into the model. Accordingly, adjusted (least-square) means are displayed and 95 % confidence intervals (CIs) were calculated. |

## SUMMARY – CONCLUSIONS

### Efficacy Results

The main study objective, i.e. to prove a statistically significant increase in the brachial artery diameter in the nebivolol group compared to metoprolol, was missed. Nebivolol was not statistically superior to metoprolol. This applies to all efficacy variables assessed. However, there are some indications for a trend in favor of nebivolol, e.g. the improvement in the ABPI and the prolongation of the walking distance. Taking the results of the brachial artery flow, claudication distance, ABPI, CLAU-S and IIEF together, the study results demonstrate that neither nebivolol nor metoprolol did influence the AOD or the erectile function negatively during a period of nearly one year. Both drugs were equally effective in lowering the blood pressure.

### Safety Results

The overall incidence of TEAEs as well as of serious TEAEs and of deaths, the latter having occurred in the nebivolol group only, was higher in the nebivolol group compared with the metoprolol group. Only one serious TEAE was judged to be causally related with the study medication (M*obitz (type) II atrioventricular block*, nebivolol group) and is a known rare possible side-effect. Four patients (all nebivolol group) died during the study. All serious TEAEs leading to death of the four patients were judged as not causally related with the study medication. Also, cardiovascular events, especially serious ones, occurred more often in the nebivolol group. The analysis of related TEAEs only, shows that there were similar overall incidences of related TEAEs in both treatment groups. More non serious unlisted TEAEs were observed in the nebivolol group compared to the metoprolol group.

**Conclusion**

- Taking the results of the brachial artery flow, claudication distance, ABPI, CLAU-S and IIEF together, the study results demonstrate that neither nebivolol nor metoprolol did influence the AOD or the erectile function negatively during a period of nearly one year, indicating that both beta-blockers can be used in the treatment of hypertension in patients with IC Fontaine's stage IIa and IIb without a relevant impact on the arterial occlusive disease. Further studies are needed to demonstrate if this observation also applies for longer treatment periods or patients with more severe arterial occlusive disease.
- Both drugs were equally effective in lowering the blood pressure.
- Nebivolol was not statistically superior to metoprolol. This applies to all efficacy variables assessed.
- The main study objective, i.e. to prove a statistically significant increase in the brachial artery diameter in the nebivolol group compared to metoprolol, was missed.
- There are some indications for a clinical improvement, i.e. the improvement in the ABPI and the prolongation of the walking distance with a trend in favor of nebivolol for both parameters. There are some observations that indicate that patients in the nebivolol group might have suffered from more severe and/or more progressive AOD than patients in the metoprolol group. This might have contributed to the study outcome that the study hypothesis could not be proven.
- There were similar overall incidences of related TEAEs in both treatment groups.
- The overall incidence of TEAEs as well as of serious TEAEs and of deaths was higher in the nebivolol. Also, cardiovascular events occurred more often in the nebivolol group. The possible higher cardiovascular risk among the nebivolol patients might have attributed to some extent to the higher incidence of these TEAEs.
- More non serious unlisted TEAEs were observed in the nebivolol group compared to the metoprolol group. As long as the causal relationship with nebivolol or metoprolol cannot be ruled out completely for these TEAEs, special attention should be directed towards them in further studies and spontaneous reports.

Date of the Report: August 09, 2010