

Efficacy and Tolerability of Once-Daily Oral Fimasartan 20 to 240 mg/d in Korean Patients with Hypertension: Findings from Two Phase II, Randomized, Double-Blind, Placebo-Controlled Studies

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ABSTRACT

Background: Fimasartan is a selective angiotensin II receptor blocker developed for once-daily dosing.

Objectives: To meet the regulatory requirements for approval of an antihypertensive treatment in Korea, this pair of studies was conducted to evaluate the efficacy and tolerability of fimasartan, to determine its dose-response relationship and minimum effective dose, and to characterize its blood pressure (BP)-reduction profile over the dosing interval.

Methods: These 2 Phase II, randomized, double-blind, placebo-controlled, parallel-group, and dose-response studies enrolled male or nonchildbearing female Korean patients aged 18 to 65 years (study 1) or 18 to 70 years (study 2) with essential hypertension (sitting diastolic BP [DBP] 95–<115 mm Hg [study 1] or 90–<110 mm Hg [study 2]). Patients were randomly assigned to receive fimasartan 20, 60, 120, or 180 mg (study 1) or 20, 60, 120, or 240 mg (study 2) or placebo in the same ratio, once daily for 4 weeks

(study 1) or 8 weeks (study 2). Clinic BP was measured at trough, and change from baseline in DBP at week 4 (study 1) or 8 (study 2) was the primary efficacy end point. In study 1, 24-hour ambulatory BP monitoring (ABPM) was conducted. Treatment-emergent adverse events (TEAEs) were assessed using a structured questionnaire, laboratory testing, physical examination, and ECG readings.

Results: Totals of 61 and 195 patients participated in studies 1 and 2, respectively (68% male; mean age, 50.1 and 55.1 years; DBP, 98.7 and 103.6 mm Hg; systolic BP, 147.0 and 158.1 mm Hg), of whom 52 (85.2%) and 169 (86.7%) completed each study. Data from ABPM were obtained from 45 patients (73.8%), and safety profile was evaluated in 225 participants.

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Four-week treatment with fimasartan 180 mg once daily was associated with a significantly greater mean reduction in DBP compared with placebo in study 1 (-16.4 vs -5.5 mm Hg; $P = 0.022$). In study 2, fimasartan 60, 120, and 240 mg once daily were associated with significantly greater reductions in DBP after 8 weeks of treatment compared with placebo (-14.4 , -14.1 , and -12.7 vs -5.8 mm Hg, respectively; $P < 0.0001$ – < 0.005). Fimasartan 60 mg once daily was the minimum effective dose, and the dose-response relationship was flat at doses >60 mg once daily. BP reduction was maintained over the full 24-hour dosing interval (trough-to-peak ratios: 0.41–0.98). The proportions of patients who experienced TEAEs were comparable among the treatment groups in both studies, with headache (9.8%) and dizziness (4.4%) being most commonly reported. No serious AEs were reported.

Conclusions: Once-daily oral administration of fimasartan was well tolerated and efficacious in reducing BP in these hypertensive Korean patient populations. ClinicalTrials.gov identifiers: NCT00937651 and NCT00923611. (*Clin Ther.* 2012;34:1273–1289) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: 24-hour ambulatory blood pressure monitoring, angiotensin II receptor blocker, efficacy, essential hypertension, fimasartan, tolerability.

INTRODUCTION

Fimasartan, an angiotensin II receptor blocker (ARB) with a selective type 1 (AT_1) receptor blockade effect,¹ has been developed for once-daily dosing to treat patients with hypertension.² Two Phase I studies conducted in healthy, mostly white volunteers reported that repeated oral administration of fimasartan up to 360 mg once daily had a safety profile comparable to that of placebo, with dizziness being the most commonly reported adverse event (AE).³ The pharmacokinetic properties of fimasartan were also favorable, that is, rapid absorption, dose-linearity, negligible metabolism (most excreted unchanged in bile), minimal accumulation ($<30\%$ when dosed once daily), unremarkable food effect (AUC lowered by 5% in the fed state), and a relatively long half-life of 14.0 to 17.9 hours.³

The pharmacodynamic results from those Phase I studies suggested that fimasartan may have potential as an effective antihypertensive treatment. For example, fimasartan was associated with significantly increased

levels of plasma renin activity, angiotensin I, and angiotensin II for up to 48 hours postdose, while aldosterone and angiotensin-converting enzyme activity were not affected.³ These pharmacodynamic effects, particularly the increase in plasma angiotensin II level, are attributed to fimasartan through its blocking of the AT_1 receptor. These effects have been noted with other ARBs, such as losartan⁴ and valsartan,⁵ and are the mechanism of action for blood pressure (BP) reduction by these and other ARBs.^{6–8} Additionally, fimasartan use was associated with reductions in supine and standing BP for up to 24 hours after administration in many healthy subjects.³ Therefore, it is reasonable to suppose that fimasartan may decrease BP in hypertensive subjects by antagonizing angiotensin II receptors, and once-daily oral administration seems appropriate to achieve this intended beneficial effect.

These results in the safety profile, pharmacokinetics, and pharmacodynamics of fimasartan have led to the following questions: (1) Does fimasartan significantly decrease BP in hypertensive patients, and is this decrease significantly greater than with placebo?; (2) What is the dose-response relationship and the minimum effective dose of fimasartan?; (3) Is once-daily administration of fimasartan able to maintain BP reduction throughout, especially toward the end of the dosing interval?; and (4) Is fimasartan treatment well tolerated? To answer these questions, 2 studies were conducted in Korean patients with essential hypertension to explore the efficacy and tolerability of fimasartan at various oral doses. Based on the results from these studies, the dose-response relationship of fimasartan was assessed, and the optimal doses for further clinical studies of fimasartan were determined. Moreover, 24-hour ambulatory blood pressure monitoring (ABPM) was used in 1 of the studies for characterization of the BP-lowering profile of fimasartan over the dosing interval. The main results of these studies are reported in this article.

PATIENTS AND METHODS

Inclusion Criteria

This pair of Phase II studies enrolled male or non-childbearing female patients aged 18 to 65 years (18–70 years in study 2) with essential hypertension (sitting diastolic BP [DBP], 95 – <115 mm Hg in study 1, 90 – <110 mm Hg in study 2, after washout of antihypertensives of ≥ 1 week and a 2-week placebo run-in, with a difference from before to after run-in of ≤ 7

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