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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.

1. SYNOPSIS

Name of Sponsor/Company: A. Menarini IFR Srl	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product:	**Volume:** International Journal of Cardiology 155 (2012)	
Name of Active Ingredient: Nebivolol + hydrochlorothiazide *vs* *irbesartan + hydrochlorothiazide*	**Page:** 279-284	

Study title :
"*Effects of nebivolol or irbesartan in combination with hydrochlorothiazide on vascular functions in newly-diagnosed hypertensive patients: The NINFE (**N**ebivololo, **I**rbesartan **N**ella **F**unzione **E**ndoteliale) study* "

Principal Investigators:
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Study centres:
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Publication (reference):
Effects of nebivolol or irbesartan in combination with hydrochlorothiazide on vascular functions in newly-diagnosed hypertensive patients: the NINFE (Nebivololo, Irbesartan Nella Funzione Endoteliale) study.
Vitale C, Marazzi G, Iellamo F, Spoletini I, Dall'Armi V, Fini M, Volterrani M.
Int J Cardiol. 155 (2012): 279-84.

Studied period: September 2008- June 2009 **date of first enrolment:** 29th September 2008 **date of last completed**: 27th June 2009	**Phase of development:** Phase IV

Objectives:
Primary objective:
To assess the hypothesis of non-inferiority of nebivolol 5 mg compared to irbesartan 150 mg - both in association with hydrochlorothiazide 12,5 mg - on endothelial function evaluated by the Reactive Hyperaemia Index (RHI) measured with the EndoPAT 2000

Secondary objective:
- Assessment of endothelial function through additional markers
- Evaluation of vascular elasticity
- Evaluation of antihypertensive efficacy
- Evaluation of safety

Methodology:

Study design

Patients matching inclusion and exclusion criteria underwent sitting BP measurement (DINAMAP, Procare 100 automatic BP recorder), electrocardiogram and a blood chemistry analyses. At baseline, following vascular function assessment as endothelial function and as arterial stiffness (Augmentation Index and Pulse Wave Velocity), patients were randomized to receive nebivolol plus hydrochlorothiazide (5 + 12.5 mg/day) or irbesartan plus hydrochlorothiazide (150 + 12.5 mg/day), both in a single daily dose, for 8 weeks.

Endothelial function

Endothelial function was non-invasively assessed with peripheral arterial tonometry (PAT), by the EndoPAT 2000 device.

The Reactive Hyperaemia Index (RHI) – as the ratio of the average amplitude of the PAT signal over a 1-min time interval, starting 1 min after cuff deflation, divided by the average amplitude of the PAT signal of a 3.5-min time period before cuff inflation (baseline) - was calculated through a computer algorithm, automatically normalized for baseline signal and indexed to the contralateral arm.

In addition, the average amplitude of PAT signal in the post-occlusion period (test signal, T) compared to that in the baseline (B) signal before occlusion, at the same time intervals as for RHI calculation but not indexed to contralateral arm (referred to as T/B ratio), was also manually obtained.

To assess endothelium-independent vasodilatation, 10min after cuff deflation sublingual nitroglycerin (0.4 mg) was administered.

Pulse wave analysis

Aortic BP waveform and central hemodynamic indices from a peripheral BP measurement were non-invasively assessed at the radial artery with the SphygmoCor Pulse Wave Analysis Px system and SCOR-2000 Version 6.31 software (AtCor Medical, Sydney, Australia), employing the principle of applanation tonometry.

Carotid-femoral pulse wave velocity

Carotid to femoral pulse wave velocity (PWV cf) was assessed by simultaneous measurements of arterial pressure waves at the carotid and femoral artery, with piezo-electronic pressure transducers (Complior SP, Artech-Medical)

Biochemical analyses

Venous blood samples were taken with a Vacutainer system (Becton-Dickinson, Franklin Lakes, NJ, USA), with patients in fasting, in the supine position after the vascular function assessments.

Number of subjects (planned and analyzed):

Eighty-three newly diagnosed patients with essential hypertension, naïve on therapy, were included.

Fifteen patients were excluded because they did not meet the inclusion criteria. Therefore, 68 patients were randomized to receive nebivolol/HCTZ (34 patients) or irbesartan/HCTZ (34 patients).

During the 8-weeks treatment period, 3 patients discontinued the study indications and were excluded.

Thus, 65 patients (n=31 nebivolol/HCTZ; n=34 irbesartan/HCTZ) completed the study protocol.

Main criteria for inclusion: grade 1 arterial hypertension, in association with a high global cardiovascular risk (according to the Systematic Coronary Risk Evaluation - SCORE risk chart) or grade 2 hypertension, in patients naïve to therapy.

Main criteria for exclusion: history of cardio and cerebrovascular events, left ventricular dysfunction, symptomatic peripheral arterial obstructive disease, arrhythmias (Lown Class >1), heart rate below 60 beats/min, hyperuricemia, pulmonary obstructive diseases, severe liver and renal failure, any contraindication to the study drugs

Test product, dose and mode of administration, batch number:
nebivolol 5 mg/day plus HCTZ 12,5 mg/day, in a single daily dose, administered in the morning (8-10 am), in fasting condition.

Batch number: CTG0825

Duration of treatment: 8 weeks

Reference product, dose and mode of administration, batch number:
irbesartan 150 mg/day plus HCTZ 12,5 mg/day, in a single daily dose, administered in the morning (between 8 to 10 am), in fasting condition.

Batch number: CTG0821
Duration of treatment: 8 weeks

Criteria for evaluation:

Primary:

Endothelial function: evaluated using the Reactive Hyperaemia Index (RHI), assessed according to the principle of Peripheral Arterial Tonometry (PAT)

Secondary:

- **Vascular Endothelial function parametres.**

Vascular inflammation markers and endothelial activation markers:

IL-6, ICAM-1, VCAM-1, E-Selectine, Trombomoduline, PCR and apoptosis induced by serum of treated patients

- **Evaluation of vascular elasticity**

Augmentation Index (central aortic pressure) and Pulse Wave Velocity

- **Evaluation of antihypertensive efficacy**

Brachial blood pressures

Safety Evaluation

Adverse events as well as compliance to the study drugs were recorded

Statistical methods:

Assuming an effect of Irbesartan of 6.7% after 8 weeks of treatment and a SD for both treatment groups of 0.9% estimates the relative margin for non inferiority was set at 9% of the mean change percentage measured in the Irbesartan group (0.6% in absolute terms).

Assuming equality of Nebivolol and Irbesartan and setting the type-I error rate at 5%, it was estimated that 29 subjects per treatment group were needed to demonstrate non inferiority of Nebivolol with a power of 80%, using one-sided t-test for independent samples.

Baseline characteristics between treatment groups were tested with a t-test and Chi-Square test for categorical data.

The effect of the two treatments on the differences from baseline was compared by ANOVA.

The hypothesis of non-inferiority was tested on the post-treatment reactive hyperemia mean estimate scores with ANCOVA, with treatment as the fixed factor and baseline reactive hyperemia scores as the covariate.

STUDY RESULTS

EFFICACY RESULTS:

Similar changes in endothelial function (RHI) were detected in both groups after treatment.

Tab. 1: Hyperemia Reactive Index HRI), comparison between the two treatment groups. ANCOVA one-sided test with Least Means Square and baseline (V1b) as covariate. Intention to Treat Population. V1b randomization; V2b end of treatment.

	Irbesartan + HCTZ *(n=34)*			Nebivolol + HCTZ *(n=31)*			Nebivolol - Irbesartan	
Visita	Mean Observed	SD	Mean Estimated [$CI_{95\%}$]	Mean Observed	SD	Mean Estimated [$CI_{95\%}$]	Differences [$CI_{95\%}$]	p-value
V1b	2.06	0.54	-	2.24	0.63	-		
V2b	1.72	0.46	1.741 [1.609; + ∞]	1.82	0.5	1.797 [1.658; + ∞]	0.055 [-0.137; + ∞]	0.3165

A significant reduction in augmentation index, adjusted for heart rate, as well as pulse wave velocity, central blood pressure was found in both treatment groups, without significant differences between groups.
Systolic and diastolic central blood pressure decreased to a similar extent after both treatments.

Sitting brachial systolic and diastolic BP decreased significantly after both nebivolol/HCTZ and irbesartan/HCTZ treatments without significant differences between the two groups: from 156.35±13.5/103.35±9.26 to 127.26±15.1/84.16±6.79 in the nebivolol/HCTZ and from 154.2±9.5/99±5.43 to 127.4±13.6/81.2±9.8 irbesartan/HCTZ groups, while a significant reduction in HR was found only in the nebivolol/HCTZ group ($P<0.0001$). No significant differences by treatment were found in laboratory parameters.

TOLERABILITY RESULTS:

Three patients (all randomized to nebivolol/HCTZ) discontinued the study during the 8-week treatment period due to bradycardia, general malaise and non compliance to the study drug scheme administration.
Compliance to treatment was 99.3% and 99.9% in the nebivolol and irbesartan group, respectively.
AE were registered in 8 study subjects: 3 (9%) in the irbesartan + HCTZ group and 5 (16%) in Nebivolol + HCTZ group. There was not a statistically significant difference in the relative risk (RR) of AEs in the 2 studied groups (RR = 1.77 [0:46; 6.81]).

CONCLUSION:

The results of this study confirm the hypothesis of non-inferiority of short-term treatment with nebivolol compared to irbesartan - both in association with hydrochlorothiazide - on endothelial function, arterial stiffness and central hemodynamic parameters in hypertensive patients naïve on therapy.

Date of the Report: October 20, 2012