2. SYNOPSIS

Title of Study: Double-blind, randomized, parallel-group, multi-center study to evaluate the effects of manidipine 20mg vs. amlodipine 10mg and the combination of manidipine 10mg plus delapril 30mg vs. amlodipine 5mg plus delapril 30mg on intraglomerular pressure in hypertensive patients	
Investigators: Prof. [redacted]	
Study Centre(s): [redacted], Germany	
Publication (reference): none	
Studied Period: **21 NOV 2007 – 27 FEB 2009**	**Phase of development:** **IIIb-IV**

Objectives:

The primary objective of this study was:

- To investigate the effects of a once daily oral dose of manidipine 20 mg, compared with once daily oral dose of amlodipine 10 mg over a 4 week treatment period on intraglomerular pressure in patients with mild to moderate essential hypertension.

The secondary objectives of this study were:

- To investigate the effects of a once daily oral dose of a combination of manidipine 10 mg plus delapril 30 mg, compared with once daily oral dose of a combination of amlodipine 5 mg plus delapril 30 mg over a 4 week treatment period on intraglomerular pressure in patients with mild to moderate essential hypertension.
- To investigate the effects of a once daily oral dose of manidipine 20 mg, compared with once daily oral dose of amlodipine 10 mg over a 4 week treatment period and of a once daily oral dose of a combination of manidipine 10 mg plus delapril 30 mg, compared with once daily oral dose of a combination of amlodipine 5 mg plus delapril 30 mg over a 4 week treatment period on renal plasma flow, glomerular filtration rate, filtration fraction, renovascular resistance, systemic blood pressure, urinary albumin excretion and adiponectin levels in patients with mild to moderate essential hypertension.
- To investigate the tolerability of a once daily oral dose of manidipine 20 mg, compared with once daily oral dose of amlodipine 10 mg over a 4 week treatment period and of a once daily oral dose of a combination of manidipine 10 mg plus delapril 30 mg, compared with once daily oral dose of a combination of amlodipine 5 mg plus delapril 30 mg over a 4 week treatment period in patients with mild to moderate essential hypertension.

Methodology*:*

8-week multicentre, randomized, double-blind, active controlled, two arms, parallel groups study with a 4-week single drug treatment (manidipine or amlodipine) phase followed by a 4-week combination treatment (manidipine + delapril or amlodipine + delapril) phase.

Number of patients:

It was planned to randomize 100 patients in the 8-week treatment period according to a 1:1 randomization scheme in order to get 86 patients evaluable for analysis. At the end of the

enrollment period, 114 patients were randomized and 104 available for efficacy analysis of the primary endpoint (i.e., with renal data of Day +28).

Diagnosis and main criteria for inclusion:

Male or female patients aged ≥18 and ≤ 65

Patients with mild to moderate hypertension defined as a mean sitting diastolic blood pressure (DBP) within the range of 90-110 mmHg and/or mean sitting systolic blood pressure (SBP) within the range of 140-180mmHg.

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

- IPERTEN®/ARTEDIL®/MANYPER® 10 mg Tablets
  Each tablet contains:
  Active Ingredient: manidipine hydrochloride 10mg
  Excipients are: Lactose monohydrate, Maize starch, Low-substituted hydroxypropyl cellulose (L-HPC-31), Hydroxypropyl cellulose (HPC-L), Magnesium stearate, Riboflavine (E 101).
- IPERTEN®/ARTEDIL®/MANYPER® 20 mg Tablets
  Each tablet contains:
  Active Ingredient: manidipine hydrochloride 20mg
  Excipients are: Lactose monohydrate, Maize starch, Low-substituted hydroxypropyl cellulose (L-HPC-31), Hydroxypropyl cellulose (HPC-L), Magnesium stearate, Riboflavine (E 101).

Duration of treatment:

After a 2-4-week run-in period, patients were included in a treatment period of 8 weeks, resulting in a total study period of 10-12 weeks.

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

- NORVASC® 5 mg Tablets
  Each tablet contains:
  Active Ingredient: amlodipine besylate 6,944 mg equivalent to 5 mg of amlodipine per tablet
  Excipients are: Microcrystalline cellulose, E460, Dibasic calcium phosphate anhydrous, Sodium starch glycollate, Magnesium stearate, E572
- NORVASC® 10 mg Tablets
  Each tablet contains:
  Active Ingredient: amlodipine besylate 13.889 mg equivalent to 10 mg of amlodipine per tablet
  Excipients are: Microcrystalline cellulose, E460, Dibasic calcium phosphate anhydrous, Sodium starch glycollate, Magnesium stearate, E572
- DELAKET® Tablets
  Each tablet contains:
  Active Ingredient: delapril 30 mg
  Excipients are lactose, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, magnesium stearate, riboflavine.

Criteria for evaluation:

Efficacy:

The primary efficacy parameter is the change from baseline (Day 0) to Day +28 in the intraglomerular pressure under monotherapy.

Safety:

- Adverse events and adverse drug reactions
- Laboratory safety data
- 12 lead ECG
- Heart rate

Statistical methods:

The primary efficacy variable was the change of intraglomerular pressure from baseline (Day 0) to Day +28.

A sample size of 43 subjects in each treatment group (43 patients on manidipine 20 mg and 43 patients on amlodipine 10 mg) was expected to provide 80% power to detect a 4 mmHg difference between the two treatment regimens on the primary objective (intraglomerular pressure) at a significance level of 0.05, assuming a common standard deviation of 6.5 mmHg. To achieve this target, it was planned to enroll approximately 100 patients after the wash-out/run-in period.

Summary statistics are presented for demographic data and baseline characteristics; no formal statistical analyses were performed on these parameters.

The primary efficacy analysis was carried out using an analysis of covariance (ANCOVA) performed on the change from baseline (Day 0) to Day +28.

Similar statistical analyses were applied for the analysis of the secondary efficacy variables.

All safety evaluations were performed on the safety population. The proportion of patients presenting adverse events, adverse drug reactions, adverse events leading to withdrawal and serious adverse events was summarized by SOC and PT for each treatment group, both for each therapy regimen and for the whole study population. ECG parameters and Heart Rate were summarized by treatment group, using descriptive statistics.

Summary – Conclusions:

Efficacy Results:

The primary efficacy parameter was the change in intraglomerular pressure between baseline (BL) and Day +28 to be compared between the two treatments. The study hypothesis was that manidipine had a better impact on intraglomerular pressure than amlodipine, i.e. that manidipine treatment was associated with no increase of the intraglomerular pressure or at least a smaller increase than what observed with amlodipine treatment. A mean reduction of 0.022 mmHg of intraglomerular pressure was observed in the group of patients treated with manidipine after 4 weeks of treatment. On the contrary, the mean intraglomerular pressure was increased at Day +28 as compared to BL by 1.623 mmHg in the amlodipine group. The calculated ANCOVA model, with treatment as factor and BL value as covariate, yielded a significant p-value (p=0.0420) for the between-group difference indicating a lower intraglomerular pressure with

manidipine than with amlodipine after 28 days of treatment (LS mean of the difference = -1.23 mmHg).

At Day +56 intraglomerular pressure was not different under amlodipine + delapril therapy as compared to manidipine + delapril.

Systolic blood pressure was reduced by 14.1 mmHg under amlodipine + delapril and 7.14 mmHg under manidipine + delapril combined therapy on average between BL and Day +56 (p-value group difference p<0.0001). Also for mean diastolic blood pressure, the amlodipine + delapril patients experienced a stronger reduction between BL and Day +56 as compared to the manidipine + delapril patients (p=0.0238, ANCOVA analysis). For heart rate, no significant group differences could be found.

Mean changes between BL and Day +28 as well as Day +56 in the further secondary efficacy parameters (i.e., renal plasma flow, glomerular filtration rate, filtration fraction, renovascular resistance, urinary albumin excretion as mmol/L and adiponectin levels) were in general not different between the two groups by ANCOVA analysis.

Finally, a significant decrease in albuminuria (expressed as albumin/creatinine ratio) was observed in the manidipine group, whereas the treatment with amlodipine was associated with a significant increase (p-value between groups <0.001)

Safety Results:

Both treatment regimens (either in monotherapy or in association with delapril) showed a favorable safety profile. The overall incidence of AEs was similar between the two groups, with a slightly higher proportion of patients experiencing at least one AE in the manidipine group (43/56) than in the amlodipine group (34/57). The same trend was observed for the total number of recorded AEs (75 AEs vs 74 AEs respectively).

Drug-related AEs also occurred in a similar rate under manidipine and amlodipine therapy (20/56 vs 16/57 patients respectively for a total of 28 vs 26 events). During monotherapy the most frequently occurring drug-related AEs were peripheral edema (10 patients under amlodipine vs. 2 patients under manidipine) and headache (4 patients of each treatment group).

Peripheral edema was the only drug-related AE observed with a significantly different rate between the two groups under monotherapy, favoring manidipine treatment (p= 0.0290 for all and drug-related AEs, Fisher's Exact Test).

Ten patients (4 of the manidipine and 6 of the amlodipine group) discontinued the study drug permanently due to adverse events. In 9 of these patients the events were suspected to be related to the study medication. Four amlodipine patients discontinued due to drug-related peripheral edema. Two patients suffered from serious AEs: One patient [redacted] experienced a serious adverse event (SAE) before the intake of amlodipine (suspicion of smoke poisoning). Another patient [redacted] experienced a serious adverse event (SAE) prior to randomization into the trial (allergic reaction during clearance). Both events were not considered to be related to the study medication. No patient died throughout the study.

Further safety measures did not yield any noteworthy results.

Conclusion:

Altogether, the efficacy results from this study indicate a more beneficial effect of manidipine on intraglomerular pressure as compared to amlodipine. This effect was no longer detectable during combination therapy with an ACE-inhibitor, mainly because of a decrease in intraglomerular pressure in the amlodipine group. Moreover, manidipine was considered safe and well tolerated especially with respect to the avoidance of peripheral edema.

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