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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

Name of Sponsor/company: MENARINI	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Nebilet® tablets 5 mg	Volume:	
Name of Active Ingredient(s): Nebivolol	Page:	

Title of the study:
Effects Of The Long-Term Administration Of Nebivolol On The Clinical Symptoms, Exercise Capacity And Left Ventricular Function Of The Patients With Diastolic Dysfunction (ELANDD)

Investigators:
Coordinating Investigators:
[redacted]
Principal Investigators:
[redacted]

Study centers:
12 cardiology centers in the Netherlands, Italy, Belgium, Germany, Spain, Portugal and Greece.

Publication:
none

Study period:	**Phase of Development:**
9 March 2005 (first enrolment) 21 December 2007 (last completed)	IIIb

Objectives:
The study was designed to assess the long-term effects of the administration of nebivolol, compared to placebo, on the clinical symptoms, exercise capacity and parameters of left ventricular function in patients with diastolic heart failure.

Methodology:
The study was a randomized, double-blind, multicenter, parallel group, placebo-controlled trial.

Patient eligibility for inclusion into the trial was assessed at the screening visit (week 0 – visit 1). Patients were randomized to receive placebo or nebivolol, which was added to the ongoing therapy. If patients were on beta-blockade they had to be switched directly to the study medication. If the administration of the beta-blocker was mandatory according to the investigator's judgment, the patient was not eligible. Heart rate and blood pressure were assessed before and 1 and 2 hours (optional) after intake of the study drug. If the drug was tolerated without untoward effects, including hypotension and/or bradycardia, the patients continued to take placebo or nebivolol for the following week at a dose of 2.5 mg once daily.

One week after randomization (week 1 – visit 2) patients were uptitrated to a dose of 5 mg once daily, unless the patient had experienced untoward effects possibly related to beta-blockade. Heart rate and blood pressure were assessed before and 1 and 2 hours (optional) after intake of the study drug. Patients who did not tolerate the 5 mg dose could be withdrawn at the investigator's discretion.
Further uptitration to a dose of 10 mg once daily was allowed after 4 weeks of treatment (week 5 – visit 3) in the patients with a resting heart rate > 50 beats/min and no hypotension (systolic blood pressure < 100 mm Hg). One week after the increase in dosage (week 6 – visit 4) the tolerability of the treatment was checked and patients who did not tolerate the 10 mg dose

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continued treatment at a dose of 5 mg once daily.
Follow-up visits were performed at week 12 (visit 5) and week 26 (end of trial, visit 6).

At baseline and at the end of the study a 6-minutes walking test, a cardiopulmonary exercise test, a physical examination and an echocardiogram were performed. Patients were asked to complete the Minnesota Living with Heart Failure™ questionnaire at several time points during the study. Throughout the study patients were assessed for safety, including safety laboratory, electrocardiogram (ECG), vital signs and adverse events. Blood samples were collected to determine plasma levels of N-Terminal pro Brain Natriuretic Peptide (NT-pro BNP) and New York Heart Association (NYHA) classification was evaluated.

Number of patients:
Planned: 150 total, 75 per treatment group.
Randomized and analyzed: 116 total, 57 in the nebivolol group and 59 in the placebo group.

Diagnosis and main criteria for inclusion:
Inclusion:

1. The patient was aged ≥ 40 years
2a. Symptoms of heart failure; a documented history of heart failure.
3a. A left ventricular ejection fraction ≥ 45% assessed by echocardiography, radionuclide ventriculography or magnetic resonance imaging (MRI)
4a. NYHA functional class II or III
6a. The patient had given written informed consent for participation in the study. The patient was able and willing to visit the hospital for the planned study visits
10. Any diastolic abnormality well documented on echocardiography following the diagnostic criteria for diastolic heart failure published by the 'European Study Group on Diastolic Heart Failure'

Exclusion:

1. The patient was unable to perform a 6-minutes walking test
3. Planned invasive cardiac procedures carried out during the study
4. The patient had recently (< 3 months) unstable angina, acute myocardial infarction or stroke treated with a beta-blocker
5. The patient had exercise induced myocardial ischemia as main cause of exercise impairment as shown by limiting symptoms (angina) or by previous exams (exercise test, exercise echocardiography or myocardial scintigraphy)
6. The patient had concomitant diseases (COPD (FEV1 < 50%), peripheral arterial disease, orthopedic disease) as main cause of exercise impairment
7. Presence of major contraindications to beta-blocker therapy, such as severe sinus bradycardia (<50 beats/min), atrio-ventricular block, bronchial asthma sensitive to beta-agonist agents
8. The patient was treated with verapamil or diltiazem
9. The patient had a systolic blood pressure < 100 mmHg
10a. The patient was pregnant, or breast feeding, or of childbearing potential without using adequate contraception
11. The patient had a history of alcohol or other illicit drug abuse
12a. The patient suffered from any other medical condition that might have excluded the patient for safety reasons or interfered with the objective of the study according to the investigator's judgment
13a. The patient was expected to have a poor compliance to the study drug therapy
14a. The patient was participating in any other clinical trial with an investigational product, or

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the patient was scheduled to receive any such product during the study or in the 4 weeks following the study

Test product, dose and mode of administration, batch number:
Nebivolol, 2.5 mg/ 5 mg/10 mg once daily in the morning, oral intake, batch nos.: 43002, 63104

Duration of treatment:
Maximum 6 consecutive months

Reference therapy, dose and mode of administration, batch number:
Placebo, ½ tablet/ 1 tablet/ 2 tablets once daily, oral intake, batch nos.: TFM0310, TFI0625

Criteria for evaluation:
Efficacy:
Primary variable: The change from baseline in walking distance in the 6-minutes walking test
Secondary variables:

- Blood pressure and heart rate in the 6-minutes walking test
- New York Heart Association classification
- Minnesota Living with Heart Failure™ Questionnaire
- Cardiopulmonary exercise test parameters, including maximal exercise capacity (VO_2 max)
- Echocardiography parameters
- Plasma levels of NT Pro-BNP

Safety:
Safety laboratory, vital signs, ECG, adverse events

Statistical methods:
Determination of sample size:
The size of the study population was calculated on the basis of the predicted change in the 6-minutes walking distance after chronic nebivolol administration. According to previous trials, patients with diastolic HF (heart failure) have a similar impairment of exercise capacity as those with systolic HF. In patients with HF the mean 6-minutes walking distance was 467+132 m and increased to 539+102 m after long-term beta-blocker therapy ($p<0.0001$). Similar results were obtained in previous published studies[13,14]. On the basis of these previous results and assuming conservatively a 20% dropout rate and a 15% difference (70 meters) in the increase in the 6-minutes walking distance between the nebivolol and the placebo treatment groups, it was calculated that a sample size of 128 patients (64 in each group) would detect a difference of 70 meters at a standard deviation of 140 meters as statistically significant at α = 0.05 (two tailed) and β=0.20 (power 80%) in the change of the 6-minutes walking distance between the two study groups.

Efficacy:
Pre-treatment comparability was evaluated for continuous variables with Student's t-test and/or ANOVA. For categorical variables the Cochran-Mantel-Haenszel test was applied or, alternatively, the Fisher's Exact test was used.
Efficacy variables were corrected for baseline. Primary analysis concerned an Intention-To-Treat (ITT) analysis applying the Last Observation Carried Forward (LOCF) principle. The baseline-corrected variables were compared statistically for the two treatment groups by using 2-way ANOVA including the appropriate contrast statements.
If variables were not normally distributed, the variables in question were subjected to an appropriate transformation (e.g., log-transformation).
All efficacy data were presented individually and descriptively (mean, SD, SEM, min, max, and median).
Analysis was performed in SAS version 9 or higher.

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Safety/tolerability:
The recorded adverse events were coded according to the MedDRA® -nomenclature version 8.1 or higher. Coded adverse events data were compared for both treatment groups using the Fisher's Exact test. If necessary the data was subjected to ANOVA after suitable transformation of the data. If appropriate, a repeated measure ANOVA was applied to detect any possible time-related change. Laboratory parameters were evaluated as baseline corrected data applying ANOVA, and individual data was appropriately labeled according to their reference values.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Intake of nebivolol over 6 months significantly reduced resting systolic and diastolic BP in the treated patients by an average of 6 mmHg (p=0.0294) and 5 mmHg (p=0.0087), respectively, as measured in the 6-minutes walking test. No significant changes from baseline in SBP (-2 mmHg; p=0.5119) and DBP (-1 mmHg; p=0.6482) were observed in the placebo group at the end of the study.
The same trend was seen in the cardiopulmonary exercise test. In the nebivolol group the mean resting BP decreased from 128 /81 mmHg at baseline to 122 /76 mmHg at the end of study (placebo: 130 /78 mmHg to 126 /78 mmHg). The mean change from baseline and its statistical significance were not analyzed in this test.
Nebivolol visibly decreased resting HR, as observed in both the 6-minutes walking test and the cardiopulmonary exercise test, while placebo led to an increase in mean HR. In the 6-minutes walking test patients had a mean resting HR of 67 beats/min at 6 months, compared to a HR of 74 beats/min at baseline (placebo: 75 beats/min compared to 73 beats/min at baseline).

The primary variable in this study was the change from baseline in the walking distance in the 6-minutes walking test. After 6 months treatment with nebivolol the distance increased by an average of 7.8 m, which was significantly less than the mean increase (33.5 m) observed in the placebo group (p=0.004). In comparison, the mean changes calculated for the PP data set were 13.7 m and 37.7 m, respectively (p=0.081).
In the cardiopulmonary exercise test, patients on nebivolol, compared to baseline, had a shorter mean exercise duration (baseline: 879 s; end of study: 564 s) and lower peak VO2 (baseline: 17.02 ml/kg/min; end of study: 16.32 ml/kg/min). This effect was not observed in patients on placebo (exercise duration (baseline: 764 s; end of study: 791 s); peak VO2 (baseline: 17.79 ml/kg/min; end of study: 18.59 ml/kg/min)). Of note is that mean exercise duration at baseline differed significantly between the nebivolol (879 s) and placebo group (764 s) (p=0.003).
This reduced exercise capacity observed in patients taking nebivolol could be related to the depressing effect of nebivolol on mean SBP (nebivolol: 167 mmHg; placebo: 182 mmHg; p=0.005) and HR (nebivolol: 117 beats/min; placebo: 134 beats/min; p=0.003) at peak exercise, as measured in the cardiopulmonary exercise test. Nebivolol had no effect on mean peak exercise DBP (87 mmHg in both treatment groups at the end of the study).

In patients with normal LV systolic function, mean LVEF did not visibly change during the study. No marked change from baseline was observed in the percentage of patients with dilated left atrium in the echocardiogram at the end of the study.
The mean score in the Minnesota Living with Heart FailureTM Questionnaire significantly decreased in both the nebivolol (p=0.0087) and placebo group (p=0.0068) at the end of the study compared to baseline. There were no marked differences between both treatment groups.

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There were no statistically significant differences between the treatment groups in the mean plasma levels of NT-pro BNP determined at 5 weeks (p=0.259) and at the end of study (p=0.642). Compared to baseline, mean plasma levels of NT-pro BNP increased in the nebivolol group and slightly decreased in the placebo group.

NYHA classification significantly changed at the end of the study, compared to baseline, in the nebivolol (p=0.0001) and placebo group (p=0.0003). In general, the number of patients in NYHA class I increased and the number of patients in NYHA class III decreased. There were no significant differences between treatment groups.

SAFETY RESULTS:

Nebivolol was safe and well tolerated at a dose of 2.5 mg to 10 mg once daily over maximal 6 months. Thirty-eight of 57 patients (66.7%) treated with nebivolol experienced at least one AE. In the placebo group a similar number of patients (39 of 59 patients, 66.1%) experienced at least one AE. The number of patients with at least one AE considered to be certainly, probably or possibly related to the study medication was higher in the nebivolol group (20 patients, 35.1%) than in the placebo group (13 patients, 22.0%).

Seven SAEs were reported in six patients in the nebivolol group, compared to six SAEs in five patients in the placebo group. Only one SAE, subcapital humerus fracture in patient 133 in the nebivolol group, was considered to be possibly related to the study medication

In patients on nebivolol, the most frequent AEs, which the investigator considered to be related to the study medication, were hypotension, nausea, dizziness and vertigo. Each of these AEs occurred in 3 of 57 patients (5.3%). In 2 patients (3.5%) hypertension, diarrhea, peripheral edema and dyspnoea were reported. All other related AEs did not occur in more than one patient in the nebivolol group. No significant differences in the frequencies of these AEs were observed in the placebo group. The mentioned AEs, except vertigo and hypertension, are not unexpected and have been reported in previous studies, as described in the SmPC (see appendix 1 in the protocol).

No clinically relevant trend was observed in the clinical laboratory results. The physical examination did not show differences between the treatment groups. There was no trend seen in the variations in BP and HR measured before and 1 and 2 hours (optional) after treatment. ECG analyses did not show relevant differences between the nebivolol and placebo group.

Date of the report: 24 October 2008