2. SYNOPSIS

Title Of Study:
A randomized, double-blind, placebo controlled study to compare the effect on sympathetic activity and hemodynamic profile of barnidipine and amlodipine in patients with mild to moderate essential hypertension

Protocol number: 00-MEP-04
EudraCT number 2007-004938-16

Investigator(s): [redacted]

Study Center(s): 1 centre in Italy – [redacted] Italy

Publication(s):

Studied Period:	First patient enrolled: 12.03.2008 Last patient completed: 23.12.2008	**Clinical Phase:** IV

Objective(s):
Primary:

- To compare the effect of barnidipine and amlodipine on sympathetic activity by assessment of plasma norepinephrine levels in the forearm after 12 weeks of therapy.

Secondary:

- To investigate tolerability (safety) and anti-hypertensive activity (efficacy) of barnidipine and amlodipine after 12 weeks of therapy.
- To compare the effect of barnidipine and amlodipine on sympathetic activity by assessing the net norepinephrine balance in the forearm after 12 weeks of therapy in responding* subjects.
- To compare the effect of barnidipine and amlodipine on forearm norepinephrine spill over after 12 weeks therapy in the first 12 responding subjects.
- To compare the effect of barnidipine and amlodipine on forearm blood flow and vascular resistance (plethysmography) after 12 weeks of therapy in responding subjects.

* SiDBP<90 mmHg and SiSBP<140 mmHg at week 12

Methodology:
A randomised, double blind, parallel-group, single centre study with two active treatment arms (barnidipine and amlodipine) in patients with mild to moderate hypertension. After a 2 week placebo run-in period, subjects were treated (ratio 1:1) with either barnidipine (10 mg, o.d.) or amlodipine (5 mg, o.d.) for a duration of 12 weeks. The dosage of barnidipine or amlodipine in subjects non-responding (SiDBP > 90 mmHg and/or a SiSBP > 140 mmHg) after six weeks of therapy, was increased according to current prescription guidelines (doubled).

Number of Subjects:
Planned: 60 randomised patients

Screened:20 patients
Randomized: 20 patients (9 to barnidipine and 11 to amlodipine).
Completed: 20(barnidipine 9; amlodipine 11)

Analyzed
- Safety: 20 patients (barnidipine 9; amlodipine 11)
- Efficacy (FAS): 20 patients (barnidipine 9; amlodipine 11)

Diagnosis and Criteria for Inclusion:
A subject was eligible for the study if all following requirements apply to him/her:

- Written informed consent has been obtained.
- A diagnosis of mild to moderate essential hypertension has been made at visit 1 in a non-hospitalised patient. For the diagnosis of mild to moderate hypertension the JNC VI guidelines and the following updates are valid: Subjects presenting a systolic blood pressure of 140 –179 mmHg inclusive and/or a diastolic blood pressure of 90 – 109 mmHg inclusive and who are not taking antihypertensive medication.
- Male or female, aged 18 to 75 years inclusive at the time of the first study visit.

- Previous treatment for hypertension took place or no anti-hypertensive treatment was in place prior to the study. "Previously treated" is defined as having received anti-hypertensive therapy within the last 14 days. "Previously treated" subjects must be able to tolerate a maximum 21 day drug free period.

Test Product, Dose, Mode of Administration, Batch No(s):
Barnidipine HCl capsule 10 mg once a day (twice a day for non-responder patients) by oral route
Batch N:

Duration of Treatment:
For the individual patient:
Run-in: 2 weeks Double-blind phase: 12 weeks
Global study duration:
Total recruitment period (first patient in to last patient in): 6 months
Study conduct (first patient in to last patient completed): 9 months

Reference Therapy, Dose, Mode of Administration, Batch No(s):
Amlodipine tablet 5 mg once a day (twice a day for non-responder patients) by oral route
Batch N:

Criteria for Evaluation:
Main efficacy criteria
Primary efficacy parameter:
- Forearm *plasma norepinephrine* levels at baseline and after 12 weeks of therapy as measured after CPT.

Secondary parameters:
- Routine SiDBP/SiSBP at baseline and after 12 weeks of therapy.
- Forearm *plasma norepinephrine* levels at baseline and after 12 weeks of therapy as measured before CPT.
- Forearm *net norepinephrine balance* at baseline and after 12 weeks of therapy as measured before and after CPT in responding subjects.
- Forearm *norepinephrine spill over* at baseline and after 12 weeks of therapy, before and after CPT in the first 12 responding subjects
- Forearm blood flow and vascular resistance at baseline and after 12 weeks of therapy before and after CPT in responding subjects

Safety criteria
- Number, nature and severity of adverse events
- Changes in physical examination
- Clinically relevant changes in ECGs
- Routine safety laboratory analysis.

Statistical Methods:
Considering the reduced sample size due to insufficient recruitment rate which caused the premature stopping of the study, none of the statistical tests of inference planned in the protocol has been performed; only descriptive statistics have been provided.

SUMMARY – CONCLUSIONS

RESULTS:

Baseline characteristics
The patient population recruited in this study consisted in patients of both sexes, with a prevalence of males (66.7% in the barnidipine group and 81.8% in the amlodipine group) and with a broad range of ages (26-64 years) with higher median age in the barnidipine group (53.7 years versus 44.9 years). On average the patients were overweight with a median BMI of about 27.6 in both treatment groups. Only two patients in the barnidipine group (22%) and one patient in the amlodipine group (9%) were taking one concomitant medication. One patient in each treatment group was taking a thyroid hormone, while one patient in barnidipine group was taking a HMG CoA reductase inhibitor.

Efficacy
Primary endpoint
Both treatment groups showed an increase of forearm plasma norepinephrine levels measured after CPT; this increase was significantly smaller in the barnidipine group (71.38 ± 52.4 in the barnidipine group versus 320.88 ± 296.33 in the amlodipine group).

Secondary endpoints
Sitting BP at baseline and at the end of 12 weeks of treatment
Diastolic blood pressure decreased similarly in the two treatment groups: from 93.89 ± 4,88 to 82.33 ± 5.05 in the barnidipine group (-11.56 ± 5.41) and from 92.45 ± 2.66 to 80.64 ± 5.90 in the amlodipine group (-11.82 ± 6.51).
The decrease of systolic blood pressure was greater in the barnidipine group: -19.00 ± 11.01 (from 148.11 ± 16.33 to

129.11 ±11.21) versus -12.91 ± 11.18 (from 141.18 ± 3.79 to 128.27 ± 11.37) in the amlodipine group.

Change from baseline in forearm plasma norepinephrine levels after 12 weeks of therapy as measured before CPT
Both treatment groups showed an increase of forearm plasma norepinephrine levels measured before CPT and this increase was smaller in the barnidipine group (135.38 ± 212.29 in the barnidipine group versus 256.63 ± 231.49 in the amlodipine group).

Change from baseline in forearm net norepinephrine balance after 12 weeks of therapy as measured before and after CPT in responding subjects
The change from baseline in forearm net norepinephrine balance after 12 weeks of therapy before and after CPT was calculated in 15 out of 16 responding subjects: 7 in the barnidipine group (77.8% of the randomized subjects) and 8 in the amlodipine group (72.7% of the randomized subjects, for 1 responding patients in the amlodipine group the forearm volume was missing).
The decrease of forearm net norepinephrine balance measured before or after CPT was greater in the barnidipine group; the decrease before CPT was -25.75 ± 68.55 in the barnidipine group versus -3.73 ± 4.12 in the amlodipine group, while the decrease after CPT was -26.20 ± 64.46 in the barnidipine group versus -3.06 ± 4.58 in the amlodipine group

Change from baseline in forearm norepinephrine spill over after 12 weeks of therapy, before and after CPT
The change from baseline in forearm net norepinephrine balance after 12 weeks of therapy before and after CPT was calculated in the first 12 responding subjects: 7 in the barnidipine group (77.8% of the randomized subjects) and 5 in the amlodipine group (45.5% of the randomized subjects).
In both groups there was for FNU (forearm norepinephrine uptake) a decrease before CPT and an increase of FNU after CPT and for FNR (forearm norepinephrine release) an increase before CPT and a decrease after CPT whit a net balance very near to zero.

Forearm blood flow after 12 weeks of therapy before and after CPT in responding subjects
After the 12 weeks of therapy there was a decrease of forearm blood flow measured before CPT in both groups, but this decrease was smaller in the barnidipine group. In effect in the barnidipine group the forearm blood flow decreases from 32.36 ± 7.53 to 30.50 ± 10.17 and in the amlodipine group from 35.29 ± 9.75 to 26.26 ± 14.83.
When the forearm blood flow was measured after CPT there was a little increase in the barnidipine group (from 24.18 ± 3.61 to 31.64 ± 7.61) and a decrease in the amlodipine group (from 28.43 ± 6.05) to 24.49 ± 15.08).

Vascular resistance after 12 weeks of therapy before and after CPT in responding subjects
Vascular resistance after 12 weeks of therapy before and after CPT was calculated in 15 responding subjects: 7 allocated to Barnidipine (77.8% of the randomized subjects) and 8 allocated to Amlodipine (72.2% of the randomized subjects).
In the Barnidipine group vascular resistance before CPT did not change after the 12 weeks of therapy, while a slight decrease in vascular resistance after CPT was observed; in the Amlodipine group after 12 weeks of therapy a slight increase of vascular resistance was observed both before and after CPT.

Safety:
No adverse events occurred during the double blind phase of this study.
During the placebo run-in period two patients randomized to barnidipine and one patients randomized to amlodipine reported hypertriglyceridaemia.

CONCLUSIONS:
The present study was prematurely stopped after the randomization of 20 patients leading to a lack of power in testing null hypothesis.
For this reason, none of the statistical tests of inference planned in the protocol has been performed and only descriptive statistics have been provided.
The primary endpoint of this study was the change of plasma norepinephrine measured after a cold pressor test at the end of 12 weeks of treatment: the results showed an increase of plasma NE significantly smaller in the barnidipine group respect to amlodipine group. Similar results were obtained for plasma norepinephrine levels measured before the cold pressor test.
Both treatment were effective in reducing blood pressure: barnidipine and amlodipine showed a similar decrease of diastolic blood pressure, while a greater decrease of systolic blood pressure was obtained with barnidipine.
The safety data collected in this study show that both drugs are very well tolerated in hypertensive patients treated for a 12 weeks period.

In conclusion, in this study a smaller increase on plasma norepinephrine measured after or before cold pressor test was observed with barnidipine respect to amlodipine, both drugs effectively reduced blood pressure and their safety profile resulted very good.