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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

Investigators:	The name of the principle investigator and co-investigators is given in Appendix 16.1.4.	
Clinical Trial Centers:	Monocenter tria[redacted]	
Publication:	None at the time of writing this report.	
Studied Period (Years): Date of First Enrolment: Date of Last Completed:	 21/07/2006 14/12/2007	**Phase of Development:** Phase IV Trial
Sponsor's Responsible Person:	Berlin-Chemie Menarini Glienicker Weg 125 D-12489 Berlin, Germany [redacted]	
Objectives:	<u>Primary objective</u> To assess the influence of Nebivolol as compared to Bisoprolol on the peak systolic and end-diastolic blood flow velocity in the short and the long posterior ciliary artery. It is assumed that Nebivolol may influence the ocular perfusion positively by peripheral vasodilatation induced by the stimulation of the NO-system. <u>Secondary objective(s)</u> To assess the influence of Nebivolol as compared to Bisoprolol - on the peak systolic and end-diastolic blood flow velocity (PSV and EDV) in the central retinal artery - on the peak systolic and end-diastolic blood flow velocity in the ophthalmic artery - on the resistive index (RI) in the: a. short posterior ciliary artery (SPCA) b. long posterior ciliary artery (LPCA) c. central retinal artery (CRA) d. ophthalmic artery (OA) - on the pulsatility index (PI) in the a. short posterior ciliary artery b. long posterior ciliary artery c. central retinal artery d. ophthalmic artery - on capillary blood flow in the retina - on the diameter of retinal vessels - on the Time average maximum velocity (TAMx) - on the Time average minimum velocity (TAMm) - on the blood pressure	
Methodology:	The clinical trial was conducted as a mono-center, active-substance controlled, randomized, double-blind, prospective phase IV parallel	

group trial with 2 independent treatment groups: 5 mg Nebivolol and 5 mg Bisoprolol.

After giving written informed consent, patients were examined according to the protocol. Patients meeting the selection criteria were allocated to Nebivolol or Bisoprolol for 42 days (maximum 45 days) under double-blind conditions.

A total of 4 visits (visit 1: day –17/-1, visit 2: day 0, visit 3: day 14 ± 3 and visit 4: day 42 ± 3) were scheduled.
Visit 1 was the screening visit at which informed consent was obtained. Patients underwent an ophthalmologic examination, applanation tonometry, visual field testing and Heidelberg Retina Tomography (HRT). Females with childbearing potential had a pregnancy test done. Most selection criteria were assessed at this visit. The visit 2 (baseline visit) was performed as soon as the results of the safety laboratory tests and the pregnancy test (if applicable) were available. After being asked to withdraw the β-blocker treatment at the time, patients meeting all selection criteria were randomised to Nebivolol or Bisoprolol. At this visit, patients underwent Doppler ultrasound (CDI) of the retrobulbar vessels, applanation tonometry and Laser-Doppler-Flowmetry. Vital signs were also measured. All study-related adverse events having taken place since visit 1 were registered. Patients were given the medication necessary until the following visit. Visit 3 took place 2 weeks (+/- 3 days) afterwards and corresponded to a safety control visit. At this visit, the concomitant medication was updated and the study drug compliance and adverse events (if any) recorded. Vital signs were measured and applanation tonometry was performed. In case of an insufficient or excess response to the study drug (SBP ≥ 160 mmHg or DBP ≥ 90 mmHg or SBP < 100 mmHg or symptoms of hypotension), the patient was withdrawn from the study.
The last visit or visit 4 was scheduled at the end of the treatment period. At this visit, the patient's compliance and adverse events were recorded. Furthermore, a blood sample was drawn for the safety laboratory panel and the lipid profile. All patients underwent an ophthalmologic examination, applanation tonometry, visual field testing, Laser-Doppler-Flowmetry and Doppler ultrasound measurement (CDI) of the retrobulbar vessels.

No. of Patients:

	planned			realized				
	total	Neb	Bis	total	Neb		Bis	
	n	n	n	n	n	%	n	%
Randomized	60	30	30	23	11	47.8	12	52.2
Evaluable - safety	60	30	30	22	10	45.5	12	54.5
- efficacy*								
- ITT	48	19	19	19	10	52.6	9	47.4
- PP	48	19	19	19	10	52.6	9	47.4

Neb = Nebivolol, Bis = Bisoprolol, ITT = Intention To Treat, PP = Per Protocol. NB: the ITT and the PP populations were the same.
*A 20% drop out was considered.

Diagnosis / Indication and Main Criteria for Inclusion:

Indication: glaucoma in hypertensive patients.
The inclusion criteria were:
1. 18 years or older
2. Stable glaucoma associated with a pathological excavation of the optical nerve head and visual field defects
3. No other previous eye surgery than cataract surgery and/or

	cyclophotocoagulation, deep sclerectomy, trabeculectomy or related surgical procedures which were performed > 4 weeks before study entry 4. Refractive error between – 6 and + 6 dpt 5. Arterial hypertension adequately and stable (≥ 3 months) treated in combination- or mono-therapy with a beta-blocker except for current treatment with Nebivolol, Bisoprolol or Carvidilol (blood pressure prior to switch of the antihypertensive medication to the trial medication: < 140 mmHg SBP and < 90 mmHg DBP) The exclusion criteria were: 1. Secondary hypertension 2. Untreated heart failure or uncompensated heart failure 3. Sick-sinus-syndrome including heart blocks (SA node) and/or AV block 2nd and 3rd degree and/or significant arrhythmia and/or bradycardia < 50 bpm (in resting condition prior to treatment) 4. Cardiogenic Shock 5. Bradycardia (< 50 bpm prior to treatment) 6. Hypotension with systolic blood pressure < 90 mmHg 7. Known hypersensitivity to Nebivolol or Bisoprolol or any of the ingredients of the trial medication or any known hypersensitivity to ß-blockers 8. Bronchial hyperreactivity, bronchial asthma, or history of bronchial spasm 9. Patients with known SGPT (ALAT) and SGOT (ASAT) levels exceeding three times the upper limit of the investigator's normal range, known serum bilirubin > 1.75 mg/dl (> 30 µ mol/l) or clinical evidence of severe hepatic disease or hepatic failure 10. Untreated pheochromocytoma 11. Metabolic acidosis 12. Peripheral arterial occlusive disease > IIa (PAOD) or Raynaud's syndrome 13. History of myocardial infarction within the last 3 months prior to study inclusion 14. Unstable angina pectoris 15. Prior or active malignancy in the previous 5 years except adequately treated basal cell/ squamous cell carcinoma of the skin or carcinoma in situ of the cervix 16. Previous treatment within 30 days prior to the beginning of the study or concomitant treatment with substances which may decrease the efficacy of the test substance(s) or may lead to drug interactions, for example: MAO inhibitors, systemic sympathomi-metics, intravenous application of calcium-antagonists of verapamil- or diltiazem-type or other antiarrhythmic agents except for intensive care, aldosterone analogues 17. Anticipated dose change of statins if patient is treated with statins already or anticipated need for statins if patient is currently not treated with statins 18. Previous topical and/or systemic glaucoma medication not stable for > 14 days prior to visit 2 19. Anticipated dose change of topical glaucoma medication (including dorzolamide) or anticipated dose change of magnesium-containing preparations 20. Patients with psychiatric diseases 21. Patients with a history of alcohol and/or drug abuse 22. Patients who are currently participating in another clinical study or who have received an investigational drug within 30 days prior to entering the study

	23. Patients who are unwilling or unable to provide informed consent or to participate satisfactorily for the entire trial period 24. Women of childbearing potential without adequate contraception (medically acceptable methods are contraceptive implant, contraceptive injection, intrauterine device (IUD), or oral contraceptives taken for at least 3 months, which the patient agrees to continue using during the study, or a double-barrier method which must consist of a combination of any of the following: diaphragma, cervical cap, condom, or spermicide) 25. Patients who are pregnant or lactate (Pregnancy should be ruled out by pregnancy test) 26. Intake of coffee and/or smoking < 2 hours before Laser Doppler Flowmetry
Test Product, Dose, Mode of Administration, Batch-No.:	Trial medication: Nebilet® Active ingredient: Nebivolol Dose: 5 mg Mode of administration: oral, once daily in the morning with breakfast Batch number: A1006041
Duration of Treatment for Each Patient:	Six weeks (42 days)
Reference Therapy, Dose, Mode of Administration, Batch-No.:	The comparator medication was Concor®. Active ingredient: Bisoprolol Dose: 5 mg Mode of administration: oral, once daily in the morning with breakfast Batch number: A1006041
Criteria for Evaluation: **<u>Efficacy:</u>**	Primary and secondary efficacy parameters as well as the method used to assess them are listed below. All these parameters were measured at visits 2 and 4. *Variable* — *Method* <u>Primary efficacy variable</u>: - PSV in the SPCA — Color Doppler imaging (CDI) - PSV in the LPCA - EDV in the SPCA - EDV in the LPCA <u>Secondary efficacy variable(s)</u>: - PSV in the CRA — Color Doppler imaging (CDI) - EDV in the CRA - PSA in the OA - EDV in the OA - RI in the SPCA — Color Doppler imaging (CDI) - RI in the LPCA - RI in the CRA - RI in the OA - PI in the SPCA — Color Doppler imaging (CDI) - PI in the LPCA - PI in the CRA - PI in the OA - Retinal capillary blood flow, velocity and volume in the parapapillary region and the fovea — Laser-Doppler-Flowmetry Color Doppler imaging (CDI)

Safety:	- TAMx in cm/sec - TAMm in cm/sec - Blood pressure — Guidelines for the clinical investigation of antihypertensive drugs, WHO 1984. Mean value of three measures. The safety parameters were the following: - Incidence and type of adverse events - Changes of Laboratory parameters (safety and lipid profiles) - Changes of heart rate, measured in sitting position after a minimum of 5 min. rest - Changes of ECG after 6 weeks of treatment Adverse events were registered at visits 2, 3 and 4. Laboratory parameters and the ECG were assessed at visits 1 and 4, whereas vital signs were measured at visits 2 and 4.
Statistical Methods:	Continuous variables were summarized with descriptive statistics (n, mean, standard deviation (SD), median, minimum (Min) and maximum (Max)). All summaries were presented on available data. Categorical data were described by the number (n) and percentage (%) of subjects in each category. Missing observations were presented in tables as a separate category. The calculation of percentages did not include the missing category. Unless otherwise specified, data were presented by treatment group and in total. In order to account for uncertainties concerning the distributional properties of the efficacy criteria, the Wilcoxon-Mann-Whitney test was applied for treatment comparisons of the primary efficacy variables. All statistical tests were two-sided with a type I error of 0.05. All analyses were performed using SAS version 9.1. ...

SUMMARY - CONCLUSIONS

Efficacy Results

Both treatment groups were similar in terms of demographics and baseline characteristics. At screening, all patients were on metoprolol either as monotherapy or with adjuvant anti-hypertensive therapy. Additionally of the 19 patients included in the ITT population, 16 were under anti-glaucoma medication, brimonidine being the agent most frequently used (n=7) followed by latanoprost (n=5).

Efficacy was analysed in the ITT population which included the same patients as the PP analysis set. Both populations comprised 19 patients (Nebivolol: n=10; Bisoprolol: n=9).

No significant differences were observed between groups for any of the primary endpoints. Only the increase in the PSV in the SPCA observed within the Nebivolol group reached statistical significance (p=0.020). The changes observed within each group for the other parameters were not significant. Overall, the mean changes were:

- In the Nebivolol group:
  - The PSV in SPCA increased by 2.00±2.23 cm/sec (p=0.020) while the PSV in the LPCA decreased by -1.12±2.21 cm/sec (p=0.164)
  - The EDV in the SPCA increased by 0.05±0.75 cm/sec (p=0.984) while in the LPCA, it decreased by -0.30±0.85 cm/sec (p=0.352)
- In the Bisoprolol group:
  - The PSV in the SPCA increased by 1.97±3.49 cm/sec (p=0.098) and by 3.85±6.47 cm/sec (p=0.195) in the LPCA

– The EDV in the SPCA increased by 0.99±1.27 cm/sec (p=0.063) and by 0.40±1.10 cm/sec (p=0.375) in the LPCA

In relation to the secondary endpoints, Nebivolol and Bisoprolol induced similar increases in the PSV and EDV in the CRA and OA (p>0.1 for all parameters). The mean changes were as follows:

- In the Nebivolol group:

– The PSV in the CRA increased by 0.16±2.31 cm/sec and by 0.40±9.21 cm/sec in the OA
– The EDV in the CRA increased by 0.08±0.62 cm/sec and by 0.20±2.72 cm/sec in the OA

- In the Bisoprolol group:

– The PSV in the CRA increased by 0.09±1.00 cm/sec and by 3.72±11.79 cm/sec in the OA
– The EDV in the CRA increased by 0.67±0.86 cm/sec and by 0.08±2.29 cm/sec in the OA

With regards of RI, switching from the patient β-blocker treatment to the study medication resulted in:

- In the Nebivolol group:

– The RI in the SPCA increased by 0.06±0.07 and in the LPCA by 0.004±0.06
– The RI in the CRA decreased by -0.01±0.08 and in the OA by -0.01±0.10

- In the Bisoprolol group:

– The RI in the SPCA decreased by -0.10±0.14 and in the CRA by -0.07±0.09
– The RI in the LPCA increased by 0.02±0.11 and in the OA by 0.03±0.14

Only the changes in the RI in the SPCA were significantly different between groups (p=0.018). Moreover, the increase observed in the RI in the SPCA within the Nebivolol group was also significant (p=0.039), but not the modulation observed within the Bisoprolol group.

The changes observed in the PI after six weeks of treatment with Nebivolol or Bisoprolol differed from those in the RI. The changes in the PI were as follows:

- In the Nebivolol group, the PI increased in each of the 4 investigated arteries (SPCA: 0.27±0.30; LPCA: 0.03±0.57; CRA: 0.14±0.70; OA: 0.34±0.97)
- In the Bisoprolol group, the PI decreased in the SPCA (-0.27±0.66), LPCA (-0.01±0.29) and CRA (-0.28±0.48) and increased in the OA (0.06±1.18)

As for the RI, only the changes observed in the PI for the SPCA were significantly different between groups (p=0.043). The increase observed within the Nebivolol group was also found significant (p=0.020), but not the decrease measured within the Bisoprolol group.

The changes in the TAMx observed after six weeks of treatment with the study medication were:

- In the Nebivolol group, the TAMx in the LPCA decreased by -0.58±0.99, by -0.20±0.97 in the CRA and by -0.04±5.83 in the OA, while the TAMx in the SPCA increased by 0.61±0.94
- In the Bisoprolol group, the TAMx in the SPCA increased by 1.09±1.54, by 1.98±3.04 in the LPCA and by 0.46±1.11 in the CRA, while the TAMx in the OA decreased by a mean of -0.10±5.52

After six weeks of treatment with the study medication, the changes in the mean TAMm were as follows:

- In the Nebivolol group, the TAMm decreased by -0.17±0.51 in the LPCA, by -0.13±0.50 in the CRA and by -0.18±3.77 in the OA, while it increased by 0.27±0.45 in the SPCA
- In the Bisoprolol group, the TAMm increased in all four arteries (SPCA: 0.54±0.80; LPCA: 0.98±1.47; CRA: 0.36±0.78; OA: 0.28±3.40)

None of the numerical differences in the TAMx or TAMm between groups reached statistical significance.

At visit 2, the retinal capillary flow, volume and velocity were measured in 4 patients randomized to Nebivolol and 3 patients randomized to Bisoprolol. After the six-week treatment period, these parameters were reassessed in 2 Nebivolol-treated patients and 1 patient treated with Bisoprolol. At visit 4, an increase was observed in the retinal capillary volume (6.71±0.19), flow (47.59±2.96) and velocity (0.14±0.01) among patients treated with Nebivolol. Treatment with Bisoprolol resulted in a decrease in the volume (-5.83), flow (-265.59) and velocity (-0.95) in retinal capillar vessels. No conclusions can be drawn from these results due to the limited number of patients undergoing this assessment.

Switching to Nebivolol or Bisoprolol resulted in a small decrease in the systolic and diastolic blood pressure. The decrease was not statistically different between groups (p>0.5 for both parameters). The decrease observed with Nebivolol was -2.5±9.7 for SBP and 0.0±7.5 for DBP. Likewise, the decrease induced by Bisoprolol was -1.3±8.4 for SBP and -2.1±9.0 for Bisoprolol.

Safety Results

The safety profile of Nebivolol and Bisoprolol was assessed in the safety population which included 23 patients (Nebivolol: n=11; Bisoprolol: n=12). Exposure to the study medication was similar between groups (mean of 36.6 days for Nebivolol and 39.6 days for Bisoprolol).

There were no differences between groups with regards to the overall adverse events experience, laboratory parameters, and vital signs.

Overall, four patients (one in the Nebivolol group and 3 in the Bisoprolol group) reported a total of five adverse events, including two SAEs (one per group). The intensity of all adverse events was considered as mild-to-moderate. The serious adverse events were cataract operation and diverticulitis of colon. None of the serious adverse events resulted in a fatal outcome. Although this adverse event was not considered related to the study medication, the diverticulitis in colon led to withdrawal from the study of patient number 15 (treated with Bisoprolol).

Only one adverse event was considered as probably related to the study medication (Bisoprolol). This adverse reaction was tiredness. The event resolved spontaneously.

Laboratory evaluations did not reveal any major changes between visit 1 and visit 4. A minor reduction was observed in SBP, DBP and heart rate in both groups.

Conclusion

No significant differences were observed between Nebivolol and Bisoprolol for any of the 4 primary efficacy parameters, i.e., PSV and EDV in the posterior ciliary arteries. Likewise, no significant differences were observed in the PSV and EDV in the CRA and OA.

The only significant differences observed between Nebivolol and Bisoprolol concerned the RI and PI. In this respect, Nebivolol induced an increase in the RI in the SPCA whereas treatment with Bisoprolol resulted in a decrease in the RI in this artery (p=0.026). Likewise, Nebivolol induced an increase in the PI in the SPCA whereas Bisoprolol decreased this parameter in this artery (p=0.043). The increase observed in the RI and in the PI in the SPCA within the Nebivolol group were both found significant.

Overall, the results do not suggest a beneficial effect of Nebivolol in the retrobulbar perfusion. The influence of this agent in ocular blood flow at least in terms of peak systolic and end diastolic velocity is equivalent to that of Bisoprolol.

Both agents had a similar capacity to maintain systolic blood pressure under control. None of these agents was associated with glaucoma progression in terms of changes in IOP or visual field defects.

Date of the Report: