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2. SYNOPSIS

Name of Sponsor: LABORATORIOS MENARINI S.A. **Name of finished product:** Nebivolol **Name of active ingredient:** Nebivolol	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Title of study:	Effects of Nebivolol and Atenolol on Central Aortic Pressure in Hypertensive Patients.
Investigators:	There were a total of 6 principal investigators [redacted]
Study centre(s):	There were a total of 6 active centres where patients were recruited: [redacted] Valencia; [redacted] (Sevilla); [redacted] (Badalona, Barcelona); [redacted] (Port de Sagunto, Valencia); [redacted] (Girona); [redacted] (Sabadell, Barcelona).
Publication (reference):	None.
Studied period (years): **(date of first enrolment):** 21/Dec/2007 **(date of last completed):** 03/Jun/2009	**Phase of development:** IV

Objectives:

Primary: To compare the mean change in augmentation index of Nebivolol and Atenolol after 10 weeks of treatment.

Secondary: The secondary objectives were to compare between treatments:

- Mean change in augmentation index at different time visits during treatment.
- Mean reduction in Central Aortic Pressure.
- Mean reduction in Brachial BP.
- Safety and tolerability parameters:
  - Adverse events.
  - Laboratory findings.
  - Physical examination.

Methodology: Phase IV, parallel group, randomized, double-blind, active-drug controlled study in two treatment groups: Nebivolol 5 mg and Atenolol 50 mg (that could be up-titrated to 100 mg).

No. of patients planned: 150 patients, 75 patients in each treatment group.

Analysed:

Population	Atenolol	Nebivolol	Total
Screened	---	---	163
Randomized	69(100.0%)	69(100.0%)	138 (100.0%)
Safety	69(100.0%)	69(100.0%)	138 (100.0%)
Full Analysis	69 (100.0%)	68 (98.6%)	137 (99.3%)
Per Protocol	62 (89.9%)	55 (79.7%)	117 (84.8%)

Diagnosis and main criteria for inclusion: The study population eligible for enrolment included ambulant patients aged between 40 and 65 years with mild or moderate essential and uncomplicated hypertension, who showed a sitting Systolic Blood Pressure ≥ 140 mmHg to ≤ 179 mmHg and a sitting Diastolic Blood Pressure ≥ 90 mmHg to ≤ 109 mmHg after two weeks of run-in placebo treatment and who had never been treated for hypertension or were

	intolerant or not responding to their current therapy.
Test product:	Nebivolol (hydrochlorothiazide 25 mg could be added for not responders, after 6 weeks of treatment)
dose:	Tablets 5 mg/day
mode of admin.:	Oral
batch no.:	73475
Duration of treatment:	The treatment duration was 12 weeks: 2 weeks run-in placebo treatment + 10 weeks active treatment.
Reference therapy:	Atenolol (Blokium®) (hydrochlorothiazide 25 mg could be added for not responders, after 6 weeks of treatment)
dose:	50 mg tablets once daily as starting dose that could be increased after 3 weeks of treatment to 100 mg/day for not responders
mode of admin.:	Oral
batch no.:	Atenolol 50 mg: Batch No: A6 Atenolol 100 mg: Batch No: A1
Criteria for evaluation:	
Efficacy:	Primary: ➢ Mean change in augmentation index with nebivolol as compared with atenolol at the end of treatment (10 weeks). Secondary: ➢ Mean change in augmentation index during treatment (up-titration and follow-up visits). ➢ Reduction of central aortic pressure. ➢ Mean reduction of brachial blood pressure.
Safety:	The tolerability of the study drug was assessed by means of: ➢ Type and frequency of Adverse Events. ➢ Physical examination (including body weight and waist circumference). ➢ Laboratory findings (hematology, biochemistry, urinalysis). ➢ ECG.
Statistical methods:	Quantitative variables were described by means of the number of available and missing observations, mean, median, standard deviation, 95% confidence interval for mean, minimum and maximum values, and interquartilic range. Quantitative values were summarized using frequency tables and percentages. Level of significance was established in the two-sided 0.05 for all the statistical analyses. An ANOVA model was used for the primary efficacy endpoints to detect statistical differences between treatment groups. Mean change in augmentation index from baseline visit to final visit (Visit 5) was considered as the dependent variable. In case of early discontinuation or missing data, the last value available after randomization was considered (Last Observation Carried Forward (LOCF) method). The Intent-to-treat (FAS) population was defined for the main analysis.

SUMMARY - CONCLUSIONS:

There were no relevant differences between the treatment groups in demographics and baseline characteristics. The patient population recruited in this study consisted of patients of both sexes, with a high prevalence of men (80 of 137, 58%) and the median age was 52.6 years.
Sixty-eight percent of patients presented at the screening visit a mild hypertension grade. Hypertension was diagnosed in the 43.5% less than one year, and the 60.1% received a pharmacological treatment for hypertension. Patients presented a normal physical examination at the screening visit.

Efficacy results:

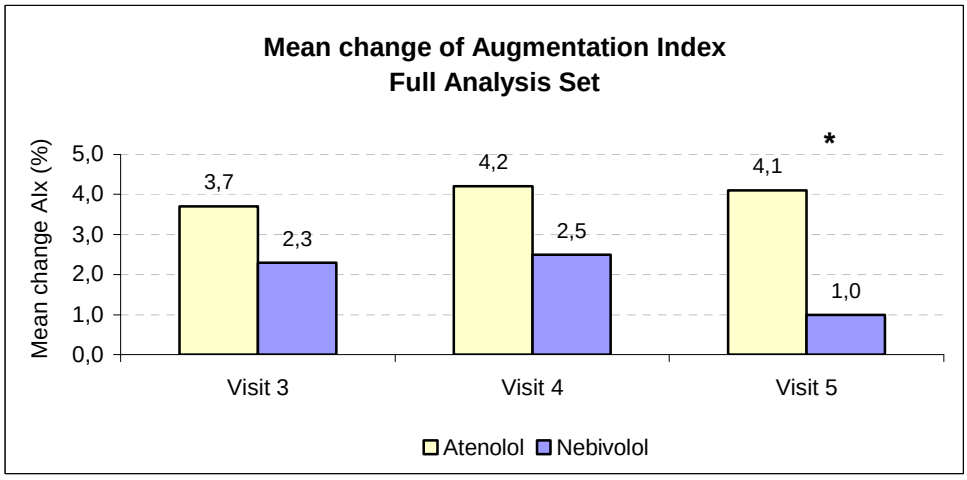
Main efficacy variable

- Nebivolol was statistically better than Atenolol according to the mean change from baseline in the augmentation index at the end of treatment (visit 5).

Mean Augmentation Index at Visit 5 (Full Analysis Set) using LOCF

Variable (mean (s.d.))	Atenolol n=69	Nebivolol n=68	Test
Baseline	30.4 (8.8)	31.1 (9.0)	
Visit 5	34.5 (10.5)	32.1 (11.0)	
Change in TSS_3	4.1 (8.4)	1.0 (8.0)	ANOVA p=0.027

Figure. Mean change of Augmentation index. Full analysis set



*p=0.027

- Similar results were reached for the per protocol population for the primary efficacy endpoint (ANOVA; p=0.049).

Secondary efficacy variables

- There were not differences between treatments for the mean change in the augmentation index at visits 3 and 4, although the change was lower and with tendency to decrease during all the study period in the nebivolol group in comparison to atenolol group.
- Nebivolol and Atenolol presented a significant reduction in central blood pressure and peripheral arterial pressure in comparison to baseline conditions but no differences between treatment were shown.
- A higher reduction of the heart rate was observed in the atenolol group in comparison to nebivolol group during all the study period with significant differences at the end of treatment (visit 5, ANOVA; p=0.016).
- A higher proportion of responder and normalized patients was observed in the nebivolol group in comparison to atenolol group on peripheral blood pressure during all the study period but statistically significant differences were not detected.

Safety results:

One hundred thirty-eight patients were randomized and included in the safety population: 69 in each one treatment group in the study:

- There were no differences regarding treatment emergent adverse events (TEAEs) between treatment groups.
- The incidence of TEAEs was low (10.1%) for both the Atenolol and Nebivolol treatment groups.
- Dyslipidaemia, reported by 3 patients (4.3%) was the most frequently observed TEAE in the atenolol group while gastroenteritis reported in two patients (2.9%) was the most common observed TEAE in the Nebivolol group.
- There were not differences between treatment groups when comparing the adverse events related to treatment.
- There was only one serious adverse event (an acute pancreatitis) which was considered as unlikely related to treatment and observed in the Nebivolol group.

Conclusions:

Nebivolol was statistically better than Atenolol in reducing the primary parameter augmentation index over a 10 weeks treatment period (p=0.027) for both the full analysis population and the per protocol population.

In summary, the study results confirm Nebivolol as an effective, safe and well tolerated drug to treat patients with hypertension over a 10 weeks period, showing a good efficacy and safety profile.

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