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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

Title of the study:Comparison the effects of Nebivolol versus Metoprolol succinate on endothelial function and large artery stiffness.A parallel group, randomized, double-blind, active control phase IV clinical trial - NEMENDAS

Investigators:	[redacted]
Clinical Trial Centers:	[redacted] Estonia
Publication:	Planned
Studied Period (Years): Date of First Enrolment: Date of Last Completed:	 29-MAR-2006 10-DEC-2008
Phase of Development:	Phase IV Trial
Sponsor's Responsible Person:	Berlin-Chemie AG [redacted] International Regulatory Affairs and Medical Marketing [redacted]
Authors of the Synopsis:	[redacted]
Objectives:	To investigate the effects of nebivolol or metoprolol succinate on endothelial function and large artery stiffness.
Methodology:	Parallel group, randomized, double-blind, active control.

No. of Patients:	planned			realized				
	total	M	CD	total	M		CD	
	n	n	n	n	n	%	n	%
Randomized	80	40	40	80	40	50	40	50
Evaluable - safety	80	40	40	80	40	50	40	50
- efficacy	80	40	40	80	40	50	40	50
- ITT	80	40	40	80	40	50	40	50
- PP	80	40	40	80	40	50	40	50

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

Diagnosis / Indication and Main Criteria for Inclusion:	• Patients with mild to moderate essential hypertension (systolic BP 140-179 mmHg and/or diastolic BP 90-109 mmHg)*; • Male and female patients aged 30-65 years; *Newly diagnosed untreated patients or previously diagnosed patients who were without treatment at least two weeks prior to screening. If the patient had taken antihypertensive medication previously, the BP values were measured after two weeks without treatment (wash-out phase) before randomization at Visit 2.

Test Product, Dose, Mode of Administration, Batch-No.:	Nebivolol (RSSS + SRRR)-[iminobis(methylene)]bis[6-fluoro-3,4-2H-1-benzopyrane-2-methanol] hydrochloride Single Dose: 5 mg Titration phase: One capsule per day containing 5 mg. Maintenance phase: One capsule per day containing 5 mg. Mode of administration: p.o. Batch-No.: 52540, 51710
Duration of Treatment for Each Patient:	12 months
Reference Therapy, Dose, Mode of Administration, Batch-No.:	Metoprolol succinate Single dose: 50 mg, 100 mg Titration phase: one capsule per day containing 50 mg. Maintenance phase: One capsule per day containing 100 mg, if blood pressure had not decreased to < 140/90 mmHg Mode of Administration: p.o. Batch-No.: GE8582A1, GF9606A1, IC8675A1, ID9743A1
Criteria for Evaluation: **Efficacy:**	Primary criteria: Effect of Nebivolol as compared to Metoprolol on: • endothelial function (e.g. increased endothelium-dependent/-independent vasodilation), • large and small arterial compliance, • large artery stiffness (e.g. change in both augmentation index and in carotid-femoral pulse wave velocity, change in estimated aortic pulse wave velocity, and change in central blood pressure). Secondary criteria: • change in carotid artery intima-media thickness, • change in left ventricular mass index, systolic and diastolic function, • change of biomarkers related to endothelial dysfunction (intracellular adhesion molecule, asymmetric dimethylarginine), oxidative stress (oxidized LDL, antibodies against oxidized LDL, homocysteine, isoprostanoids) and chronic inflammation (high sensitive C-reactive protein, fibrinogen, interleukin-6).

Safety:	• Number and frequency of adverse events, possibly or probably related to the trial medication, • ECG parameters (assessment of abnormal morphology of PR-, QRS- and ST-complexes), • Biochemical safety parameters: sodium, potassium, urea, creatinine, ASAT, ALAT, glucose, • Haematological safety parameters: haemoglobin, haematocrit, white cell count, red cell count, platelet count, • Urinalysis (leucocytes, blood, protein, ketones and glucose, urine sediment), • Arterial blood pressure by sphygmomanometer using the same arm, • Physical examination.
Statistical Methods:	For continuous variables arithmetic mean and standard deviation were computed. For categorical variables, the contingency tables were obtained and chi-square or Fisher's exact test was used to compare the distributions of two randomized groups. With continuous variables, which weren't normally distributed in at least one group, Wilcoxon rank sum test was used to test the difference between groups. Wilcoxon test was also used when variables variance was not equal in both groups. Otherwise the t-test was used to test for the difference. Changes from baseline to endpoint were also tested for difference from zero with t-test or signed rank test. The Wilcoxon rank sum test can be considered a non-parametric equivalent of the unpaired t-test. The method is a sum of ranks comparison. The test compares the locations of two populations, determines if one population is shifted with respect to other. Because it is non-parametric, it makes only limited assumptions about the distribution of data. Where possible, Pearson chi-square test was used to test for the difference. When sample size in a group was too small, Fisher's exact test was used. Fisher's exact test is an alternative to chi-square test to test whether some proportion of interest differs between two groups. It is suitable for small samples due to the fact that it does not make any approximations – it calculates the exact probability.

SUMMARY - CONCLUSIONS

Efficacy Results

Concerning primary efficacy variables (endothelium-dependent vasodilatation, large artery compliance, small artery compliance, augmentation index, carotid-femoral PWV, central systolic or diastolic blood pressure, and estimated aortic PWV), there were no significant differences of mean values between the Nebivolol and the Metoprolol treatment group except for the augmentation index at Visit 2 (27.2% versus 19.2%, p = 0.0046) and Visit 8 (28.9% versus 19.1%, p = 0.0012), central pulse pressure at Visit 2 (49.2 mmHg versus 44.0, p=0.038), and the endothelium-dependent vasodilatation at Visit 6 (8.3% versus 5.75, p = 0.0492). In the Nebivolol group, there were significant decreases at Visit 8 compared to baseline (Visit 2) in central systolic blood pressure (p = 0.0006), central diastolic blood pressure (p = 0.0105) and central pulse pressure (p = 0.0025). No significant changes for these parameters were detected in the Metoprolol group (p = 0.2377, p = 0.1357 and p = 0.7489, respectively. In the Metoprolol group, significant changes were found only for large artery compliance (13.7 ml/mmHG*10 to 16.0 ml/mmHg*10, p = 0.0221).

Concerning secondary efficacy parameters (change in carotid artery IMT, change in left ventricular mass index, and change of biomarkers related to endothelial dysfunction), no significant difference between groups was found for any parameter. In the Nebivolol group, there were significant changes to baseline for the parameters ICAM (decrease from 235.7 IU/L to 200.8 IU/L, p = 0.0014), oxLDL (decrease from 85.5 IU/L to 62.0 IU/L, p = 0.0019), isoprostanoids (decrease from 446.0 IU/L to 225.3 IU/L, p = 0.0016), isoprostanoids/ u-creatinine (decrease from 43.0 to 21.8, p = 0.0114), and posterior wall thickness (decrease from 1.0 mm to 0.9 mm, p = 0.0002). In the Metoprolol group, there were significant changes to baseline for the parameters ICAM (decrease from 234.0 IU/L to 213.1 IU/L, p = 0.0006), oxLDL (decrease from 88.6 IU/L to 65.5 IU/L, p = 0.0001), and OLAB (increase from 554.8 IU/L to 617.7 IU/L, p = 0.0406). There were no significant differences for the changes from baseline of any secondary variable between the groups.

Safety results

20 (50%) patients in the Nebivolol group and 17 (42.5%) patients in the Metoprolol group experienced at least one AE, but the difference was not statistically significant. There were no serious adverse events. Four patients had to be permanently withdrawn from treatment due to AEs, which were all at least possibly related to trial medication. Three of these patients were treated with Nebivolol and one with Metoprolol. These AEs were of mild to moderate severity. No AE symptom occurred more than 6 times in any treatment group. Most symptoms were recorded only once.

No significant differences concerning changes in haematology and blood chemistry over time were found between the treatment groups. The numbers of patients with normal urine analysis results did not differ significantly between treatment groups. Despite the difference between groups not being significant, the percentage of patients in the Nebivolol group with a normal erythrocyte count decreased from a maximum of 52.5% at Visit 1 to 39.3% at Visit 8, resulting in an almost significant difference to the Metoprolol group (p = 0.0526), where the percentage of patients with a normal erythrocyte count was more stable over time. One patient had a clinically significant abnormality of leukocytes.

At the end of the trial (Visit 8), peripheral blood pressure parameters and heart rate decreased significantly compared to baseline in both treatment groups. The reduction of right arm peripheral systolic blood pressure was greater in the Nebivolol group than in the Metoprolol group (16.8 mmHg versus 9.0 mmHg, p = 0.0207). There were no other significant differences

between the treatment groups concerning the changes in peripheral systolic and diastolic blood pressures.
The pulse frequency of the treatment groups was significantly different at Visit 8 (Nebivolol: 58.3 bpm, Metoprolol: 66.0 bpm, p = 0.0105). The decrease from baseline to Visit 8 was significant only in the Nebivolol group (p = 0.0001), and the changes from baseline differed significantly between the treatment groups (p = 0.0051). The PR-interval was significantly different between the groups Visit 2 (Nebivolol: 160.8 ms, Metoprolol: 149.2 ms, p = 0.0449). The decrease from baseline to Visit 8 was significant only in the Nebivolol group (p = 0.0022), and the changes from baseline differed significantly between the treatment groups (p = 0.0494). The QRS-intervals did not differ significantly between groups at any Visit. The change from baseline to Visit 8 was significant only in the Nebivolol group (p = 0.0062), but the changes were not significantly different between groups. The QT-intervals of the treatment groups differed significantly at Visit 8 (Nebivolol: 435.3 ms, 409.6 ms, p = 0.0001).The changes from baseline were significant in both treatment groups (Nebivolol: p = 0.0001, Metoprolol: p = 0.0132), and the changes from baseline differed significantly between treatment groups (p = 0.0001). The QTC-interval was not significantly different between treatment groups at any visit, but changed significantly from baseline in the Metoprolol group (p = 0.0170). The changes from baseline did not differ significantly between the treatment groups.

Abnormal waveforms were noted for few patients per treatment group and visit. Three patients in the Nebivolol group had an abnormal QRS-interval at Visit 8. Abnormal T-waves in the Nebivolol group were documented in 3 patients at Visit 3 and 2 patients at Visit 1, and in 3 patients in the Metprolol group at Visit 6. Other abnormalities did not occur in more than 1 patient per visit and treatment group.

Conclusion

The analyses of efficacy variables of the Nebvivolol and Metoprolol treatment groups showed that the parameters AIx, mean of mean IMT and central pulse pressure were significantly different at baseline for both treatment groups. That is, it cannot be concluded from the significant difference in AIx at Visit 8 that there was an effect of Nebivolol treatment on this parameter. Changes in central blood pressures (central systolic pressure, central diastolic pressure and central pulse pressure) from baseline were significant only in the Nebivolol group. Nebivolol did not significantly effect any changes of other primary efficacy parameters from baseline to trial end, and so did Metoprolol for all variables, except for a significant increase in the large artery compliance.

Left and right systolic and diastolic pressures and pulse rate were significantly decreased in both groups.

Nebivolol significantly decreased the plasma concentrations of ICAM, oxLDL, isoprostanoids and isoprostanoids/u-creatinine, while Metoprolol was efficient in significantly decreasing concentrations of ICAM, oxLDL and OLAB. However, OLAB was the only parameter a significant difference between treatments was shown for.

The safety parameters of this trial did not significantly differ between the Nebivolol and Metoprolol groups. No SAEs were documented in this trial. Four out of 80 patients had to be withdrawn due to AEs. All of these patients had AEs that were at least possibly related to trial medication. One of these patients was treated with Metoprolol and three were treated with Nebivolol. Attention should be paid to the high percentage of patients with abnormal erythrocyte counts in urine in the Nebivolol group, even if this was not significantly different from the Metoprolol group and may have been caused by the patients' hypertension itself.

ECG measurements revealed few differences between treatments, including significantly longer QT-intervals in the Nebivolol group at Visits 6 and 8. No safety issues seem to be raised here, as very few patients developed abnormal waveforms under any treatment, with 3 out of 80 concerning one parameter (T-wave) being the maximum.

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