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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.

SYNOPSIS

Name of Sponsor: Menarini Benelux NV	**Individual Study Table Referring to Part of the Dossier**	(For national authority only)
Name of Finished Product: nebivolol 5 mg/HCTZ 12.5 mg		
Name of Active Ingredient(s): SRRR-nebivolol, RSSS-nebivolol and hydrochlorothiazide (HCTZ)	**Volume**: **Page**:	

Title of study:

The effects of Nebivolol/HCTZ versus Metoprolol/HCTZ on Central Arterial Pressure
a randomized double-blind cross-over trial (NeMeCAP-Study)

Principal Investigator:

[redacted]

Study centre:

[redacted]

Publication (reference): [redacted] Journal of Hypertension 2013, 31:2447-2454.

Study period:	**Phase of development**:
First patient included: 23 February 2010 Last patient completed: 16 August 2011	Phase IV

Objectives:

Primary objective:

- To compare differences in central and peripheral blood pressure between nebivolol/HCTZ and metoprolol/HCTZ as assessed non-invasively by applanation tonometry.

Secondary objectives:

- To compare the effects of nebivolol/HCTZ and metoprolol/HCTZ on:
  - insulin sensitivity,
  - lipid-profile.

Tertiary objectives:

- To compare the effects of nebivolol/HCTZ and metoprolol/HCTZ on:
  - Blood pressure, cardiac output and systemic vascular resistance as measured by the Nexfin device,
  - The haemodynamic response to nitroglycerin.

Study design:

The study had a double-blind, randomized cross-over design and included 24 patients with grade 2 hypertension. After a 4-week placebo run-in period, patients were randomized to receive either metoprolol 100 mg in combination with HCTZ 12.5 mg once daily for 4 weeks or nebivolol 5 mg in combination with HCTZ 12.5 mg once daily for 4 weeks. The first active treatment period was followed by a 4-week placebo wash-out. Hereafter, patients were to receive the alternate treatment once daily for 4 weeks; those having received nebivolol/HCTZ received metoprolol/HCTZ and vice versa. In total, the study took 16 weeks to complete. During this period study participants were asked to visit the hospital 6 times (Day 1, Day 14, Week 4, Week 8, Week 12, Week 16), with each visit lasting approximately 45 minutes. Blood pressure and heart rate measurements were performed during each

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visit. Adverse events were evaluated during each visit. Blood sample for glucose, insulin, creatinine and lipid profile were taken at visits 1, 3, 4 and 6.

Number of patients:

Planned: 24

Included: 24

Completed: 22

Withdrawals: 2

Diagnosis and criteria for inclusion:

Eligible patients were healthy patients of European descent, aged 40-70 years, with untreated stage 2 hypertension (office brachial blood pressure 160-179/ 100-109 mmHg), or stage 1 (140-159/ 90-99 mmHg) hypertension while using one or two BP lowering drugs.

Study product(s), dose and mode of administration, batch number:

Study products: nebivolol 5 mg/HCTZ 12.5 mg tablets containing 5 mg nebivolol (as nebivolol hydrochloride): 2.5 mg SRRR-nebivolol (or d-nebivolol) and 2.5 mg RSSS-nebivolol (or l-nebivolol) combined with 12.5 mg hydrochlorothiazide.

Dose and mode of administration: Daily oral administration of nebivolol 5 mg in combination with hydrochlorothiazide 12.5 mg.

Batch numbers: CTM0904

Duration of treatment:

The total duration of the study was 16 weeks. The study was separated into 4 cycles of 4 weeks each during which patients received chronologically:

- Placebo (from Week 1 to Week 4)
- Study treatment or comparator drug (from Week 5 to Week 8)
- Placebo (from Week 9 to Week 12)
- Study treatment or comparator drug (from Week 12 to Week 16). Patients who received study treatment from Week 5 to Week 8 were to receive comparator drug from Week 12 to Week 16, and vice versa.

Reference therapy, dose and mode of administration, batch number:

Comparator drug: metoprolol 100 mg containing metoprolol succinate extended release 95 mg combined with 12.5 mg hydrochlorothiazide.

Dose and mode of administration: Daily oral administration of metoprolol 100 mg in combination with hydrochlorothiazide 12.5 mg.

Batch numbers: CTL0914

Criteria for evaluation:

Efficacy:

Primary criterion:

- Differences in central and peripheral blood pressure as assessed non-invasively by applanation tonometry.

Secondary criteria:

- Differences in insulin to glucose ratio as assessed by standard laboratory techniques from fasting

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venous blood samples.

- Differences in lipid profile as assessed by standard laboratory techniques from fasting venous blood samples.

Safety:

Adverse events were to be reported and categorized according to:

- The relationship with the study product, defined as certain, probable, possible, unlinkely, not related or unassessable. Adverse events with relationship to study drug being certain, probable or possible were to be qualify as adverse drug reactions,
- The seriousness (see protocol Section 10.2.4 for description of serious adverse events),
- The intensity, defined as mild, moderate or severe (see protocol Section 10.2.5),
- The expectedness (See protocol Section 10.2.6).

Statistical methods:

Statistical analyses were performed using the Statistical Package for Social Sciences version 19.0.0.1 (SPSS Inc.,Chicago, Illinois, USA). Data are expressed as mean ± standard deviation for continuous variables and as n (%) for categorical variables. Differences in outcome measures between the two treatments were tested for statistical significance using a general linear model for repeated measurements with age, gender, BMI and the first allocated active treatment as covariates. Pairwise comparisons based on estimated marginal means, corrected according to least significant difference, were performed for nebivolol/HCTZ and metoprolol/HCTZ vs. baseline, and for nebivolol/HCTZ vs. metoprolol/HCTZ. A p-value<0.05 was considered statistically significant.

Summary and conclusions:

Demography:

Thirty-two patients were screened for participation. Twenty-four subjects fulfilled all entry criteria and were subsequently enrolled. Two patients were withdrawn from the study due to non treatment-related reasons, leaving twenty-two patients for the efficacy analysis.

Efficacy results:

Primary criteria:

- The mean unadjusted augmentation index (AIx) was increased by 1.0 ± 7.8% (p=0.53) for nebivolol/HCTZ and for by 2.4 ± 6.5% (p=0.07) metoprolol/HCTZ compared to baseline, while AIx corrected for heart rate was decreased by 2.8 ± 6.9% (p=0.08) for nebivolol/HCTZ and by 1.8 ± 5.7% (p=0.14) for metoprolol/HCTZ.
- The mean central blood pressure was lowered by 15.8 ± 14.9 mmHg systolic and 10.5 ± 8.4 mmHg diastolic for nebivolol/HCTZ compared to 13.5 ± 12.3 mmHg systolic and 9.5 ± 6.8 mmHg diastolic for metoprolol/HCTZ (all p<0.001).
- The mean peripheral blood pressure was lowered by 16.3 ± 14.9 mmHg systolic and 10.1 ± 8.2 mmHg diastolic for nebivolol/HCTZ versus 15.2 ± 13.0 mmHg systolic and 9.1 ± 6.9 mmHg diastolic for metoprolol/HCTZ (all p<0.001).
- The mean heart rate was lowered by 8.1 ± 5.4 beats·min^{-1} for nebivolol/HCTZ and 8.6 ± 4.9 beats·min^{-1} for metoprolol/HCTZ (both p<0.001).
- The mean ejection duration was increased by 17.2 ± 13.8 ms for nebivolol/HCTZ and by 16.0 ± 21.5 for metoprolol/HCTZ.
- There were no significant differences between nebivolol/HCTZ and metoprolol/HCTZ in effects on aortic wave augmentation, central blood pressure, peripheral blood pressure, heart rate or ejection duration (all p>0.05).

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Secondary criteria:

- Both nebivolol/HCTZ and metoprolol/HCTZ significantly decreased the mean HDL-cholesterol levels by 0.13 ± 0.13 mmol/L and 0.16 ± 0.16 mmol/L respectively (both p<0.001).
- The mean triglyceride levels increased by 0.29 ± 0.34 mmol/L for nebivolol/HCTZ and by 0.34 ± 0.42 mmol/L for metoprolol/HCTZ (both p=0.02).
- The mean LDL-cholesterol levels did not significantly change with either treatment (p=0.12 for nebivolol/HCTZ and p=0.49 for metoprolol/HCTZ).
- The mean homeostatic model assessment of insulin resistance was not affected by nebivolol/HCTZ treatment (p=0.72), whereas metoprolol/HCTZ tended to increase it (by 0.6 ± 1.1, p=0.07).
- There was no significant difference between nebivolol/HCTZ and metoprolol/HCTZ on the insuline to glucose ratio and on the lipid profile.

Tertiary criteria:

- After measurements with the Nexfin device, both nebivolol/HCTZ and metoprolol/HCTZ treatments were shown to decrease the mean hearth rate (both p<0.001) and mean cardiac output (both p<0.001) while leaving systemic vascular resistance unaffected (p=0.46 for nebivolol/HCTZ and p=0.68 for metoprolol/HCTZ).
- There were no significant differences between nebivolol/HCTZ and metoprolol/HCTZ on blood pressure, cardiac output and systemic vascular resistance.

Safety results:

- A total of 54 AEs were reported (by 22 patients) during the study. Among these, 28 were reported during the active treatment periods and 26 during the run-in or washout period.
- All AEs reported during the treatment period had mild severity. No AE required specific action or medicine.
- Out of the 28 AEs that occurred during the active treatment periods, 10 were considered to be related to one of the study drugs. The causality relationship was estimated probable for two AEs, possible for six AEs and unlikely for two AEs.
- The safety profile of nebivolol/HCTZ and metoprolol/HCTZ was similar in terms of treatment-related AEs (5 AEs associated with each treatment).
- No death was reported.
- No SAE or SUSAR was reported.
- No significant adverse event was reported.

Conclusions:

- There were no significant differences between nebivolol/HCTZ and metoprolol/HCTZ in effects on aortic wave augmentation, central blood pressure, peripheral blood pressure, heart rate or ejection duration.
- There was no significant difference between nebivolol/HCTZ and metoprolol/HCTZ on the insuline to glucose ratio and on the lipid profile.
- There were no significant differences between nebivolol/HCTZ and metoprolol/HCTZ on blood pressure, cardiac output and systemic vascular resistance.
- The safety profile of nebivolol/HCTZ and metoprolol/HCTZ was similar, with only mild intensity AEs reported. No death and no SAE were reported.

Date of the report: 07 March 2014