AstraZeneca

D4385L00001

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: PLENDIL™

ACTIVE INGREDIENT: Felodipine

Trial title (number): A randomized, open-label study to evaluate the effects on blood pressure control, pulse wave velocity, as well as safety and tolerability of felodipine sustained release, alone and in combination with metoprolol, lisinopril or hydrochlorothiazide, in Chinese patients with mild to moderate essential hypertension

Developmental phase: IV
First subject recruited: 26 December 2005
Last subject completed: 17 August 2006
Approval date: 20 December 2006

OBJECTIVES

Primary objective

The primary objective of the study was to estimate and compare the rate of controlled blood pressure after 12 weeks of treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide in Chinese patients with mild to moderate essential hypertension and inadequate blood pressure control with felodipine sustained release 5 mg monotherapy. (Blood pressure control was defined as both SBP <140 mmHg and DBP <90 mmHg).

Secondary objectives

1. To estimate and compare the rate of controlled blood pressure after 4 and 8 weeks of treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide.
2. To estimate and compare the systolic and diastolic blood pressure reduction from baseline among all randomized subjects after 4, 8 and 12 weeks of treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide. (Baseline blood pressure was defined as the blood pressure after treatment with felodipine sustained release 5 mg for 2 weeks).
3. To estimate and compare the systolic and diastolic blood pressure reduction from baseline among the subjects who reached target (defined as < 140 / 90 mmHg) after 4, 8

and 12 weeks treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide. (Baseline blood pressure was defined as the blood pressure after treatment with felodipine sustained release tablet 5 mg for 2 weeks.)

4. To evaluate the safety and tolerability after 12 weeks treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide.
5. To estimate and compare the effect on pulse wave velocity after 12 weeks treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide.
6. To estiment the effect on pulse wave velocity after 2 and 14 weeks treatment with felodipine sustained release 5 mg monotherapy.
7. To estimate the systolic and diastolic blood pressure reduction from baseline at 2, 6, 10 and 14 weeks among the subjects who reached target blood pressure (defined as < 140 / 90 mmHg) after 2 weeks treatment with felodipine sustained release 5 mg monotherapy.(Baseline blood pressure was defined as the blood pressure at screening.).

METHODS

Inclusion Criteria:

1. Written informed consent to participate in the trial
2. Female or male aged 35-79 years
3. Mild to moderate essential hypertensive patients who met any of the following criteria:
    - Newly diagnosed, drug-naive, or without any antihypertension treatment for at least 3 months, moderate essential hypertension patients. (160mmHg£ mean SiSBP<180mmHg or 100mmHg£ mean SiDBP<110mmHg)
    - Newly diagnosed, drug-naive, or without any antihypertension treatment for at least 3 months, mild essential hypertension patients. (140mmHg£ mean SiSBP<160mmHg or 90mmHg£ mean SiDBP<100mmHg) with high or extremely high cardiovascular risk* (having >3 risk factors and/or target organ lesion and/or diabetes mellitus). * according to Chinese guideline for prevention and treatment of patients with hypertension 2004.
    - Patients already receiving the starting dosage of any single antihypertensive drug therapy (excluding drugs containing felodipine), but with inadequate blood pressure control (140mmHg £ mean SiSBP <160mmHg or 90mmHg £ mean SiDBP <100mmHg). After stopping the drug for 5 elimination half-lifes, the patients should meet any of the following:
        - 160mmHg£ mean SiSBP<180mmHg or 100mmHg£ mean SiDBP<110mmHg.
        - 140mmHg£ mean SiSBP<160mmHg or 90mmHg£ mean SiDBP<100mmHg) with high or extremely high cardiovascular risk (having >3 risk factors and/or target organ lesion and/or diabetes mellitus).

Exclusion criteria:

Any of the following was regarded as a criterion for exclusion from the study:

1. Known or suspected secondary hypertension
2. Resting heart rate < 55 bpm.
3. Sick sinus syndrome
4. Atrioventricular block of first degree (P-R interval >0.24 s), or of second or third degree
5. Other clinically significant arrhythmia
6. Unstable and/or decompensated congestive heart failure
7. Angina pectoris, acute myocardial infarction, percutaneous coronary intervention (PCI), or cardiac surgery
8. Asthma or moderate to severe chronic obstructive pulmonary disease
9. Type 1 diabetes mellitus
10. Gout history
11. Fasting serum glucose greater than 200 mg/dl (11.1 mmol/L), or type 2 diabetes mellitus in need of insulin therapy
12. ALT >3 times above upper limit of normal (ULN)
13. Cr >1.5 mg/dl
14. Pregnancy or lactation
15. Alcohol or drug abuse
16. Known need for other concomitant antihypertensive therapy during the study in addition to study drugs
17. Known or suspected allergy to study drugs or non-active ingredients of study drugs, or known allergy to other beta-blockers, calcium antagonists, diuretics, or angiotensin converting enzyme inhibitors
18. Contraindications for any of the study drugs
19. Suspected white-coat hypertension based on investigator's judgement.

Investigational product, Batch No. dosage and mode of administration:

Felodipine sustained release tablet (Plendil) 5 mg/tablet, Batch No 0508001, one to two tablets, once daily, orally.

Metoprolol succinate prolonged-release tablet (Betaloc ZOK) 47.5 mg/tablet, Batch No 0507022, one tablet, once daily, orally.

Metoprolol succinate prolonged-release tablet (Betaloc ZOK) 95 mg/tablet, Batch No 0507024 and 0507026, one tablet, once daily, orally.

Lisinopril (Zestril) 10 mg/tablet, Batch No CD 242, one to two tablets, once daily, orally.

Hydrochlorothiazide 25 mg/tablet, Batch No 051001 and 050701, half to one tablet, once daily, orally.

Duration of treatment

Screening stage:

Eligible subjects who met the No.1 or No.2 blood pressure inclusion criterion entered directly into the therapy stage, Step 1. Eligible subjects who met the No.3 blood pressure inclusion criterion entered the therapy stage Step 1 after a wash-out period of 5 elimination half-lifes of any previously used antihypertensive drug.

Therapy stage:

Step 1: Felodipine sustained release single drug therapy (1st week- 2nd week). Eligible subjects first took felodipine 5mg once daily for 2 weeks.If blood pressure was controlled after 2 weeks,

the subjects continued the treatment until the end of the study (14th week). If blood pressure was not controlled after 2 weeks, the subjects entered step 2.
Step 2: Combined drug therapy based on 5 mg felodipine sustained release tablet (3rd week- 6th week).Eligible subjects were randomized into 3 different combined drug therapy groups:

- Group 1: felodipine sustained release 5mg once daily combined with metoprolol succinate prolonged-release tablet (Betaloc ZOK) 47.5 mg once daily;
- Group 2: felodipine sustained release 5mg once daily combined with Lisinopril (Zestril) 10 mg once daily.
- Group 3: felodipine sustained release 5mg once daily combined with hydrochlorothiazide 12.5 mg once daily;If blood pressure was controlled after 4 weeks, the subjects continued the same treatment until the end of the study (14th week). If blood pressure was not controlled after 4 weeks, the subjects entered step 3.

Step 3: Combined drug therapy based on 2x5 mg felodipine sustained release tablet (7th week-10th week).The dosage of felodipine sustained release tablet was increased to 10 mg (2x5 mg tablets) once daily, while the dosage of the combined (added) drug remained the same. If blood pressure was controlled after 4 weeks, the subjects continued the same treatment until the end of the study (14th week). If blood pressure was not controlled after 4 weeks, the subjects entered step 4.
Step 4: Double dose combined (added) drug therapy and 2x5 mg felodipine sustained release tablet (11th week-14th week).The dosage of felodipine sustained release tablet was kept at 10 mg (2x5 mg tablet) once daily, while the dosage of the different combined (added) drugs was doubled to metoprolol 95 mg once daily, lisinopril 20 mg once daily, and hydrochlorothiazide 25 mg once daily, respectively.All the subjects finished the study after 14 weeks.Sitting blood pressure was measured before the next scheduled administration of medication, and after the subjects had been resting for 5 minutes in the sitting position.

Endpoints
Outcome variables (Primary and Secondary):
Efficacy (Primary variable)

Primary outcome variable:
The percentage of subjects reaching blood pressure target (defined as < 140 / 90 mmHg) after 12 weeks treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide.

Secondary outcome variables:
The percentage of subjects reaching blood pressure target (defined as < 140 / 90 mmHg) after 4 and 8 weeks treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide.
The systolic and diastolic blood pressure reduction from baseline among all randomized subjects after 4, 8 and 12 weeks treatment with felodipine sustained release in combination with

metoprolol, lisinopril or hydrochlorothiazide. (Baseline blood pressure was defined as the blood pressure after treatment with felodipine sustained release tablet 5 mg for 2 weeks.)
The systolic and diastolic blood pressure reduction from baseline among the subjects who reached target (defined as < 140 / 90 mmHg) at 4, 8 and 12 weeks treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide. (Baseline blood pressure was defined as the blood pressure after treatment with felodipine sustained release tablet 5 mg for 2 weeks.)
The change of pulse wave velocity after 12 weeks treatment with felodipine sustained release in combination with metoprolol, lisinopril or hydrochlorothiazide.
The change of pulse wave velocity at 2 and 14 weeks monotherapy with felodipine sustained release 5 mg.
The systolic and diastolic blood pressure reduction from baseline among the subjects who reached target (defined as < 140 / 90 mmHg) after 2 weeks monotherapy with felodipine sustained release 5 mg. (Baseline blood pressure was defined as the blood pressure at screening.)
Safety:

- Adverse events
- Laboratory variables:
    - Hematology
    - Urinalysis
    - Clinical Chemistry:
        - Fasting Glucose (FPG), Liver Function (ALT, AST),
        - Lipids (TC, LDL-C,HDL-C,TG),
        - Renal Function (Cr), K+, Na+, Uric Acid.

Other safety measurements:

- Physical examination
- Sitting heart rate
- 12-lead ECG (Electrocardiogram)

Statistical methods:
Only patients who had inadequate blood pressure control after 2 weeks monotherapy with felodipine 5 mg and, therefore, randomized to combination therapy were subject to formal intention-to-treat (ITT) and per protocol (PP) analyses. The ITT population was defined as all patients who received at least one dose of study drug after randomization and had measurements of blood pressure at baseline and from at least one visit after randomization. The PP population was defined as all ITT subjects who met all inclusion criteria and none of the exclusion criteria and finished the 14-week study with no major protocol violations or deviations. The safety population was defined as all subjects who received at least one dose of study drug. Efficacy data were analyzed both in the ITT population and the PP population (as supportive information). Only descriptive statistics is given for data in patients whose blood pressure was controlled after 2 weeks monotherapy with felodipine 5 mg.Comparisons of the percentage of

patients who reached the treatment target in the three combination treatment groups were performed using a logistic analysis model with factors fitted for centre, treatment, the severity of primary hypertension (mild, moderate) and their interactions. The results are presented as odd ratios and associated 95% confidence intervals.Comparisons of the magnitude of systolic and diastolic blood pressure reductions from baseline (week 2) in the three combination treatment groups were performed in all randomized patients using an ANOVA model with factors fitted for centre, treatment, the severity of primary hypertension (mild, moderate) and their interactions, and with baseline systolic and diastolic blood pressure as covariates. The results are presented as least square means and associated 95% confidence intervals.Other secondary efficacy variables were summarized with no formal comparisons between treatment groups.Descriptive statistics of N, mean, standard deviation, median, minimum and maximum were used to summarize continuous data, and N and percentage for categorical data.Safety was summarized as the number and percentage of patients who reported adverse events, and the number and percentage of patients with clinically significant changes in laboratory measurements. Tolerability was defined as the proportion of patients who discontinued due to AEs.

RESULTS

A total of 529 patients attended the screening visit, and 522 were given felodipine 5 mg once daily. Of these, 38 patients did not complete the 2-week felodipine monotherapy period. Of the remaining 484 patients, 222 (46%) had adequately controlled blood pressure (SBP <140 mmHg and DBP <90 mmHg) at 2 weeks, and continued felodipine monotherapy for the duration of the study. Thus, 262 patients (54%) were not adequately controlled with felodipine monotherapy for 2 weeks, and were randomized to combination therapy with felodipine plus metoprolol (N=85), or felodipine plus lisinopril (N=85), or felodipine plus hydrochlorothiazide (N=92). Three patients were excluded from ITT population (one in felodipine plus metoprolol group, one in felodipine plus lisinopril group,one in felodipine plus hydrochlorothiazide group).Overall 100 patients were discontinued during the study, 80 during monotherapy with felodipine and 20 during combination therapy. All patients were Chinese, 44.7% women and 55.3% men. The mean age was 54.9 years.Efficacy results： In the ITT analysis, the blood pressure control rate at 12 weeks in the felodipine plus metoprolol group, the felodipine plus lisinopril group, and the felodipine plus hydrochlorothiazide group was 74.1%, 80.5%, and 80.2%, respectively. There were no statistically significant differences in control rate between the three treatment groups ($p > 0.05$). Similarly, there were no statistically significant differences in control rate at 4 and 8 weeks between the three treatment groups ($p > 0.05$). These results were supported by similar findings in the PP analysis ($p > 0.05$).The blood pressure reduction from baseline (Baseline was defined as the time after treatment with felodipine sustained release tablet 5 mg for 2 weeks.)among all randomized subjects at 12 weeks was 16.6/10.7 mmHg, 18.0/12.8 mmHg , and 16.8/10.6 mmHg in the felodipine plus metoprolol group, the felodipine plus lisinopril group, and the felodipine plus hydrochlorothiazide group, respectively. There were no significant differences in blood pressure reduction between the three treatment groups ($p > 0.05$). The blood pressure reduction from baseline among all randomized subjects at 8 weeks was 17.8/11.3 mmHg, 17.3/12.1 mmHg, and 16.4/10.7 mmHg in the felodipine plus metoprolol group, the felodipine plus lisinopril group, and the felodipine plus hydrochlorothiazide group, respectively. At 4 weeks, the blood pressure reductions were 10.3/7.3 mmHg, 13.4/9.9 mmHg, and 9.8/6.0 mmHg, respectively. The only

statistically significant difference (p <0.05) in blood pressure reduction between treatment groups was for diastolic blood pressure at 4 weeks when comparing felodipine plus lisinopril and felodipine plus hydrochlorothiazide (9.9 mmHg vs 6.0 mmHg). The change in pulse wave velocity from baseline among all randomized subjects at 12 weeks was –0.06 m/s, –0.12 m/s, and –0.44 m/s, respectively, in the felodipine plus hydrochlorothiazide group, the felodipine plus metoprolol group, and the felodipine plus lisinopril group. There were no statisitically significant differences in change in pulse wave velocity between these three treatment groups (p>0.05). Among the subjects who reached blood pressure target, the change in pulse wave velocity from baseline was greater (p< 0.05) in the felodipine plus lisinopril group than in the felodipine plus hydrochlorothiazide group (–0.72 m/s vs +0.16 m/s).The blood pressure reductions from baseline(Baseline was defined as screening period.) among all subjects in the felodipine monotherapy group at 2, 6, 10, and 14 weeks were 21.4/14.2 mmHg, 22.4/15.6 mmHg, 23.4/16.8 mmHg, and 24.8/17.3 mmHg, respectively. The change in pulse wave velocity from baseline(Baseline was defined as screening period.) was –0.58 m/s and –0.86 m/s at 2 and 14 weeks, respectively, in the felodipine monotherapy group. The change in pulse wave velocity at 14 weeks compared to baseline was significant (p< 0.05). Safety Evaluation Results:All treatment regimens were safe and well tolerated. The overall adverse event (AE) rate was 26.1% (mild 17.6%, moderate 7.5%, severe 1.0%). Overall, 136 patients experienced at least one AE during the study; 70 patients (26.9%) in the felodipine monotherapy group, 21 patients (24.7%) in felodipine plus metoprolol group, 28 patients (32.9%) in felodipine plus lisinopril group, and 17 patients (18.5%) in the felodipine plus hydrochlorothiazide group. There were 56 (10.7%) patients who were discontinued from the study due to AEs; 44 patients (16.9%) in felodipine monotherapy group, 2 patients (2.4%) in felodipine plus metoprolol group, 6 patients (7.1%) in felodipine plus lisinopril group, and 4 patients (4.3%) in the felodipine plus hydrochlorothiazide group.The most common AEs (occuring in >1% of the patients) included the following: headache (8.8%), flushing (5.4%), dizziness (3.8%), cough (3.6%), oedema peripheral (1.9%), palpitation (1.7%), nausea (1.3%), indisposition (1.0%), and insomnia (1.0%). No deaths were reported during study. Two of the patients treated with felodipine monotherapy had serious adverse events (SAEs). None of these were considered drug related according to the investigator. There were no SAEs in any of the combination therapy groups.There were no clinically significant changes in vital signs, laboratory variables, or ECG examinations.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Plendil™ (felodipine), Healthcare Professionals should view their specific country information.