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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.

SYNOPSIS

Name of Sponsor: Istituto Farmacobiologico Malesci S.p.A.

Name of finished product: Olpress **(**Olmesartan medoxomil)

Name of active ingredient: Olmesartan medoxomil

Title of study: Efficacy and safety of olmesartan in elderly patients with mild to moderate hypertension

Protocol number: OLM/CLIN/I-12/03

Principal Investigator: [redacted]

Study centre(s): 195

Publication (reference): Not applicable

Studied period (years): 2005-2009

Phase of development: Phase III

Objectives:

The primary objective of the study was to assess the efficacy of 12 weeks of double-blind treatment with olmesartan 10 to 40 mg once-daily in reducing clinic systolic blood pressure (SBP) and diastolic blood pressure (DBP) as compared to ramipril 2.5 to 10 mg once-daily in elderly mild-moderate essential hypertensive patients.

Secondary objectives of the study were:

- The assessment of percentage of normalised (SBP<140 mmHg and DBP<90 mmHg for non-diabetic patients and SBP <130 mmHg and DBP <80 mmHg for diabetic patients) or responder patients (reduction in SBP ≥20 mmHg and of DBP ≥10 mmHg) after 2, 6 and 12 weeks of treatment with olmesartan as compared to ramipril
- The assessment of the antihypertensive efficacy of the two drugs by ambulatory blood pressure monitoring (ABPM) during the 12-week double blind phase
- Safety and tolerability of study dugs
- Patient's compliance to treatment
- The assessment of antihypertensive efficacy of 36 weeks of open label treatment with olmesartan 40 mg once-daily on clinic BP and ABP
- The evaluation of long-term safety of olmesartan 40 mg once-daily

Methodology:

Trial design/type: Multicentre, randomised, double-blind, parallel group study

Study population: Male and female outpatients aged 65 to 89 years, with mild to moderate essential hypertension.

Blinding: The study was double blind. Blinding of the treatment was obtained using encapsulated drugs. Blinding treatment code was sealed and held by investigators, and could be broken only for safety reasons. An open label phase was foreseen after the double-blind period (see below).

Randomisation: A randomisation list was prepared using blocks, and stratified by centre.

Number of patients (planned and analysed):

Planned: 1,222 to be randomised (611 by treatment group), to have 1,056 evaluable patients. Screened: 1,242. Randomised: 1,102. Analysed: 1,081 (double-blind phase).

Number of centres: Planned: 195. Each centre had to include 08 patients (04 patients per arm). Actual: 195 (120 enrolled patients)

Diagnosis and main criteria for inclusion:

New diagnosis of grade 1 or 2 essential arterial hypertension (sitting clinic SBP 140-179 mmHg and/or sitting clinic DBP 90-109 mmHg) or essential arterial hypertension not controlled with current treatment or with intolerance to current treatment

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

Capsules containing olmesartan 10, 20 or 40 mg tablets were used during the double-blind period, following 2 weeks of placebo run-in.

The starting treatment dose of olmesartan was 10 mg. During the double-blind phase patients not normalised (BP ≥140/90 mmHg for non diabetic patients and BP ≥130/80 mmHg for diabetic patients) at each visit had to receive a double dose of the study drug, until a maximum dose of 40 mg/day.

Patients taking olmesartan 40 mg/day at the end of the 12-week double-blind treatment period could continue an open treatment with the drug for further 36 weeks. During this open phase, non-diabetic patients not normalised at the end of the double-blind phase had to be treated with the addition of hydrochlorothiazide (HCTZ) 12.5 mg/day which could be doubled to 25 mg/day at the subsequent visit in case of lack of BP normalisation. Diabetic patients not normalised (SBP ≥130 mmHg

and DBP ≥80 mmHg) after double-blind phase had to be treated with the addition of zofenopril 15 mg/day, which could be doubled to 30 mg/day in case of non-normalisation. In case patients were not normalised with the highest drug dose combination (olmesartan 40 mg plus HCTZ 25 mg or olmesartan 40 mg plus zofenopril 30 mg), they had to be withdrawn from the study.

The study medication was taken once a day between 8-10 a.m. all days except on the visit days when the patient was asked to take the medication after all the examination had been completed. Patients were instructed to swallow the tablet and the capsule with a glass of water.

Duration of treatment:

84 days (12 weeks) double-blind. 252 days (36 weeks) open label.

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

Capsules containing ramipril 2.5, 5 or 10 mg. The starting treatment dose was 2.5 mg. Ramipril up-titration followed the same scheme as for olmesartan (see above).

Criteria for evaluation:

Efficacy :

All efficacy variables were analysed on the intention-to-treat (ITT, all randomised patients who have taken at least one dose of the study drug and performed at least one measurement of the BP after the randomisation) and per-protocol population (PP, all randomised patients who have satisfied all inclusion criteria and no exclusion criteria and have completed the study respecting the specified protocol, with no major protocol violations).

The primary efficacy variable was the between-treatment comparison in the changes in sitting clinic SBP and DBP from baseline (visit 0) to the end of double-blind treatment (visit 3, 12 weeks of treatment).

The secondary efficacy variables were the between-treatment comparison in the:

- The percentage of normalised (sitting clinic SBP <140 mmHg and DBP <90 mmHg for non diabetic patients and sitting clinic SBP <130 mmHg and DBP <80 mmHg for diabetic patients) and responder patients (reduction of 20 mmHg in SBP and 10 mmHg in DBP) after 2 (visit 1), 6 (visit 2) and 12 weeks (visit 3) of treatment
- Changes in mean 24h SBP and DBP from baseline to the end of the double-blind treatment period (12 weeks - baseline)
- Changes in mean day-time SBP and DBP values from baseline to the end of the double-blind treatment period (12 weeks - baseline)
- Changes in mean night-time SBP and DBP values from baseline to the end of the double-blind treatment period (12 weeks - baseline)
- Changes in the last 6h of the dosing interval for SBP and DBP from baseline to the end of the double-blind treatment period (12 weeks - baseline)
- Percentage of subjects with morning hypertension at baseline and at the end of the double-blind treatment period. Morning hypertension was defined by an average ABP in the morning (between 6:00 or waking time and 9:59) ≥135/85 mmHg. This parameter is useful to assess the degree of blood pressure control in a period of the day often associated with an increased risk of cardiovascular events
- Change in the morning surge from baseline to the end of the double-blind treatment period (12 weeks - baseline). Morning surge was computed as the difference between the lowest SBP values during night sleep (average of 3 readings centred on the lowest value) and the average SBP in the two hours immediately following awakening. The higher the morning surge, the lower is the blood pressure control and the greater is the risk of cardiovascular events.
- Percentage of subjects with morning surge above normal values (>55 mmHg) at baseline and at the end of the double-blind treatment period
- Change in the Ambulatory Arterial Stiffness Index (AASI) from baseline to the end of the double-blind treatment period (12 weeks - baseline). The AASI was computed as [1 - (1 - (1 - b)) / r], where (b) is the regression slope and (r) the correlation coefficient of DBP on SBP. The stiffer the arterial tree, the higher is the AASI (ranging from 0 to 1)
- Trough-to-peak ratio for SBP and DBP at 12 weeks. The trough-to-peak ratio was calculated as the ratio between the trough and the peak BP difference (12 weeks of treatment - baseline). Peak blood pressure change was calculated by taking the interval between the 2nd and 8th hour from drug administration (when the peak effect is expected to occur), and by averaging the hour in which the blood pressure fall was maximal and the adjacent hour in which the blood pressure fall was greater. Trough blood pressure change was calculated by averaging the changes over the last 2h of the 24h monitoring period
- Smoothness index (SI) for DBP and SBP at 12 weeks. The SI was computed as the ratio between the average of 24 hourly changes from baseline and the corresponding standard deviation. The higher this index, the greater is the homogeneity of the blood pressure control by antihypertensive treatment

Compliance: it was computed at each study visit as the ratio between the number of galenic units taken and the number of galenic units which should have been taken. The result was expressed as percent.

Safety:

All randomised patients taking at least one dose of active study drug were included in the safety analysis. The extent of exposure, the total number of adverse events (AE) reported, the number of AEs leading to discontinuation of the study drugs and the number of patients having developed at least one AE or serious adverse event (SAE) was collected.

Statistical methods:

As far as the primary variable is regarded an analysis of covariance (ANCOVA) was applied using baseline as covariate and treatment as main effect. Significant factors and interactions were investigated. If the covariates were significant, additional tabular data summaries were produced displaying the primary variable means by covariate categories. If the treatment effect was not significant, no further models were fitted in the main analysis. If the treatment effect was significant, the model was refitted with terms for treatment by covariate interactions, to assess the robustness of the treatment effect across covariates. Least square adjusted means were computed. A global test for treatment by covariate interaction was investigated by entering all the interaction terms in the model. If the global test for interaction was significant at 10% significance level, then single interaction was explored. For significant interaction, an estimate for confidence interval of the treatments odds-ratio was presented, at 25^{th}, 50^{th}, and 75^{th} percentiles of the covariates.

Secondary efficacy analysis included the comparison in the percentage of normalised, and normalised and responders patients between the two groups using the Chi-square test, and the analysis of the ABPM data.

Comparison between the two groups for the changes in 24h, day-time, night-time, last 6h, morning surge and AASI was carried out by ANCOVA. The analytical model included the treatment factor and the baseline value as covariate. For trough-to-peak ratios formal comparisons between treatment groups was performed using a Mann-Whitney non-parametric test, providing the median values and the 5^{th} and 95^{th} percentile of the distribution. The same test was applied to changes in AASI (which do not have a normal distribution). Comparison of the SIs at the end of treatment was done by analysis of variance with treatment as main factor. Comparison of the between-treatment prevalence in morning hypertension and abnormal morning surge was carried out by a Chi-square test. These tests were applied to the analysis of the double-blind treatment period. Analysis of the open label period was kept descriptive.

Analysis of clinic BP changes, normalised and normalised or responder patients was also carried out in two study subgroups according to:

- Age groups: 65-69 years, 70-79 years and ≥80 years
- Type of hypertension: isolated systolic hypertension (SBP ≥140 mmHg and DBP <90 mmHg), isolated diastolic hypertension (SBP <140 mmHg and DBP ≥90 mmHg) and systo-diastolic hypertension (SBP ≥140 mmHg and DBP ≥90 mmHg)

Primary and secondary analyses were also extended to the open label phase, but mostly kept descriptive, given the safety purpose of this phase.

All statistical analyses were two-sided. All comparisons were tested at the 5% level of significance.

Concerning the safety analysis, the number of patients reporting AEs and the types of AE were summarised by treatment group. Vital signs were listed and summary statistics presented. Abnormal laboratory data were presented, along with ECG findings. Concomitant medications were summarised and listed. No formal statistical analyses were performed.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: A total 1,242 patients entered the screening phase of the study, 1,102 (97.2%) were randomised to active treatment, and 980 (88.9%) completed the double-blind phase. The most common reasons for dropping-out from the study were withdrawal of consent (n=42), lost to follow-up (n=22) and occurrence of an AE (n=20). 194 randomised patients entered and 144 completed the open label phase. Number of patients with valid ABP recordings at baseline and end of double-blind phase were in total 630, those with valid ABPM at the end of the open label phase were 80.

The ITT population consisted of 1,081 patients (542 olmesartan and 539 ramipril), while the PP population was formed by 917 patients (468 olmesartan and 449 ramipril), for the double-blind period. The ITT population for the ABPM subgroup and for the double blind period was formed by 318 patients for the olmesartan group and by 312 patients for the ramipril group. PP population consisted of 309 patients randomised to olmesartan and by 301 patients randomised to ramipril. In the open phase the patients valid for ITT analysis were 189 and those for the PP analysis 144 (clinic BP). For the ABPM subgroup, the numbers for the ITT and PP population were 80 and 76, respectively.

Compliance to treatment did not different between olmesartan and ramipril.

In the next paragraphs, results are summarised for the ITT population. No substantial difference were observed between the ITT and PP population for all efficacy variables.

Clinic BP during the double-blind phase

The full dose of olmesartan was taken at the end of the double-blind period by 42.5% of patients and the full dose of ramipril by 51.6% of patients. The average study drug dose at the end of the double-blind period was 25.9±12.6 mg for olmesartan (63% of the maximal dose) and 7.1±3.1 mg for ramipril (71% of the maximal dose).

Baseline-adjusted reductions in sitting clinic SBP and DBP were always significantly greater under olmesartan (mean±SD: 17.8±13.3 mmHg SBP and 9.4±8.1mmHg DBP) than under ramipril (15.8±13.5 and 7.5±8.3 mmHg; $p<0.05$ for SBP and $p<0.001$ for DBP). Superiority in the BP lowering effect of olmesartan vs. ramipril was evident throughout the whole double-blind period. Sitting clinic SBP and DBP reductions were greater for each age group under olmesartan than under ramipril: this between-treatment difference achieved statistical significance in the youngest group of subjects for both BPs and in the oldest group for DBP only. In the systo-diastolic group sitting clinic SBP and DBP reductions were significantly

(p<0.01) greater under olmesartan (19.3±12.3 mmHg) than under ramipril (16.7±13.1mmHg), while differences observed in the patients with isolated systolic hypertension did not achieve statistical significance. As for the whole study group, also for the two subgroups of patients according to type of hypertension, clinic BP reductions were larger under olmesartan than under ramipril during each study visit.

The rate of normalised patients at the end of the double-blind period was significantly (p<0.05) larger under olmesartan (52.6%) than ramipril (46.0%). This was the case also for the percentage of normalised plus responder patients (59.0% olmesartan vs. 52.9% ramipril, p<0.05). The proportion of normalised patients progressively increased during the double-blind treatment phase: the difference in favour of olmesartan for this variable was larger than that observed under ramipril also at week 2 (26.0% vs. 21.0%, p=0.05) and 6 (43.5% vs. 34.3%, p<0.01). No statistically significant difference in the proportion of normalised patients was observed between treatment groups when different age ranges were considered. Clinic BP normalisation rates achieved with olmesartan were significantly (p<0.05) larger than those under ramipril in the systo-diastolic hypertension group (53.2% olmesartan vs. 44.7% ramipril), while a non significant difference was observed in patients with isolated systolic hypertension.

ABP during the double-blind phase

80 patients out of the 318 randomised to olmesartan (25.2%) and 59 patients out of the 312 randomised to ramipril (18.9%) in the subgroup of patients with valid ABPM were treated with the lowest dosage, 114 (35.8%) and 89 (28.5%) with the intermediate dosage, and 124 (39.0%) and 164 (52.6%) with the highest dosage, which was the most represented, in each group.

Baseline adjusted mean 24h SBP and DBP changes were significantly greater (p<0.05) under olmesartan [mean and 95% confidence interval or CI: 11.0 (12.2 / 9.9) mmHg SBP and 6.5 (7.2 / 5.8) mmHg DBP] than under ramipril [9.0 (10.2 / 7.9) mmHg and 5.4 (6.1 / 4.7) mmHg]. BP reductions under olmesartan were always greater than under ramipril, also for the day-time and night-time subperiods, the difference being always statistically significant, except for night-time DBP. Average hourly reductions were most of the time larger with olmesartan than with ramipril, with a particularly evident and consistent between-treatment difference in the last 6h from the drug intake [SBP: 10.5 (11.8 / 9.0) mmHg olmesartan vs. 7.3 (8.7 / 5.9) mmHg ramipril, p<0.01; DBP: 6.1 (7.0 / 5.3) mmHg vs. 4.5 (5.3 / 3.6) mmHg, p<0.01]. The prevalence of morning hypertension was reduced by both treatments, with a non statistically significant trend to a greater rate of normalisation and a lower rate of development of morning hypertension in the olmesartan treatment group. The magnitude of the morning surge was reduced by olmesartan [2.8 (5.0 / 0.6) mmHg] while was increased by ramipril [+1.2 (1.0 / +3.4)] the net difference between the two treatment groups being statistically significant (p<0.05). The same was observed for the rate of subjects with an abnormal morning surge, and with a normalisation or development of an abnormal morning surge, though the difference was not statistically significant. The AASI was slightly reduced with treatment, but differences between olmesartan and ramipril were not statistically significant.

The quantification of the distribution of the antihypertensive effect of the study treatments throughout the 24h was assessed by calculation of the trough-to-peak ratio and the SI. Trough-to-peak ratios of SBP were significantly (p<0.01) greater under olmesartan [0.57 (-1.44 / 2.46)] than under ramipril [0.36 (-2.94 / 3.01)], while no significant between-treatment differences were observed for DBP. For both SBP and DBP, SIs were significantly (p<0.01) higher under olmesartan (SBP: 0.82±0.98 and DBP 0.68±0.80) than under ramipril [0.62±0.89 and 0.51±0.74].

Open label phase

Most of the patients normalised at the end of the double-blind period (84.4%) had their BP under control at the end of the open label period. In the subgroup of diabetic patients, BP normalisation rate increased from 17.9% to 48.2%.

During the open label phase clinic SBP and DBP were further significantly reduced by treatment (9.5±13.3 mmHg and 5.1±7.3 mmHg, p<0.01). This was observed for all visits, for all patients, and for the subgroups of patients taking monotherapy or with diabetes.

Also 24h, day-time and night-time SBP and DBP were further reduced at the end of the open label phase as compared to the end of the 12 weeks double-blind phase. This was evident also for each hour of the 24h and for the last 6h of the recording. The prevalence of morning hypertension was halved at the end of the open label phase as compared with the end of the double-blind treatment, while the magnitude of the reduction in the morning surge at the end of the open label phase was similar to that observed at the end of the double-blind randomised treatment. The AASI did not show any relevant change at the end of both study periods. The trough-to-peak ratio and the SI were greater at the end of the open label period than at the end of the 12 weeks of double-blind treatment.

SAFETY RESULTS:

During the placebo wash-out period 12 patients reported an AE, of which only one was judged as drug related. All these patients were screening failure.

Double-blind phase

A total of 175 AEs were reported in 136 (12.3%) patients in the double-blind phase. The greatest proportion (68.6%) of AEs in all treatment groups was mild in severity.

Drug related AEs were 40 (22.9% of all events), of which the majority (65.0%) was of a mild intensity. Overall 40 patients experienced drug-related AEs (29.4%). Thus the extent of drug adverse reactions was limited to at most one-third of the treated patients.

The number of AEs (98 olmesartan and 77 ramipril) and the proportion of patients who experienced AEs (13.7% vs. 11.0%) were similar between the two study groups. The greatest proportion of AEs was related to abnormal laboratory values

(17.1%), followed by respiratory, thoracic and mediastinal disorders (14.9%), nervous system disorders (12.6%) and gastrointestinal disorders (9.7%). Cough was much more commonly observed in the ramipril group. The number of AEs leading to study drug discontinuation was 33 (18.9% of all AEs) and occurred in 33 (24.3% of patients with AEs) patients (18.6% of patients with AE under olmesartan and 31.1% of patients with AE under ramipril).

11 SAE were reported in 8 patients, but only in one case the SAE was judged as related to study medication (the patient was treated with ramipril). In 4 patients SAEs led to study drug discontinuation. No death occurred during the study.

Open label phase

A total of 35 AEs were recorded in 29 patients (14.9%) in the open label phase: a small number of them were drug related (14.3%), while the majority was of mild intensity. The proportion of patients with AEs during the open label phase was similar to that of the double-blind phase (14.9%).

The number of AEs leading to study drug discontinuation was 4 (11.4% of all AEs) and occurred in 4 patients (13.8%).

4 SAE were reported by 4 patients: one of them was drug related and led premature withdrawal from the study. All SAEs resolved. No death occurred during this phase.

Few patients displayed significant changes in laboratory values during the study, and there were no remarkable or consistent trends in abnormal haematological or biochemical findings between of the treatment groups.

No overt change occurred in urinary parameters (namely glucose, protein or blood in urine) at end of study versus baseline.

A slight reduction in HR was observed with both treatments, with no remarkable between-treatment difference.

No differences were observed for physical examination performed at baseline and along the study for each patient.

There was no difference with regard to the incidence of abnormalities in ECG between treatment groups. No consistent trends in the number of changes from normal to abnormal ECG findings between baseline and end of treatment were observed.

CONCLUSION: results of the present study demonstrated the greater efficacy of olmesartan 10 to 40 mg as compared to ramipril 2.5 to 10 mg on both clinic and ABP in mild-moderate elderly essential hypertensive patients. The primary efficacy variable (sitting clinic SBP and DBP changes after 12 weeks of treatment) indicated a significantly larger reduction with olmesartan than with ramipril. This was true also when the proportion of normalised or normalised plus responder patients were taken into account. Superiority was particularly evident in the systo-diastolic group and in the patients with an age between 65 and 69 years (youngest patients).

Also SBP and DBP changes over the 24h by ABPM were significantly greater under olmesartan, as well as the reduction in the last 6h from drug intake, at awakening (morning surge) and the SI, which taken together indicate a consistent, long-lasting and homogeneous BP control throughout the dosing interval.

Both clinic and ambulatory BPs were further reduced during the open label period, in the group taking olmesartan monotherapy with eventually addition of HCTZ or zofenopril.

Both olmesartan medoxomil and ramipril were well tolerated, but the former was associated with a lower rate of cough, which was indeed the most common among the treatment-emergent AEs recorded in the ramipril group.