A Randomized, Multicenter, Double-blind, Placebo-controlled, 3 × 3 Factorial Design, Phase II Study to Evaluate the Efficacy and Safety of the Combination of Fimasartan/Amlodipine in Patients With Essential Hypertension

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ABSTRACT

Purpose: The objective of this study was to evaluate the efficacy and safety of a fimasartan/amlodipine combination in patients with hypertension and to determine the optimal composition for a future single-pill combination formulation.

Methods: This Phase II study was conducted by using a randomized, multicenter, double-blind, placebo-controlled, 3 × 3 factorial design. After a 2-week placebo run-in period, eligible hypertensive patients (with a sitting diastolic blood pressure [SiDBP] between 90

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and 114 mm Hg) were randomized to treatment. They received single or combined administration of fimasartan at 3 doses (0, 30, and 60 mg) and amlodipine at 3 doses (0, 5, and 10 mg) for 8 weeks. The primary efficacy end point was the change in SiDBP from baseline and at week 8; secondary end points included the change in SiDBP from baseline and at week 4 and the changes in sitting systolic blood pressure from baseline and at weeks 4 and 8. Treatment-emergent adverse events (AEs) were also assessed.

Findings: 420 Korean patients with mild to moderate hypertension were randomly allocated to the 9 groups. Mean (SD) SiDBP changes in each group after 8 weeks were as follows: placebo, –6.0 (8.5) mm Hg; amlodipine 5 mg, –10.6 (9.2) mm Hg; amlodipine 10 mg, –15.9 (7.2) mm Hg; fimasartan 30 mg, –10.1 (9.1) mm Hg; fimasartan 60 mg, –13.0 (10.0) mm Hg; fimasartan 30 mg/amlodipine 5 mg, –16.2 (8.5) mm Hg; fimasartan 30 mg/amlodipine 10 mg, –19.5 (7.5) mm Hg; fimasartan 60 mg/amlodipine 5 mg, –16.6 (6.9) mm Hg; and fimasartan 60 mg/amlodipine 10 mg, –21.5 (8.3) mm Hg. All treatment groups produced significantly greater reductions in blood pressure compared with the placebo group. In addition, all combination treatment groups had superior reductions in blood pressure compared with the monotherapy groups. In the combination treatment groups, doubling fimasartan dose in the given dose of amlodipine did not show further BP reduction, whereas doubling amlodipine dose showed significantly further BP reduction in the given dose of fimasartan. During the study period, 75 (17.9%) of 419 patients experienced 110 AEs. Ninety-five AEs were mild, 9 were moderate, and 6 were severe in intensity. Eight patients discontinued the study due to AEs. There was no significant difference in incidence of AEs among groups ($P = 0.0884$). The most common AE was headache (12 patients [2.9%]), followed by dizziness (11 patients [2.6%]) and elevated blood creatine phosphokinase levels (6 patients [1.4%]).

Implications: Fimasartan combined with amlodipine produced superior blood pressure reductions and low levels of AEs compared with either monotherapy. Therefore, a single-pill combination with fimasartan 60 mg/amlodipine 10 mg will be developed. ClinicalTrials.gov: NCT01518998. (*Clin Ther.* 2015;37:2581–2596)

Key words: amlodipine, angiotensin receptor blocker, calcium channel blocker, fimasartan, hypertension.

INTRODUCTION

Hypertension guidelines emphasize that monotherapy can effectively reduce blood pressure (BP) in only a limited number of patients with hypertension and that most patients require the combination of at least 2 drugs to achieve BP control.[1] The combination of renin-aldosterone system inhibitors and calcium channel blockers is widely used because it offers proven complementary mechanisms for reducing adverse effects such as leg edema; in addition, it reportedly reduces the occurrence of cardiovascular events in patients with hypertension.[2,3]

Fimasartan, developed by Boryung Pharmaceutical Co, Ltd (Seoul, Korea), is an angiotensin II receptor blocker (ARB) with a selective type 1 receptor blockade effect.[4] Fimasartan at the range of 30 to 120 mg once daily has been shown to have an effective BP-lowering effect in patients with mild to moderate hypertension.[4–7] In an efficacy comparison study with other antihypertensive agents, once-daily fimasartan produced a better trough-to-peak ratio, reaching 0.74 (60 mg/d) to 0.81 (120 mg/d), which was better than that of valsartan 80 mg/d.[6] In addition, fimasartan 60/120 mg was suggested to have an in-office BP reduction superior to that of losartan 50/100 mg.[4] Excellent safety and tolerability were reported in a large-population, observational study of fimasartan.[8]

Pharmacokinetic/pharmacodynamic studies of fimasartan have been performed to evaluate the possibility of drug or food interactions[9–12] as well as drug metabolism in special populations such as the elderly and those with hepatic dysfunction.[13,14] To aid in the development of single-pill combinations, a Phase I pharmacokinetic study evaluated the effect of the coadministration of fimasartan and amlodipine on the steady-state pharmacokinetics of each drug in healthy volunteers; no significant interactions with amlodipine were reported.[15]

Based on these early clinical study results, the present study was conducted to evaluate the efficacy and safety of the fimasartan (0, 30, and 60 mg) and amlodipine (0, 5, and 10 mg) combination in patients with hypertension. Our goal was to determine the optimal composition for a future single-pill combination formulation.

PATIENTS AND METHODS

Patients

Eligible participants were male or nonchildbearing female patients with essential hypertension, aged 20 to 75 years whose sitting diastolic BP (SiDBP) was in the range of 95 to 114 mm Hg after a 2-week placebo run-in