This Synopsis of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can not be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

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.

1. SYNOPSIS

Name of Sponsor/Company: Menarini International Operations	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: Nebivolol + Hydrochlorothiazide	**Page:**	

Study : A multicentre randomised, double blind, active controlled, parallel group comparison of Nebivolol plus HCTZ and Irbesartan plus HCTZ in the treatment of isolated systolic hypertension in elderly patients: The NEHIS study

[redacted]

Study centres: 13 general practices in The Netherlands and Belgium

Publication (reference): n.a.

Studied period: **date of first enrolment:** 21/10/2011 **date of last completed**: 04/07/2013	**Phase of development** IV

Objectives:

Primary objective: To demonstrate the superiority of the combination Nebivolol plus HCTZ versus Irbesartan plus HCTZ in term of SBP reduction after 12 weeks of treatment in elderly patients with isolated systolic hypertension.

Secondary objective: To investigate the tolerability of the combination Nebivolol plus HCTZ versus Irbesartan plus HCTZ.

Methodology: Randomized, double-blind, two parallel groups study

Number of subjects (planned and analyzed):

- planned for completion: 150
- screened: 476
- enrolled and randomized: 124
- withdrawals: 9
- ITT population 122
- completed as per protocol: 115

Main criteria for inclusion:

- Male or female aged at least 60 years;
- Office Systolic blood pressure ≥140 mmHg and office diastolic blood pressure ≤ 90 mmHg;
- Willing to give written informed consent.

Main criteria for exclusion:

- Systolic blood pressure equal to or greater than 180 mmHg at the end of washout (visit 2) or run-in period (visit 3b);
- Current treatment with more than 2 antihypertensive agents within the last 6 months;
- History of stroke, myocardial infarction, PCI or coronary bypass surgery within the last 12 months
- Symptomatic lower limb ischemia i.e. claudicatio intermittens
- Secondary hypertension (i.e.renovascular, adrenal, endocrine, tumor ..);
- Serum creatinine > 150 µmol/L
- Hepatic impairment defined as ASAT or ALAT >2 x upper normal limit;
- Chronic administration of any medication known to affect blood pressure.

Test product, dose and mode of administration, batch number:

Test drug 1	: Nebivolol+HCTZ
Formulation	: capsule
Strength	: 5 mg+12.5 mg
Batch number	:
Dose regimen	: Nebivolol 5 mg + HCTZ 12.5 once daily for 12 weeks.

Duration of treatment: 12 weeks

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

Reference drug 1	: Irbesartan+HCTZ
Formulation	: capsule
Strength	: 150 mg /12.5 mg
Batch number	:
Dose regimen	: Irbesartan 150 mg +HCTZ 12.5 mg once daily for 12 weeks

Duration of treatment: 12 weeks

Criteria for evaluation:

Primary

The primary efficacy variable was the change from baseline (Day 0) to the end of treatment (Day +84) in systolic blood pressure.

Secondary

- Percentage of normalized patients (mean SBP ≤ 140 mmHg)at the end of treatment (Day +84);
- Percentage of responding patients (decrease of mean SBP ≥ 20 mmHg)at the end of treatment (Day +84);
- Change from baseline to the end of treatment (Day +84) in the 24-hour mean SBP, measured by ABPM;
- Change from baseline to the end of treatment (Day +84) in the 24-hour mean DBP, measured by ABPM;
- Change from baseline to the end of treatment (Day +84) in SBP in the last six hours of the 24-hour dose period (as measured by 24-hour ABPM);
- Change from baseline to the end of treatment (Day +84) in DBP in the last six hours of the 24-hour dose period (as measured by 24-hour ABPM);
- Change from baseline to the end of treatment (Day +84) in SBP and DBP for other time intervals [i.e. daytime mean (06:00-00:00), and night-time mean (00:00-6:00)] (as measured by 24-hour ABPM).
- Change from baseline to the end of treatment (Day +84) in arterial stiffness/distensibility

Tolerability:

Adverse events and serious adverse were recorded at each visit or –if applicable- when the patient reported to the clinical facility with complaints.
Standard laboratory parameters

Statistical methods:

Data were analyzed in SAS (version 9.1).
Quantitative data were tested using Students' t-test or –if applicable analysis of variance (ANOVA). Semi-quantitative data were tested using Cochran-Mantel-Haenszel test (CMH). Qualitative data and dichotomies were tested using the $\chi 2$ test or Fishers exact probability test. All tests were performed at α=0.05 (two-tailed). No correction for multiple testing was applied.

RESULTS

EFFICACY RESULTS:
With respect to office blood pressure measurements, Nebivolol+HCTZ and Irbesartan+HCTZ reduced systolic and diastolic blood pressure statistically significantly vs. baseline. The blood pressure lowering efficacy of Nebivolol+HCTZ with regard to office systolic blood pressure was significantly greater as compared to Irbesartan+HCTZ. The difference between Nebivolol+HCTZ and Irbesartan+HCTZ with regards to response rates and normalization rates was not statistically significant.

TOLERABILITY RESULTS:
The number of subjects with adverse events, severity and causality was not different for both treatment groups.

CONCLUSION:
Nebivolol+HCTZ treatment induced a significantly lower heart rate as compared to Irbesartan+HCTZ.
The blood pressure lowering efficacy of Nebivolol+HCTZ with regard to office systolic blood pressure was significantly greater as compared to Irbesartan+HCTZ. The reduction of diastolic blood pressure and pulse pressure were similar for Nebivolol+HCTZ and Irbesartan+HCTZ. The difference between Nebivolol+HCTZ and Irbesartan+HCTZ with regards to response rates and normalization rates was not statistically significant.

With regards to overall ambulatory blood pressure measurements the blood pressure lowering effect on systolic and diastolic blood pressure as well on mean arterial pressure and pulse pressure of Nebivolol+HCTZ and Irbesartan+HCTZ is comparable, at daytime, night-time and overall.
However blood pressure variability of systolic blood pressure, mean arterial pressure and pulse pressure, as expressed by standard deviation and coefficient of variation, at daytime and overall is significantly lower after Nebivolol+HCTZ treatment as compared to Irbesartan+HCTZ.
Furthermore blood pressure load at daytime was significantly lower during Nebivolol+HCTZ treatment.
The Peak-to-trough ratio was significantly reduced by Nebivolol+HCTZ and not by Irbesartan+HCTZ.
Arterial stiffness parameters Distensibility Coefficient and Compliance coefficient did not change during Nebivolol+HCTZ or Irbesartan+HCTZ treatment. In this study treatment was well tolerated with a low incidence of adverse events.
The number of subjects with adverse events, severity and causality was not different for both treatment groups.
The most frequently reported adverse events with Nebivolol+HCTZ were tiredness (5 patients), nausea (3 patients) and headache (2 patients). For Irbesartan the most frequently reported adverse events were Diarrhoea (4 patients), headache (2 patients), pyrosis (2 patients) and dizziness (2 patients).