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CLINICAL TRIAL REPORT

Efficacy and Safety of Fimasartan/Indapamide Combination Therapy versus Fimasartan Monotherapy in Patients with Essential Hypertension Inadequately Responding to Fimasartan 30 mg (FINEDUO): A Randomized, Double-Blind, Multicenter, Phase III Study

Jong-Chan Youn[1,2,*], So-Young Lee[1,2,*], Cheol Woong Yu[3], Ki-Chul Sung[4], Jinho Shin[5], Ju Hyeon Oh[6], Jin Oh Na[7], Dae-Hee Kim[8], Eun Joo Cho[9], Hyuck-Jun Yoon[10], Chan Joo Lee[11], Han Cheol Lee[12], Hae-Young Lee[13], Il Suk Sohn[14], Kyu-Sun Lee[15], Doo Il Kim[16], Woong Gil Choi[17], Wook-Jin Chung[18], Eun Mi Lee[19], Seung-Hyuk Choi[20], Seonghoon Choi[21], Tae Soo Kang[22], Sang-Hyun Ihm[2,23]

[1]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Catholic Research Institute for Intractable Cardiovascular Disease, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [4]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]Department of Internal Medicine, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea; [6]Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea; [7]Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [8]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [9]Department of Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [10]Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University College of Medicine, Daegu, Republic of Korea; [11]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [12]Department of Internal Medicine, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Republic of Korea; [13]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [14]Department of Cardiology, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, Republic of Korea; [15]Department of Internal Medicine, Eulji University Hospital, Eulji University School of Medicine, Daejeon, Republic of Korea; [16]Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea; [17]Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Republic of Korea; [18]Department of Cardiovascular Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea; [19]Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Goyang, Republic of Korea; [20]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [21]Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea; [22]Department of Internal Medicine, Dankook University Hospital, Dankook University College of Medicine, Cheonan, Republic of Korea; [23]Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

*These authors contributed equally to this work

Correspondence: Sang-Hyun Ihm, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, Tel +82 32 340 7027, Email limsh@catholic.ac.kr

Purpose: Effective blood pressure (BP) control in hypertension frequently requires combination therapy, particularly in patients whose BP is inadequately controlled by monotherapy. This study evaluated the efficacy and safety of fimasartan (FMS) and indapamide (IND) sustained release (SR) combination therapy.

Patients and Methods: In this randomized, double-blind, phase III trial, patients with hypertension who remained uncontrolled after a 4-week run-in with FMS 30 mg, were randomized to FMS 30 mg/IND SR 1.5 mg or FMS 30 mg, followed by forced titration to

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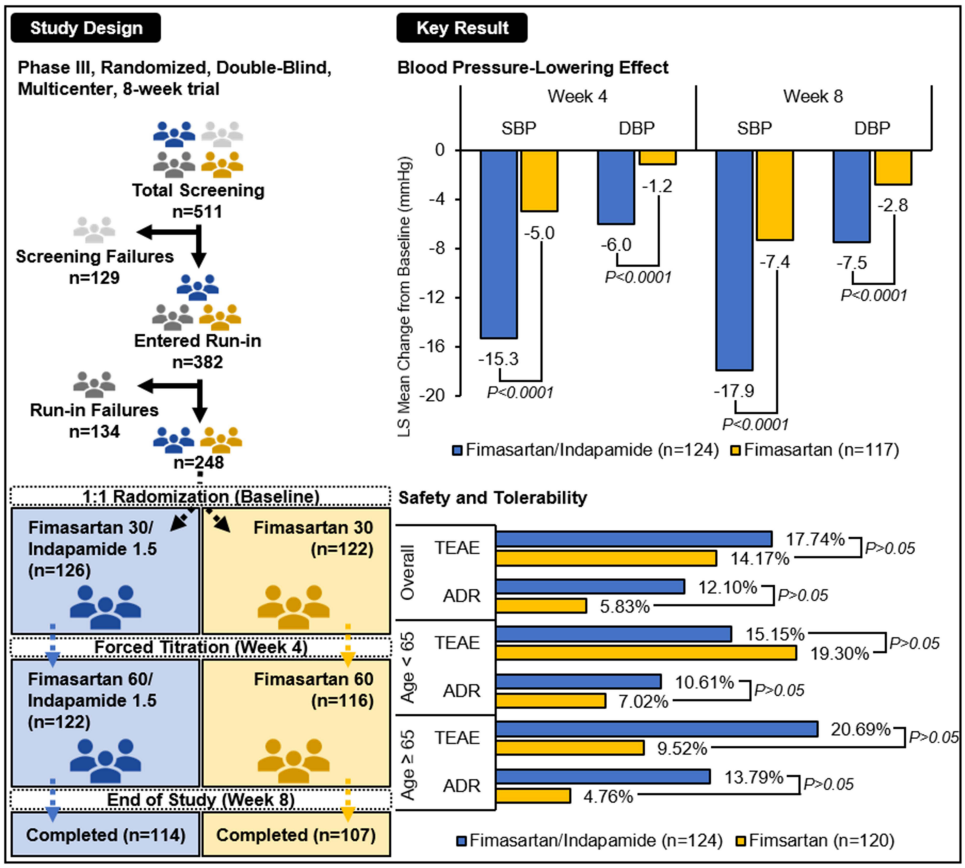
FMS 60 mg/IND SR 1.5 mg or FMS 60 mg after 4 weeks. The primary endpoint was the change in sitting systolic BP (SiSBP) at week 8. Secondary endpoints included changes in sitting diastolic BP (SiDBP), BP control rates, response rates, and safety outcomes.

Results: Two hundred forty-eight patients were randomized (FMS/IND SR, n=126; FMS, n=122). At week 8, the least square mean reduction in SiSBP was greater with FMS/IND SR than with FMS (−17.9 vs −7.4 mmHg, $P<0.0001$). Significant improvements were also observed for SiSBP at week 4, SiDBP at week 4 and 8, and BP control rates and response rates. The safety profile was comparable between groups, with no significant differences in adverse events, including patients aged 65 years and older.

Conclusion: FMS/IND SR combination therapy demonstrated superior antihypertensive efficacy, rapid BP control, and comparable safety to FMS monotherapy. This regimen may serve as an effective therapeutic option, particularly in elderly or high-risk hypertensive patients.

Clinical Trial Registration: https://www.clinicaltrials.gov, NCT05878561.

Graphical Abstract



Keywords: blood pressure control, combination therapy, fimasartan, indapamide sustained release, hypertension

Introduction

Effective blood pressure (BP) control often requires combination therapy, especially in patients whose hypertension is not adequately managed with monotherapy.[1–4] Real-world data suggest that BP control with monotherapy is frequently suboptimal. In a real-life cohort of patients receiving monotherapy, only 36.6% of patients achieved office BP < 140/90 mmHg, and the control rate fell to 14.0% under the 2018 European Society of Cardiology/European Society of

Hypertension targets. In another real-world study using both office and home BP criteria, only 6.7–8.5% of monotherapy-treated patients achieved BP control, indicating that the vast majority remained uncontrolled under more stringent assessment.[5,6] Current guidelines recommend combining agents with complementary mechanisms of action, such as an angiotensin II receptor blocker (ARB) with either a calcium channel blocker or a thiazide-type diuretic, to enhance antihypertensive efficacy.[1–4] Among these, ARB and diuretic combinations are especially effective in patients with resistant or salt-sensitive hypertension.[7,8] This combination provides complementary BP-lowering effects by concurrently targeting the renin-angiotensin-aldosterone system (RAAS) and sodium/volume overload, yielding greater BP reductions than monotherapy. Moreover, ARBs can counteract the compensatory RAAS activation induced by diuretics and may attenuate metabolic adverse effects such as hypokalemia.[9]

ARB/HCTZ combinations are widely used and have consistently demonstrated greater BP lowering and higher target BP achievement than ARB monotherapy.[10] Chlorthalidone-containing regimens may provide stronger and more sustained BP reduction, but their clinical use can be limited by a higher incidence of electrolyte abnormalities, particularly hypokalemia.[11–13] These observations highlight the need to evaluate alternative thiazide-like diuretic components that may preserve antihypertensive potency while improving tolerability.

Fimasartan (FMS) is a potent and highly selective ARB developed in Korea and currently used in many countries.[14,15] Its antihypertensive efficacy at doses of 30–120 mg has been shown to be comparable to or greater than that of other ARBs, with a favorable safety profile.[16–19]

Indapamide (IND), a thiazide-like diuretic, exerts its BP-lowering effects through natriuresis in the distal renal tubules and direct vascular action.[20] Several studies have demonstrated that IND and chlorthalidone are more effective than hydrochlorothiazide (HCTZ) in reducing BP.[11,12,21] However, thiazide-like diuretics have been associated with an increased risk of electrolyte disturbances, such as hyponatremia and hypokalemia, especially at higher doses or in elderly patients. Chlorthalidone has shown a higher incidence of such abnormalities compared to HCTZ,[13] and similar findings have been reported with the immediate release (IR) formulation of IND.[22]

The development of a sustained release (SR) formulation of IND has addressed these safety concerns. Compared with IND IR 2.5 mg, IND SR 1.5 mg provides a smoother 24-hour pharmacokinetic profile with lower peak plasma concentrations and has been associated with a lower incidence of hypokalemia while maintaining comparable antihypertensive efficacy in previous studies. Importantly, IND SR has also been shown to be effective and well tolerated in older patients.[23–28] Given the high prevalence of salt-sensitive hypertension among elderly patients, IND SR may serve as an effective and well-tolerated therapeutic option. In addition to its BP-lowering effect, IND has demonstrated benefits in renal and cardiovascular outcomes and a neutral impact on glucose and lipid metabolism.[29–34] Accordingly, several clinical guidelines recommend thiazide-like diuretics including IND over conventional thiazide for the management of hypertension.[1,35]

Given the potent antihypertensive efficacy of IND and the improved tolerability of its SR formulation, the combination of FMS and IND SR may provide greater BP reduction than FMS monotherapy while maintaining safety in patients with essential hypertension not adequately controlled with FMS monotherapy. However, the efficacy and safety of this combination therapy have not yet been investigated. Therefore, we conducted the clinical trial to evaluate the efficacy and safety of FMS/IND SR combination therapy in patients with essential hypertension who did not achieve target BP levels with FMS monotherapy.

Methods

Study Design

The FINEDUO (FImasartan-INdapamide Effective DUO) was a randomized, double-blind, multicenter, phase III clinical study conducted at 22 clinical sites in Korea (Supplementary Table S1). The protocol was approved by the institutional review board of each participating clinical site and the Ministry of Food and Drug Safety. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guideline. All patients provided written informed consent before undergoing any procedures.

After voluntary agreement to participate in this study, all patients received FMS 30 mg during the wash out and the run-in period for 4 weeks. After the run-in period, patients were re-evaluated to confirm that they met the inclusion and exclusion

criteria and were randomly assigned in a 1:1 ratio to receive either FMS 30mg/IND SR 1.5 mg (treatment group) or FMS 30 mg (control group). Patients were given the study drug once daily for 4 weeks, followed by forced dose titration to FMS 60mg/IND SR 1.5 mg or FMS 60 mg for 4 weeks (Figure 1). (ClinicalTrials.gov identifier: NCT05878561)

Patients

Adults who were ≥ 19 years old with essential hypertension were included if they failed to respond after 4 weeks of FMS 30 mg, with their medication adherence of at least 70% during the run-in period. Hypertension was defined as mean sitting systolic BP (SiSBP) ≥ 140 mmHg and < 180 mmHg for those who had not taken antihypertensive medications prior to the screening visit. For those taking antihypertensive medications, hypertension was defined as mean SiSBP ≥ 130 mmHg and < 180 mmHg.

Participants were excluded from the study if they had secondary hypertension, severe hypertension (SiSBP ≥ 180 mmHg or sitting diastolic BP (SiDBP) ≥ 110 mmHg), symptomatic orthostatic hypotension, heart failure (New York Heart Association Class III and IV), significant structural heart disease or arrhythmia, clinically relevant or unstable cardiovascular diseases (CVDs) within 6 months prior to the screening visit, uncontrolled diabetes mellitus (DM, glycosylated hemoglobin level > 9%), or were taking three or more antihypertensive drugs of different classes. Only patients receiving fewer than three antihypertensive drug classes were eligible for enrollment.

Participants were withdrawn from the study if any of the following criteria were met: withdrawal of consent, occurrence of clinically significant adverse drug reactions (ADRs, including hypersensitivity), clinically significant abnormalities in BP or laboratory parameters (eg, elevated alanine aminotransferase, aspartate aminotransferase or decreased estimated glomerular filtration rate (eGFR) or decreased serum potassium, sodium), violation of key inclusion/exclusion criteria, pregnancy, use of prohibited concomitant medications, loss to follow-up, or at the investigator's discretion.

Randomization and Masking

Randomization was performed using a stratified block method, with clinical sites as the stratification factor. An independent statistician generated the randomization sequence using SAS version 9.4, and participants were centrally assigned to treatment groups via an interactive web response system for randomization and study drug management.

Sponsor prepared and labeled the study drugs in accordance with the randomization list, and the study drugs were packaged for the treatment and control groups. To maintain double-blinding, identical labeling was applied to the outer packaging of all study drugs, including the placebo. This ensured that participants and investigators were kept blinded to group allocation during the treatment period. Moreover, access to the randomization codes of study drugs were strictly controlled, and the codes were disclosed only after trial completion, following the data lock and unblinding procedures.

Efficacy and Safety Evaluation

The primary endpoint was the change in SiSBP from baseline to week 8. The secondary endpoints were the change in SiSBP from baseline to week 4, the changes in SiDBP from baseline to week 4 and 8, the BP control rates (the proportion of participants who achieved SiSBP/SiDBP < 130/80 mmHg for patients with CVD, DM or chronic kidney disease (CKD) with albuminuria, SiSBP/SiDBP < 140/90 mmHg for the others) and response rates (the proportion of participants with a decrease in SiSBP ≥ 20 mmHg or SiDBP ≥ 10 mmHg) at week 4 and 8.

At each visit, BP was measured three times with at least 2-minute intervals using a validated automated BP monitor (UA-1020, A&D Company, Ltd., Tokyo, Japan) after at least 5 minutes of rest in a seated position. The mean of the three BP measurements was calculated. At the screening visit, BP was measured in both arms, and the arm with the higher mean SiSBP was designated as the reference arm for subsequent visits. If mean SiSBP was equal, the arm with higher mean SiDBP was designated as the reference arm. To ensure consistency, all subsequent measurements were performed on the same arm. Participants were instructed to avoid caffeine intake, smoking, and strenuous exercise for at least 30 minutes prior to BP measurement.

The safety assessment was based on the incidence of treatment emergent adverse events (TEAEs) observed on physical examinations, laboratory tests, vital signs, and electrocardiogram. TEAEs were defined as AEs that occurred on

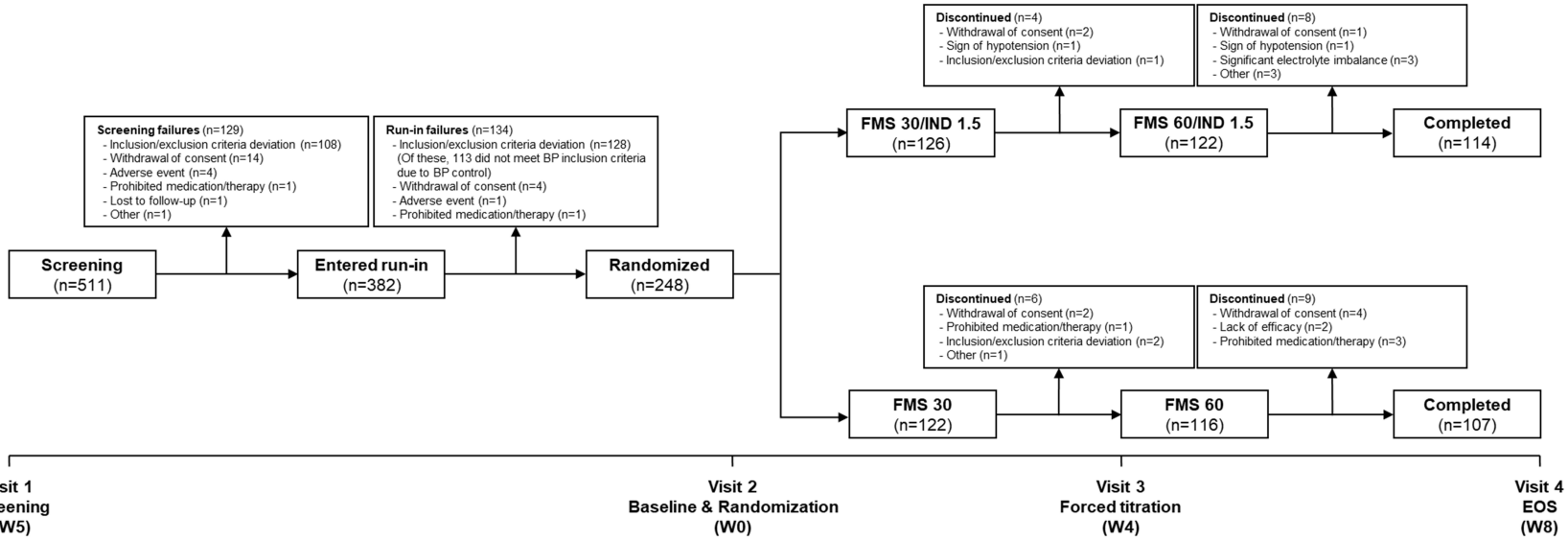


Figure 1 Summary of patient disposition.
Abbreviations: FMS, fimasartan; IND, indapamide sustained release; BP, blood pressure; EOS, end of study.

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or after the first administration of the study drug. ADRs were defined as TEAEs for which a causal relationship with the study drug could not be ruled out, as assessed by the investigator using predefined causality categories.

Laboratory tests were performed at screening, baseline, and each scheduled visit (weeks 4 and 8) to monitor participant safety. Abnormal laboratory values, including hypokalemia and hyponatremia, were initially identified based on the local laboratory reference ranges at each clinical site and classified as AEs by the investigators.

Medication adherence was assessed at baseline and each subsequent visit by using pill counts, based on the number of study drugs dispensed and returned.

Statistical Analysis

Because no previous studies have evaluated the effects of the combination therapy on BP, the expected difference in mean change and standard deviation (SD) were conservatively estimated based on pooled results from published studies of similar combination therapies.[36–38] The estimated difference in the reduction in SiSBP between the FMS/IND SR group and the FMS group was 5.5 mmHg with SD of 14 mmHg. Sample size was calculated using a two-sided, two-sample *t*-test assuming equal variance, with 80% statistical power and a 5% significance level. This calculation indicated that 103 participants per group were required for a 1:1 randomization. With a dropout rate of 15%, the total number of participants was determined to be 244.

This study was conducted in accordance with the intention-to-treat principle. Efficacy data were primarily analyzed in the full analysis set (FAS), which included all randomized patients who received at least one dose of the study drug and had at least one efficacy assessment after baseline, and also in the per-protocol set (PPS).

The primary and secondary endpoints (except the BP control rates and response rates) were compared using an analysis of covariance with the baseline value as a covariate. The BP control rates and response rates were analyzed using logistic regression model with the baseline BPs as covariates. Safety was assessed in patients who received at least one dose of the study drug (safety set). For safety assessment, the difference in the incidence of TEAEs and ADRs between the two groups was assessed using the chi-square test or Fisher's exact test. No statistical adjustment was made for multiplicity arising from multiple comparisons or tests.

Missing outcome data due to loss to follow-up or early treatment discontinuation were handled according to predefined statistical analysis plan. For FAS analyses, missing data were imputed using the last observation carried forward (LOCF) method, including measurements from unscheduled visits when available. If LOCF was not applicable, observed data were analyzed without imputation. For PPS analyses and all safety endpoints, no imputation was performed, and observed data were analyzed as recorded.

Subgroup analyses were conducted to assess the consistency of primary endpoint and safety outcomes using the same statistical methods as those applied to the primary endpoint and safety outcomes. Subgroup analyses were performed to evaluate the primary endpoint according to the following baseline factors: age (< 65 or ≥ 65 years), sex (male or female), body mass index (< 25 or ≥ 25 kg/m^2), drinking status (current non-drinker or current drinker), smoking status (non-smoker, current smoker or ex-smoker), duration of essential hypertension (< 5 or ≥ 5, < 10 or ≥ 10 years), baseline systolic BP (SBP) and diastolic BP (DBP) (each categorized into two groups based on the observed median: < 147 or ≥ 147 mmHg for SBP, and < 93 or ≥ 93 mmHg for DBP), and the presence of comorbidities (DM: clinical history of diabetes and antidiabetic medication use, or HbA1c $\geq 6.5\%$ at screening; dyslipidemia; CKD: clinical history of CKD or eGFR < 90 mL/min/1.73 m^2 at baseline; coronary artery disease (CAD)). In addition, a subgroup analysis by age (< 65 or ≥ 65 years) was performed for the safety.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Patients

A total of 511 patients were screened, and 248 patients were randomized to receive either FMS/IND SR (n=126) or FMS (n=122). Of randomized patients, 221 patients completed the study (Figure 1). Two hundred forty-one patients were evaluated for efficacy and 244 patients for safety. The demographic and baseline characteristics were well balanced between the two groups (Table 1).

Table 1 Demographic and Baseline Characteristics (Full Analysis Set)

Characteristic	FMS/IND (N=124)	FMS (N=117)	P-value
Age (years)			
Mean (SD)	61.69 (12.87)	62.36 (11.85)	0.6517[a]
Subgroup, n (%)			0.3347[b]
<65	66 (53.23)	55 (47.01)	
≥65	58 (46.77)	62 (52.99)	
Sex, n (%)			0.9834[b]
Male	86 (69.35)	81 (69.23)	
Female	38 (30.65)	36 (30.77)	
Weight (kg)			
Mean (SD)	72.84 (13.90)	72.04 (13.65)	0.6978[a]
BMI[c] (kg/m^2)			
Mean (SD)	26.65 (3.75)	26.33 (3.91)	0.5804[a]
Subgroup, n (%)			0.5387[b]
<25	44 (35.48)	46 (39.32)	
≥25	80 (64.52)	71 (60.68)	
Drinking status, n (%)			0.7230[b]
Current non-drinker	46 (37.10)	46 (39.32)	
Current drinker	78 (62.90)	71 (60.68)	
Smoking status, n (%)			0.9595[b]
Non-smoker	61 (49.19)	59 (50.43)	
Current smoker	24 (19.35)	21 (17.95)	
Ex-smoker	39 (31.45)	37 (31.62)	
Duration of essential hypertension[d] (years)			
Mean (SD)	9.31 (9.13)	8.13 (7.35)	0.5535[a]
Subgroup, n (%)			0.4628[b]
<5	55 (44.35)	48 (41.03)	
≥5, <10	17 (13.71)	23 (19.66)	
≥10	52 (41.94)	46 (39.32)	
SBP at baseline (mmHg)			
Mean (SD)	150.65 (10.54)	151.52 (11.08)	0.5572[a]
Median	147.15	147.70	
Subgroup, n (%)			0.7344[b]
<147	61 (49.19)	55 (47.01)	
≥147	63 (50.81)	62 (52.99)	
DBP at baseline (mmHg)			
Mean (SD)	92.36 (9.41)	93.82 (8.45)	0.2657[a]
Median	92.30	94.00	
Subgroup, n (%)			0.3270[b]
<93	64 (51.61)	53 (45.30)	
≥93	60 (48.39)	64 (54.70)	
eGFR[e] ($mL/min/1.73m^2$)			
Mean (SD)	87.78 (16.44)	87.78 (15.29)	0.9124[a]
Median	89.82	90.00	
Diabetes mellitus, n (%)			0.9546[b]
Yes	29 (23.39)	27 (23.08)	
No	95 (76.61)	90 (76.92)	
Dyslipidemia, n (%)			0.5760[b]
Yes	73 (58.87)	73 (62.39)	
No	51 (41.13)	44 (37.61)	

(*Continued*)

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Table 1 (Continued).

Characteristic	FMS/IND (N=124)	FMS (N=117)	P-value
Chronic kidney disease, n (%)			0.7459[b]
Yes	63 (50.81)	57 (48.72)	
No	61 (49.19)	60 (51.28)	
Coronary artery disease, n (%)			0.8946[b]
Yes	22 (17.74)	20 (17.09)	
No	102 (82.26)	97 (82.91)	

Notes: [a]Testing for difference between-treatment groups (two sample *t*-test or Wilcoxon rank sum test). [b]Testing for difference between-treatment groups (chi-square test or Fisher's exact test). [c]BMI (kg/m²) = weight (kg) / (height (cm) / 100)². [d]Duration of essential hypertension (years) = (visit 1 - diagnosis date + 1) / 365.25. [e]eGFR was calculated using the CKD-EPI equation.

Abbreviations: FMS, fimasartan; IND, indapamide sustained release; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate.

Blood Pressure-Lowering Effect

After 8 weeks of treatment, the mean (SD) change in SiSBP was −17.7 (16.0) mmHg in the FMS/IND SR and −7.6 (16.3) mmHg in the FMS (all $P < 0.0001$). The least square (LS) mean difference (standard error (SE)) between the two groups was −10.5 (2.0) mmHg ($P < 0.0001$), indicating that BP-lowering effect of FMS/IND SR combination therapy was superior to that of FMS monotherapy at week 8. Similar findings were also observed at week 4. The mean (SD) change in SiSBP at week 4 was −15.1 (15.1) mmHg in the FMS/IND SR and −5.3 (14.2) mmHg in the FMS ($P < 0.0001$ and $P = 0.0001$, respectively). The LS mean difference (SE) between the two groups was −10.2 (1.8) mmHg ($P < 0.0001$). Furthermore, the LS mean changes in SiDBP from baseline to week 4 and 8 were significantly greater in the FMS/IND SR than in the FMS (all $P < 0.0001$) (Table 2 and Figure 2).

Table 2 Change in Blood Pressure From Baseline to week 4 and 8 (Full Analysis Set)

Variable	FMS/IND (N=124)	FMS (N=117)	P-value
SiSBP, mmHg			
Baseline (week 0)	150.7 (10.5)	151.5 (11.1)	0.5572[a]
At week 4	135.7 (13.7)	146.3 (14.9)	
LS mean change (SE)	−15.3 (1.2)	−5.0 (1.3)	
Difference (95% CI) vs FMS	−10.2 (−13.7 to −6.8)	-	<0.0001[b]
At week 8	132.9 (14.9)	143.9 (17.9)	
LS mean change (SE)	−17.9 (1.4)	−7.4 (1.4)	
Difference (95% CI) vs FMS	−10.5 (−14.4 to −6.6)	-	<0.0001[b]
SiDBP, mmHg			
Baseline (week 0)	92.4 (9.4)	93.8 (8.5)	0.2657[a]
At week 4	86.4 (9.3)	92.2 (9.4)	
LS mean change (SE)	−6.0 (0.7)	−1.2 (0.7)	
Difference (95% CI) vs FMS	−4.8 (−6.7 to −2.9)	-	<0.0001[b]
At week 8	85.1 (9.5)	90.8 (10.8)	
LS mean change (SE)	−7.5 (0.7)	−2.8 (0.8)	
Difference (95% CI) vs FMS	−4.7 (−6.8 to −2.6)	-	<0.0001[b]

Notes: Values are presented as the mean (SD). [a]Testing for difference between treatment groups (Wilcoxon rank sum test). [b]Testing for difference between treatment groups (ANCOVA model with baseline BP as a covariate).

Abbreviations: FMS, fimasartan; IND, indapamide sustained release; SiSBP, sitting systolic blood pressure; SE, standard error; CI, confidence interval; SiDBP, sitting diastolic blood pressure; LS, least square; SD, standard deviation; ANCOVA, analysis of covariance.

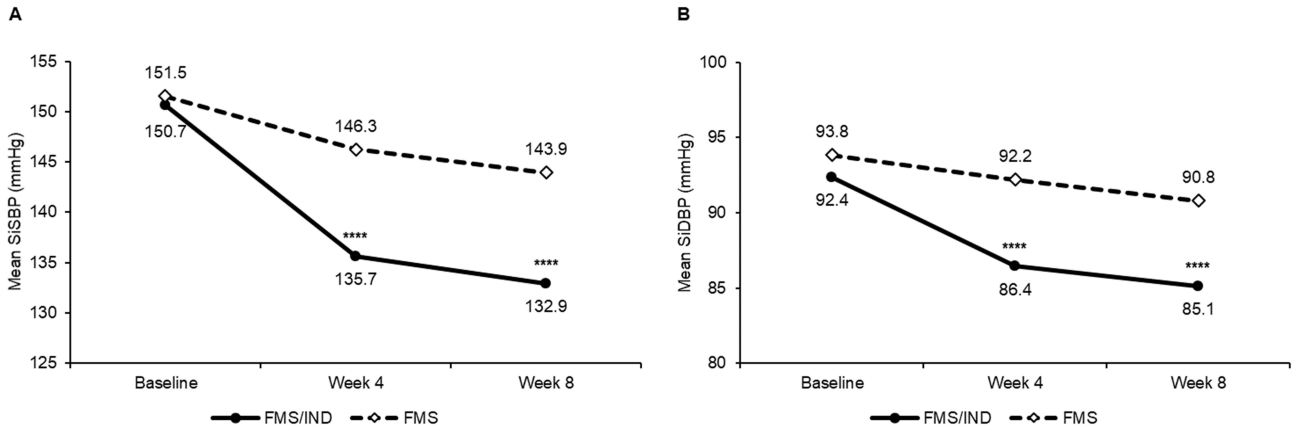

Figure 2 Mean SiSBP (**A**) and SiDBP (**B**) from baseline to week 4 and 8.
Notes: Statistical analyses are performed using analysis of covariance (ANCOVA) with baseline values as covariates to compare changes between treatment groups at each time point. The number of participants is n = 124 for the FMS/IND group and n = 117 for the FMS group. The FMS/IND group is represented by filled circles (●), and the FMS group is represented by open diamonds (◇). Statistical significance is indicated as follows: ****P < 0.0001.
Abbreviations: FMS, fimasartan; IND, indapamide sustained release; SiSBP, sitting systolic blood pressure; SiDBP, sitting diastolic blood pressure.

The BP control rates and response rates at week 4 and 8 in the FMS/IND SR and the FMS are shown in Figure 3. These rates of the FMS/IND SR were significantly higher than those of the FMS, both at week 4 and 8. Similar results were confirmed in terms of BP control rates according to target BP values of < 140/90 and < 130/80 mmHg regardless of comorbidities (Figure 4).

Additionally, results of all subgroup analyses of the primary endpoint were consistent with those in the overall study population including patients aged 65 and older (Table 3 and Figure 5).

Safety and Tolerability

Among 244 patients in the safety set, 15.98% of patients experienced at least one TEAE (Table 4). The incidence of TEAEs was 17.74% in the FMS/IND SR and 14.17% in the FMS ($P = 0.4461$). The most frequently reported TEAE was dizziness (4.10%), followed by postural dizziness (1.64%), headache (1.23%) and hypokalemia (0.82%). Hyponatremia, although not among the most frequently reported TEAEs, was observed in only one patient in the FMS/IND SR. There was also no

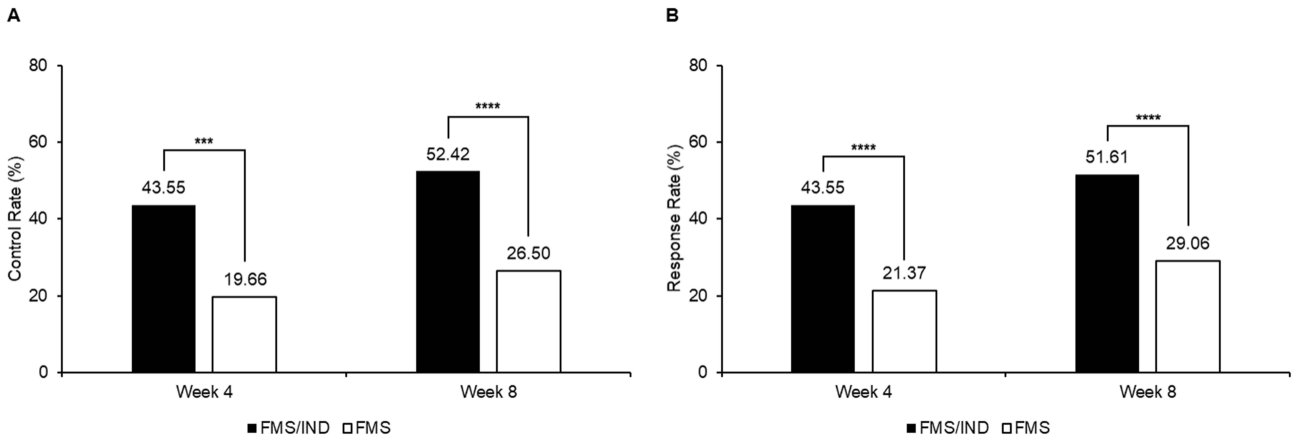

Figure 3 Blood pressure control rates (**A**) and response rates (**B**) from baseline to week 4 and 8.
Notes: The control rate is defined as SiSBP < 140 mmHg and SiDBP < 90 mmHg (SiSBP < 130 mmHg and SiDBP < 80 mmHg for the patients with CVD, DM, CKD with albuminuria). The response rate is defined as a fall in SiSBP ≥ 20mmHg or SiDBP ≥ 10mmHg. Data are presented as the proportion (%) of participants achieving the target at week 4 and 8. The number of participants is n = 124 for the FMS/IND group and n = 117 for the FMS group. Testing for between treatment groups: Logistic regression model with treatment group as a factor and baseline value as covariates at each time point. Statistical significance is indicated as follows: ***P < 0.001, ****P < 0.0001.
Abbreviations: CKD, Chronic Kidney Disease; CVD, cardiovascular disease; DM, Diabetes Mellitus; FMS, fimasartan; IND, indapamide sustained release; SiSBP, sitting systolic blood pressure; SiDBP, sitting diastolic blood pressure.

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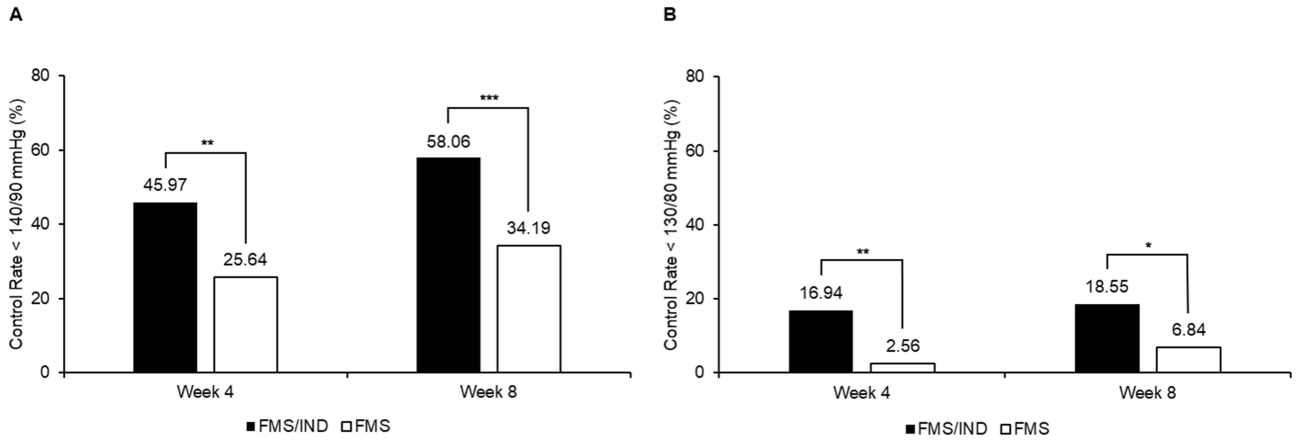

Figure 4 Blood pressure control rates < 140/90 mmHg (**A**) and control rates < 130/80 mmHg (**B**) regardless of comorbidities from baseline to week 4 and 8.
Notes: The control rate is defined, regardless of comorbidities, as SiSBP < 140 mmHg and SiDBP < 90 mmHg for Graph A, and SiSBP < 130 mmHg and SiDBP < 80 mmHg for Graph B. Data are presented as the proportion (%) of participants achieving the target at week 4 and 8. The number of participants is n = 124 for the FMS/IND group and n = 117 for the FMS group. Testing for between treatment groups: Logistic regression model with treatment group as a factor and baseline value as covariates at each time point. Statistical significance is indicated as follows: *P < 0.05, **P < 0.01, ***P < 0.001.
Abbreviations: FMS, fimasartan; IND, indapamide sustained release; SiSBP, sitting systolic blood pressure; SiDBP, sitting diastolic blood pressure.

significant difference in each incidence of all TEAEs between the two groups. One patient in the FMS/IND SR experienced mechanical ileus, which was not related to the study drug. Furthermore, 9.02% of patients experienced at least one ADR. There was no statistically significant difference in ADRs between the two groups. No serious ADR was reported during the study period. Differences in the study drug discontinuation due to TEAEs and ADRs were not significant between groups. Subgroup analysis of patients aged 65 and older showed no statistically significant differences in TEAEs and ADRs between groups and similar results were observed in the patients under 65 years old (Table 5).

Additionally, both groups' laboratory test results for renal function and electrolyte levels exhibited only slight variations and stayed within the typical reference limits (Table 6).

Table 3 Change in SiSBP From Baseline to week 8 According to Subgroup Analyses (Full Analysis Set)

Subgroup[a]	FMS/IND			FMS			LS Mean Difference[b] (95% CI) vs FMS
	N	Baseline (Week 0)	At Week 8	N	Baseline (Week 0)	At Week 8	
Overall	124	150.7 (10.5)	133.0 (14.9)	117	151.5 (11.1)	144.0 (17.9)	−10.5 (−14.4 to −6.6)
Age Group (years)							
<65	66	149.7 (9.1)	131.3 (14.1)	55	150.3 (10.5)	141.6 (16.0)	−10.1 (−15.4 to −4.8)
≥65	58	151.7 (12.0)	134.9 (15.6)	62	152.6 (11.6)	146.0 (19.3)	−10.6 (−16.4 to −4.8)
Sex							
Male	86	149.8 (9.5)	134.4 (15.4)	81	150.8 (9.7)	145.7 (17.9)	−10.7 (−15.5 to −6.0)
Female	38	152.5 (12.5)	129.7 (13.0)	36	153.1 (13.6)	139.9 (17.6)	−9.9 (−16.5 to −3.3)
BMI[c] (kg/m^2)							
<25	44	151.4 (11.1)	133.3 (16.3)	46	150.2 (11.2)	143.6 (18.1)	−11.0 (−17.7 to −4.4)
≥25	80	150.3 (10.3)	132.7 (14.1)	71	152.4 (11.0)	144.2 (17.9)	−10.4 (−15.3 to −5.5)
Drinking status							
Current non-drinker	46	151.7 (11.6)	130.4 (14.3)	46	153.6 (12.1)	144.7 (19.4)	−13.4 (−20.2 to −6.6)
Current drinker	78	150.0 (9.9)	134.4 (15.0)	71	150.1 (10.2)	143.4 (17.0)	−9.0 (−13.7 to −4.2)
Smoking status							
Non-smoker	61	151.5 (11.6)	131.5 (14.5)	59	151.8 (11.6)	141.8 (19.5)	−10.1 (−15.9 to −4.4)
Current smoker	24	150.7 (8.5)	133.9 (17.2)	21	151.5 (10.3)	146.0 (15.3)	−12.1 (−22.1 to −2.1)
Ex-smoker	39	149.3 (10.1)	134.6 (14.0)	37	151.2 (11.0)	146.2 (16.5)	−10.3 (−16.6 to −4.0)

(*Continued*)

Table 3 (Continued).

Subgroup[a]	FMS/IND			FMS			LS Mean Difference[b] (95% CI) vs FMS
	N	Baseline (Week 0)	At Week 8	N	Baseline (Week 0)	At Week 8	
Duration of essential hypertension (years)							
<5	55	149.5 (9.5)	131.3 (14.8)	48	149.3 (10.5)	141.3 (16.0)	−10.0 (−15.8 to −4.3)
≥5, <10	17	149.3 (11.9)	130.0 (18.7)	23	153.2 (11.3)	144.9 (17.2)	−11.9 (−22.2 to −1.6)
≥10	52	152.3 (11.1)	135.6 (13.3)	46	153.0 (11.5)	146.3 (20.0)	−10.3 (−16.8 to −3.9)
SBP at baseline (mmHg)							
<147	61	142.0 (3.8)	129.4 (13.8)	55	142.5 (3.6)	136.5 (14.5)	−6.8 (−12.0 to −1.6)
≥147	63	159.0 (7.9)	136.4 (15.1)	62	159.5 (9.2)	150.6 (18.1)	−14.0 (−19.8 to −8.2)
DBP at baseline (mmHg)							
<93	64	148.7 (10.7)	133.7 (15.6)	53	148.1 (9.8)	142.3 (15.3)	−8.9 (−14.1 to −3.7)
≥93	60	152.7 (10.0)	132.1 (14.1)	64	154.3 (11.4)	145.3 (19.8)	−12.5 (−18.4 to −6.5)
Diabetes mellitus							
Yes	29	153.7 (10.7)	138.7 (15.3)	27	150.6 (11.8)	140.9 (19.6)	−3.7 (−12.8 to 5.4)
No	95	149.7 (10.4)	131.2 (14.3)	90	151.8 (10.9)	144.8 (17.4)	−12.5 (−16.9 to −8.2)
Dyslipidemia							
Yes	73	150.7 (11.6)	132.1 (14.2)	73	150.1 (11.0)	141.2 (16.8)	−9.3 (−14.1 to −4.4)
No	51	150.6 (8.9)	134.1 (15.8)	44	153.9 (11.0)	148.6 (19.0)	−12.2 (−18.9 to −5.6)
Chronic kidney disease							
Yes	63	152.0 (11.7)	134.6 (15.1)	57	151.4 (11.1)	144.9 (19.4)	−10.7 (−16.6 to −4.7)
No	61	149.2 (9.1)	131.3 (14.5)	60	151.7 (11.1)	143.0 (16.5)	−10.4 (−15.7 to −5.1)
Coronary artery disease							
Yes	22	151.0 (12.0)	132.1 (11.3)	20	146.1 (11.0)	142.2 (14.8)	−11.7 (−19.7 to −3.7)
No	102	150.6 (10.3)	133.1 (15.6)	97	152.6 (10.8)	144.3 (18.5)	−10.0 (−14.5 to −5.5)

Notes: Values are presented as the mean (SD). [a]No significant interaction effects were observed for subgroups of baseline factor. [b]Testing for difference between treatment groups (ANCOVA model with baseline SiSBP as a covariate). [c]BMI (kg/m²) = weight (kg) / (height (cm) / 100)².

Abbreviations: SiSBP, sitting systolic blood pressure; FMS, fimasartan; IND, indapamide sustained release; LS, least square; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; ANCOVA, analysis of covariance.

Discussion

This trial demonstrated that combination therapy with FMS and IND SR was significantly more effective than FMS monotherapy in lowering BP among patients with essential hypertension inadequately controlled with FMS 30 mg. The combination therapy resulted in greater reductions in both SiSBP and SiDBP as early as week 4, with this effect persisting through week 8, without compromising safety.

At week 8, the LS mean reduction in SiSBP was −17.9 mmHg in the FMS/IND SR and −7.4 mmHg in the FMS, yielding an LS mean difference of −10.5 mmHg. Moreover, the BP control rates and response rates were approximately twice as high in the combination group. Notably, the FMS 30 mg/IND SR 1.5 mg combination achieved more rapid BP reduction at week 4 than FMS 60 mg monotherapy achieved by week 8, underscoring the clinical advantage of early combination therapy. These findings are consistent with previous studies demonstrating that low- to standard-dose dual combination therapy is more effective than standard-dose monotherapy in reducing BP, without increasing the rate of discontinuation due to AEs.[39]

IND, a thiazide-like diuretic, has been shown to exert a longer duration of action and a more potent BP-lowering effect than HCTZ, and its efficacy is comparable to that of chlorthalidone.[11,12,21] However, prior studies have associated both chlorthalidone and the IR formulation of IND with a higher incidence of electrolyte disturbances, including

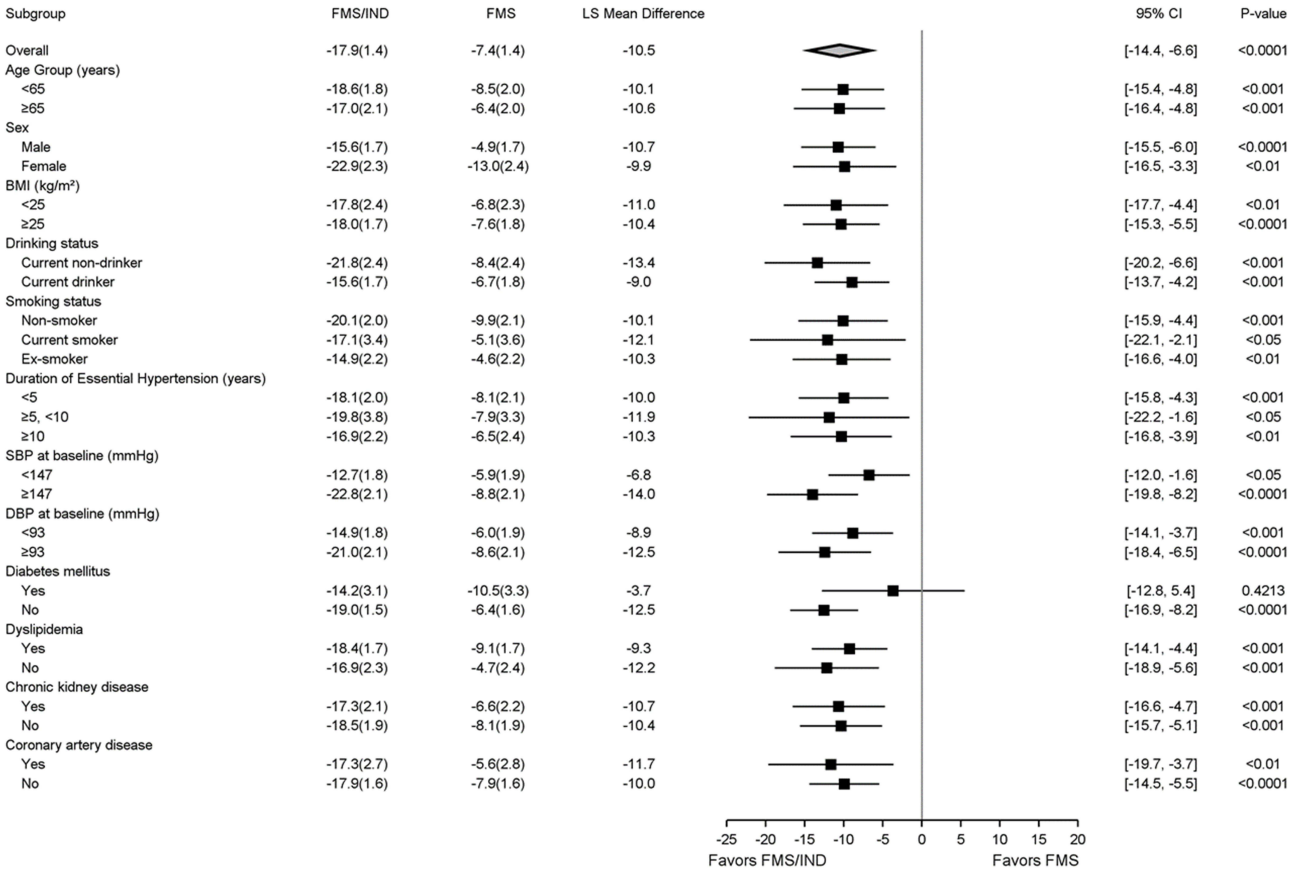

Figure 5 Forest plot of subgroup analyses for comparison of FMS/IND combination therapy and FMS monotherapy of the changes in SiSBP from baseline to week 8.
Note: Values are presented as the LS mean change (SE).
Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; FMS, fimasartan; IND, indapamide sustained release; LS, least square; SBP, systolic blood pressure; SE, standard error; SiSBP, sitting systolic blood pressure.

hypokalemia and hyponatremia.[13,22] In this context, the present findings suggest that the FMS/IND SR combination may successfully balance efficacy and safety. IND promotes natriuresis and reduces plasma volume, while FMS counteracts diuretic-induced RAAS activation and mitigates associated hypokalemia.[9,20] Furthermore, the SR formulation of IND

Table 4 Summary of TEAEs and ADRs

Variable	FMS/IND (N=124)	FMS (N=120)	P-value[a]
Patients with TEAEs	22 (17.74)	17 (14.17)	0.4461
Severity			
Mild	26	22	
Moderate	4	1	
Severe	0	0	
Patients with TEAEs leading to drug discontinuation	6 (4.84)	2 (1.67)	0.2814
Patients with serious TEAEs[b]	1 (0.81)	0 (0.00)	1.0000
Incidence of TEAEs ≥ 1% in each treatment group			
Dizziness	7 (5.65)	3 (2.50)	0.3341
Dizziness postural	4 (3.23)	0 (0.00)	0.1221
Headache	1 (0.81)	2 (1.67)	0.6173
Hypokalemia	2 (1.61)	0 (0.00)	0.4981

(*Continued*)

Table 4 (Continued).

Variable	FMS/IND (N=124)	FMS (N=120)	P-value[a]
Patients with ADRs	15 (12.10)	7 (5.83)	0.0877
Patients with ADRs leading to drug discontinuation	4 (3.23)	1 (0.83)	0.3702
Patients with serious ADRs	0 (0.00)	0 (0.00)	-

Notes: Severity is displayed as "number of events" and others are displayed as "number of participants (percentage of participants)". [a]Testing for difference between treatment groups (chi-square test or Fisher's exact test). [b]A serious TEAE that occurred in the FMS/IND was mechanical ileus. Causal relationship was assessed as "not related" by an investigator.
Abbreviations: TEAEs, treatment-emergent adverse events; ADRs, adverse drug reactions; FMS, fimasartan; IND, indapamide sustained release.

Table 5 Summary of TEAEs and ADRs by Age

Subgroup (Years)	Age Group ≥ 65			Age Group < 65		
Variable	**FMS/IND (N=58)**	**FMS (N=63)**	**P-value[a]**	**FMS/IND (N=66)**	**FMS (N=57)**	**P-value[a]**
Patients with TEAEs	12 (20.69)	6 (9.52)	0.0847	10 (15.15)	11 (19.30)	0.5422
Severity						
Mild	17	7		9	15	
Moderate	1	0		3	1	
Severe	0	0		0	0	
Patients with TEAEs leading to drug discontinuation	3 (5.17)	1 (1.59)	0.3489	3 (4.55)	1 (1.75)	0.6229
Patients with serious TEAEs	0 (0.00)	0 (0.00)	-	1 (1.52)	0 (0.00)	1.0000
Incidence of TEAEs ≥ 2% in each treatment group						
Dizziness	6 (10.34)	3 (4.76)	0.3088	1 (1.52)	0 (0.00)	1.0000
Dizziness postural	2 (3.45)	0 (0.00)	0.2277	2 (3.03)	0 (0.00)	0.4986
Headache	0 (0.00)	0 (0.00)	-	1 (1.52)	2 (3.51)	0.5960
Hypokalemia	0 (0.00)	0 (0.00)	-	2 (3.03)	0 (0.00)	0.4986
Patients with ADRs	8 (13.79)	3 (4.76)	0.0843	7 (10.61)	4 (7.02)	0.4868
Patients with ADRs leading to drug discontinuation	2 (3.45)	0 (0.00)	0.2277	2 (3.03)	1 (1.75)	1.0000
Patients with serious ADRs	0 (0.00)	0 (0.00)	-	0 (0.00)	0 (0.00)	-

Notes: Severity is displayed as "number of events" and others are displayed as "number of participants (percentage of participants)". [a]Testing for difference between-treatment groups (chi-square test or Fisher's exact test).
Abbreviations: TEAEs, treatment-emergent adverse events; ADRs, adverse drug reactions; FMS, fimasartan; IND, indapamide sustained release.

Table 6 Changes in Laboratory Tests Values of Renal Function and Electrolyte From Baseline to week 8

Variable	FMS/IND (N=124)	FMS (N=120)	P-value[a]
Serum creatinine, mg/dL			
Baseline	0.86 (0.18)	0.87 (0.21)	
Week 8	0.94 (0.44)	0.87 (0.18)	
Change from baseline to week 8	0.08 (0.39)	0.00 (0.08)	0.0013
P-value[b]	< 0.0001	0.4420	
Serum uric acid, mg/dL			
Baseline	5.53 (1.37)	6.03 (1.62)	
Week 8	6.23 (1.75)	5.93 (1.45)	
Change from baseline to week 8	0.73 (0.99)	−0.09 (0.94)	< 0.0001
P-value[b]	< 0.0001	0.7557	

(*Continued*)

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Table 6 (Continued).

Variable	FMS/IND (N=124)	FMS (N=120)	P-value[a]
Serum sodium, mmol/L			
Baseline	139.80 (2.34)	140.10 (2.08)	
Week 8	139.18 (2.32)	139.90 (1.94)	
Change from baseline to week 8	−0.72 (2.18)	−0.29 (1.85)	0.0754
P-value[b]	0.0003	0.0735	
Serum potassium, mmol/L			
Baseline	4.41 (0.39)	4.40 (0.36)	
Week 8	4.30 (0.39)	4.39 (0.37)	
Change from baseline to week 8	−0.12 (0.38)	−0.01 (0.38)	0.0380
P-value[b]	0.0013	0.7522	
eGFR[c], mL/min/1.73m^2			
Baseline	87.78 (16.44)	87.91 (15.28)	
Week 8	84.41 (17.48)	86.99 (14.61)	
Change from baseline to week 8	−3.53 (7.92)	−0.59 (6.41)	0.0050
P-value[b]	< 0.0001	0.3271	

Notes: Values are presented as the mean (SD). Baseline is the last observed value prior to the first dose of study intervention. [a]Testing for difference between treatment groups (two sample *t*-test or Wilcoxon rank sum test). [b]Testing for change within group (paired *t*-test or Wilcoxon signed rank test). [c]eGFR was calculated using the CKD-EPI equation.

Abbreviations: FMS, fimasartan; IND, indapamide sustained release; eGFR, estimated glomerular filtration rate; SD, standard deviation.

was specifically designed to achieve more stable plasma concentrations and reduce peak-related metabolic AEs.[29] Consistent with this rationale, the present trial showed that FMS/IND SR produced greater BP reduction than FMS monotherapy, with a comparable tolerability profile over 8 weeks.

Importantly, nearly half of the study population consisted of patients aged 65 years or older. Subgroup analyses revealed that both the antihypertensive efficacy and safety profile of FMS/IND SR were consistent in this older cohort. Although elderly patients with hypertension are at increased risk for electrolyte abnormalities such as hypokalemia,[40] no such TEAEs were observed in this subgroup. Furthermore, intensive BP reduction and antihypertensive therapy are frequently associated with dizziness in older adults.[41–43] Despite the greater BP reduction observed in the combination group, the incidence of dizziness did not differ significantly between groups, reinforcing the favorable tolerability of this regimen in elderly populations. These findings align with previous study, which demonstrated that IND SR is both effective and well-tolerated in older adults.[24] Taken together, these results support the use of FMS/IND SR as a particularly suitable option in elderly patients with salt-sensitive hypertension. Beyond age, the efficacy of the FMS/IND SR combination in reducing SiSBP was consistently observed across all other subgroups, regardless of baseline characteristics. This suggests that FMS/IND SR may be a broadly effective therapeutic option for patients whose BP is inadequately controlled with FMS monotherapy.

Given its favorable efficacy and safety profile, IND SR may represent a promising alternative to conventional diuretic components in ARB-based combination therapies. In line with current hypertension guidelines that increasingly advocate early combination therapy, this trial provides important clinical evidence supporting ARB-thiazide-like diuretic combinations. Unlike hydrochlorothiazide, indapamide SR offers stable pharmacokinetics and lower metabolic risk, while maintaining potent antihypertensive efficacy. The superior efficacy and favorable tolerability of FMS/IND SR in this trial, including elderly patients at high risk for electrolyte abnormalities, highlight its potential as a novel and clinically relevant alternative to conventional ARB-diuretic regimens. In addition, both agents have individually demonstrated cardiovascular and renal protective benefits in high-risk populations.[29–32,44–50] Therefore, these data support the potential of the FMS/IND SR combination as a comprehensive treatment strategy for hypertension in high-risk individuals. Further long-term studies are warranted to evaluate its impact on cardiovascular and renal outcomes in this population.

There are some limitations in this study. First, although the 8-week treatment period was sufficient to assess short-term antihypertensive efficacy and early tolerability, it was not long enough to evaluate long-term safety, metabolic effects, renal outcomes, or cardiovascular endpoints. Accordingly, the present findings should be interpreted as evidence of short-term efficacy and tolerability rather than long-term clinical effectiveness. Second, the sample size was relatively small, which may have limited the ability to fully characterize the tolerability profile and detect uncommon AEs. Third, no direct comparison with other established ARB–diuretic combinations was performed; therefore, the present results should not be interpreted as demonstrating comparative clinical effectiveness versus HCTZ- or chlorthalidone-based regimens. Lastly, all participants were Koreans thus the generalization of the results to patients outside of this population would be difficult.

Conclusion

The FINEDUO study was the first clinical trial to evaluate the BP-lowering efficacy and tolerability of FMS/IND SR combination therapy in patients with essential hypertension inadequately controlled with FMS monotherapy. The combination regimen demonstrated superior antihypertensive efficacy in this population, with a safety profile comparable to that of FMS monotherapy. Notably, FMS/IND SR maintained robust BP-lowering effects while minimizing AEs such as electrolyte disturbances, even in elderly patients at elevated risk for metabolic complications. These findings support FMS/IND SR as an effective treatment option in patients with essential hypertension inadequately controlled with FMS monotherapy. Further longer-term and head-to-head studies are needed to define its safety and comparative clinical effectiveness relative to other ARB–diuretic regimens.

Abbreviations

ADR, adverse drug reaction; AE, adverse event; ANCOVA, analysis of covariance; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EOS, end of study; FAS, full analysis set; FMS, fimasartan; FINEDUO, FImasartan-INdapamide Effective DUO; HCTZ, hydrochlorothiazide; IND, indapamide; IR, immediate release; LOCF, last observation carried forward; LS, least square; PPS, per-protocol set; RAAS, renin-angiotensin-aldosterone system; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SR, sustained release; TEAE, treatment emergent adverse event.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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