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Original Research

Efficacy and Safety of Combination Therapy With Low Dose of Telmisartan and S-Amlodipine in Patients With Hypertension: A Randomized, Double-Blind, Multicenter, Therapeutic Confirmatory, Phase III Clinical Trial

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ABSTRACT

Purpose: This randomized, double-blind, multicenter, phase III clinical trial aimed to evaluate the efficacy and safety of telmisartan 20 mg and s-amlodipine 1.25 mg, a fixed-dose combination (Tel/S-Amlo) versus telmisartan 20 mg single therapy or s-amlodipine 1.25 mg single therapy for initial treatment in patients with hypertension.
Methods: After a wash-out/therapeutic lifestyle change period of ≥4 weeks, a total of 235 eligible patients were randomized and received 1 of 3 treatments for 8 weeks: (1) telmisartan 20 mg/s-amlodipine 1.25 mg (Tel/S-Amlo), (2) telmisartan 20 mg (Tel), or (3) S-amlodipine 1.25 mg (S-Amlo). The primary endpoint was the efficacy

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evaluation of Tel/S-Amlo by comparing changes in mean sitting systolic blood pressure (msSBP) from baseline after 8 weeks of treatment.

Findings: At 8 weeks, the least square (LS) mean (SE) change in msSBP was −20.04 (1.46) mm Hg in the Tel/S-Amlo group, compared with –16.44 (1.46) mm Hg in the Tel group (between-group difference –3.60 (1.78) mm Hg, *P*-value = 0.0451). Similarly, the Tel/S-Amlo group showed a change of −21.12 (1.33) mm Hg versus −15.58 (1.32) mm Hg in the S-Amlo group (between-group difference –5.53 (1.61) mm Hg, *P*-value = 0.0008). There were no statistically significant differences in the incidence of overall AEs and adverse drug reactions among the 3 groups, and no serious adverse events occurred during the study.

Implications: Combination therapy with a low-dose of telmisartan and s-amlodipine may be a promising initial treatment for patients with hypertension.

Clinical trial registration: This study was registered in ClinicalTrials.gov (NCT06121518).

Introduction

Raised blood pressure is a leading cause of death globally and is the most common risk factor for development of hypertensive heart disease.[1,2] Consequently, hypertension remains a significant public health concern, contributing to the onset of cardiovascular diseases, stroke, and premature death. Despite its prevalence, hypertension is often underdiagnosed and undertreated. According to the WHO global report on hypertension, only 54% of hypertensive adults are diagnosed, 42% receive treatment, and a mere 21% achieve adequate control of their hypertension. These findings highlight the substantial gaps in hypertension management and underscore the urgent need for more effective strategies for diagnosis and treatment of hypertension.

A critical initial step in hypertension management and preventing complications is early diagnosis and early, effective treatment.[3] Pharmacological therapy for hypertension should be initiated as early as possible following diagnosis. In individuals with markedly elevated blood pressure or evidence of end-organ damage, immediate initiation of treatment is strongly recommended.[4]

More than 70% of adults undergoing treatment for primary hypertension will eventually require at least 2 anti-hypertensive agents. Combination drugs from different drug classes can produce a synergistic effect in lowering blood pressure, thereby enhancing treatment efficacy and providing a more effective strategy for preventing hypertension-related complications. Additionally, the use of drugs with distinct mechanisms of action may mitigate the potential side effects associated with each individual BP-lowering agent. These benefits of combination therapy have led to the development and widespread use of single-pill combinations (SPCs), which improve persistence in BP-lowering treatment and are associated with lower all-cause mortality, by increasing adherence.[1,5,6] According to European Society of Cardiology (ESC) guideline, for most patients with hypertension, a single-pill combination, initially containing 2 of these major drug classes, and initially at low dose, is recommended: angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), thiazide diuretics, calcium channel blockers.[6]

Various SPCs have been developed and are currently in use, demonstrating improved patient adherence due to their simplified dosing regimens.[5,6] Although a variety of SPCs are available, they are typically prescribed only when monotherapy fails to achieve adequate blood pressure control. As a result, the use of combination therapy remains limited among patients who are newly diagnosed with hypertension and initiating pharmacological treatment. In general, combination therapy (or SPCs) demonstrates greater efficacy compared to each monotherapy.

Therefore, this study specifically investigated the lowest approved doses of telmisartan and s-amlodipine to determine whether an initial low-dose fixed combination could achieve effective BP reduction with improved tolerability. This would address the unmet need of initiating therapy in newly diagnosed or mildly hypertensive patients who may be prone to adverse effects at higher doses. To our knowledge, this is the first randomized phase III confirmatory trial evaluating this specific low-dose combination, thus providing new clinical evidence.

Notably, there is no commercially available SPC formulation combining telmisartan 20 mg and s-amlodipine 1.25 mg, the lowest recommended doses for each component according to their respective labeling.[7,8] Such a formulation could offer an effective, well-tolerated initial therapy option for hypertensive patients.

The aim of this study was to compare and evaluate the efficacy of the BP control effect and safety of combination therapy with telmisartan 20 mg and s-amlodipine 1.25 mg (Tel/S-Amlo) versus telmisartan 20 mg single therapy (Tel) or s-amlodipine 1.25 mg single therapy (S-Amlo) in hypertensive patients.

Participants and Methods

Study Population

Adult patients aged over 19 years who met the following criteria were included: (1) Mean sitting SBP (msSBP) ≥ 140 mm Hg and < 180 mm Hg at screening (subjects who took antihypertensive drugs: msSBP ≥ 130 mm Hg and < 180 mm Hg) (2) msSBP ≥ 140 mm Hg and < 180 mm Hg, and mean sitting diastolic blood pressure (msDBP) < 110 mm Hg after a ≥4-week wash-out/therapeutic lifestyle change (TLC) period. Patients with msSBP ≥ 180 mm Hg or msDBP ≥ 110 mm Hg at screening, or a BP difference between both arms of msSBP ≥ 20 mm Hg or msDBP ≥ 10 mm Hg were excluded from the study. Patients with secondary hypertension, type 1 diabetes, or uncontrolled diabetes (HbA1c > 9.0%) were also excluded.

Study Design

This study was a randomized, double-blind, multicenter, therapeutic confirmatory, phase III clinical trial. The enrollment of subjects was conducted at 26 nationwide sites in the Republic of Korea from July 2023 to March 2024. This study was conducted by the International Conference on Harmonization of Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. Additionally, the Institutional Review Boards (IRBs) of each participating center approved the study protocol. This study was registered with ClinicalTrials.gov (NCT06121518).

Study Procedure

The study design is presented in Figure 1. This study consists of screening and placebo run-in period, and administration period. Eligible subjects at screening were instructed to follow at least 4 weeks of wash-out/therapeutic lifestyle change (TLC) before randomization. All anti-hypertension medications were prohibited for at least 4 weeks. Subjects received education on lifestyle change and underwent diet and exercise therapy for at least 4 weeks. Subjects maintained TLC during the treatment period.

At randomization, subjects who met the inclusion/exclusion criteria were 1:1:1 randomly assigned to either the Tel/S-Amlo, Tel, or S-Amlo groups within strata and were treated for 8 weeks. All subjects received 3 investigational drugs, including a placebo to maintain double-blinding. The Tel/S-Amlo group received 2 active tablets, telmisartan 20 mg and

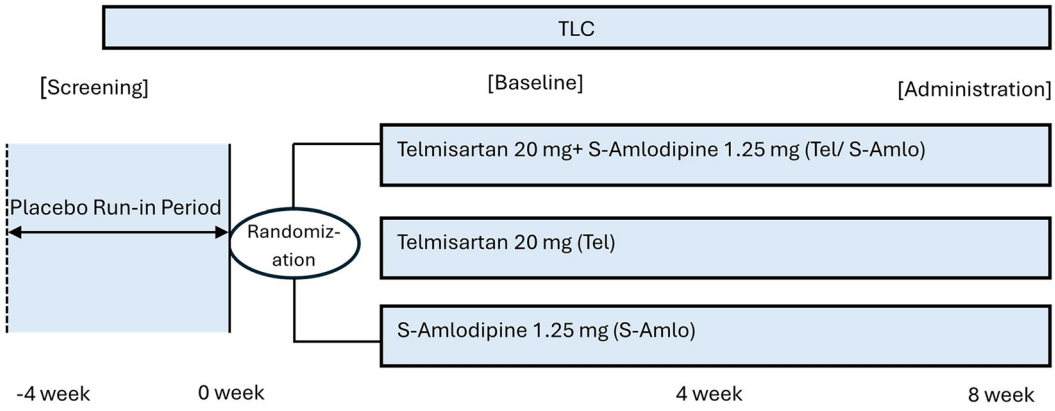


Figure 1. Study design.

s-amlodipine 1.25 mg. The Tel group received 1 active tablet, telmisartan 20 mg, and 1 placebo tablet of s-amlodipine. The S-Amlo group received 1 active tablet, s-amlodipine 1.25 mg and 1 placebo tablet for telmisartan. The placebo tablets had the same appearance as each active tablet.

During the clinical trial period, all subjects were guided to take the prescribed investigational drugs once a day, at a fixed time every day, if possible. No dose adjustment was performed during the entire clinical trial period.

Study Outcomes

The primary endpoints were the mean changes in msSBP from baseline to week 8 compared between the Tel/S-Amlo and comparator groups (Tel group and S-Amlo group). The secondary endpoints included (1) the mean changes in msSBP and msDBP from baseline to week 4 and 8, (2) the rate of subject who achieved target BP (msSBP/msDBP < 140/90 mm Hg), and (3) the rate of subject who show response of BP (msSBP reduction ≥ 20 mm Hg and msDBP reduction ≥ 10 mm Hg) at week 8 of treatment compared between the Tel/S-amlo and comparator groups. BP was evaluated after the subject relaxed for at least 5 minutes, using the same arm and sphygmomanometer. BP was measured 3 times, and mean SBP and DBP were calculated from the average of the 3 measurements.

Adverse events (AEs), laboratory tests, concomitant drugs, vital signs, and physical examination were evaluated for safety endpoints.

Statistical Analysis

This study was designed under assumptions that Tel/S-Amlo combination is superior to Tel alone and S-Amlo alone in reducing BP levels. The expected difference in mean change (SD) in BP from baseline between the Tel/S-Amlo and Tel groups was –6.8 mm Hg, and the expected difference in mean change (SD) in BP from baseline between the Tel/S-Amlo and Tel groups was –7.2 mm Hg.[9,10] Sample sizes were calculated for each estimate with 90% power and a 2-sided level set at 5%; the larger number was selected, which was the size to assess the change in BP between Tel/S-amlo and Tel groups. A sample size of 228 patients was produced considering a 7% drop-off rate and the randomization ratio of 1:1:1 (76 patients in each group).

The major analysis set for evaluation of efficacy was full analysis sets (FAS). Changes in BP from baseline were compared between groups and analyzed using an Analysis of Covariance (ANCOVA) model, considering the stratification factors (baseline msSBP). The achievement rate of the BP target and the response rate of the BP were compared between groups using the Cochran-Mantel-Haenszel test, in which the stratification factor (baseline msSBP) was corrected as a covariate. The major analysis set for evaluation of safety was safety analysis set. Between-group comparisons of the adverse events incidence rates were conducted using Pearson's chi-square test. When more than 20% of the cells have an expected frequency less than 5, Fisher's exact test was applied instead. All analyses were 2-sided, and P values < 0.05 were considered statistically significant. The Last Observation Carry Forward (LOCF) method was used to handle missing data. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc, Cary, NC, USA).

Results

Subject Disposition and Baseline Characteristics

A total of 235 subjects were randomized to receive Tel/S-Amlo (n = 78), Tel (n = 78), or S-Amlo (n = 79) therapy (Figure 2), Of 235 subjects, 6 subjects dropped out of the study, and 229 completed treatments. All randomized 235 subjects were analyzed for safety evaluation. For efficacy, 234 subjects were included in the FAS, excluding 1 subject whose BP had not been evaluated during the clinical trial. The demographic and baseline clinical characteristics were similar among all groups (Table 1). No significant differences were observed.

Efficacy

In the FAS, the least square (LS) mean (SE) changes in msSBP from baseline after 8 weeks of treatment were −20.04 (1.46) and −16.44 (1.46) mm Hg in the Tel/S-Amlo and Tel groups, and –21.12 (1.33) and –15.58 (1.32) mm Hg in the Tel/S-Amlo and S-amlo groups, respectively (Table 2). Treatment with Tel/S-amlo resulted in a statistically significant reduction in BP than treatment with both Tel and S-Amlo groups (differences, −3.60 mm Hg [95% CI, −7.13 to −0.08 mm Hg], –5.53 mm Hg [95% CI, –8.72 to –2.35 mm Hg], all P-value < 0.05). The LS mean (SE) change in msDBP from baseline to 8 weeks was –7.54 (0.98) and −6.27 (0.98) mm Hg in Tel/S-amlo and Tel groups, and –8.17 (0.97) and -4.92 (0.95) mm Hg, respectively. Treatment with Tel/S-Amlo resulted in a greater reduction in BP than treatment with both of Tel and S-Amlo groups (differences, –1.27 mm Hg [95% CI, –3.65 to 1.11 mm Hg], –3.24 mm Hg [95% CI, –5.55 to –0.94 mm Hg], P-value = 0.2926, 0.0062).

A higher rate of subjects achieved target BP at week 8 in the Tel/S-Amlo group (54.55%, 42 subjects) compared to both comparator groups (Tel: 46.15%, 36 subjects, S-Amlo: 37.97%, 30 subjects) (Figure 3A). In addition, the response rate was greater at week 8 in the Tel/S-Amlo group (31.17%, 24 subjects) compared to both comparator groups (Tel: 20.51%, 16 subjects, S-Amlo: 13.92%, 11 subjects) (Figure 3B).

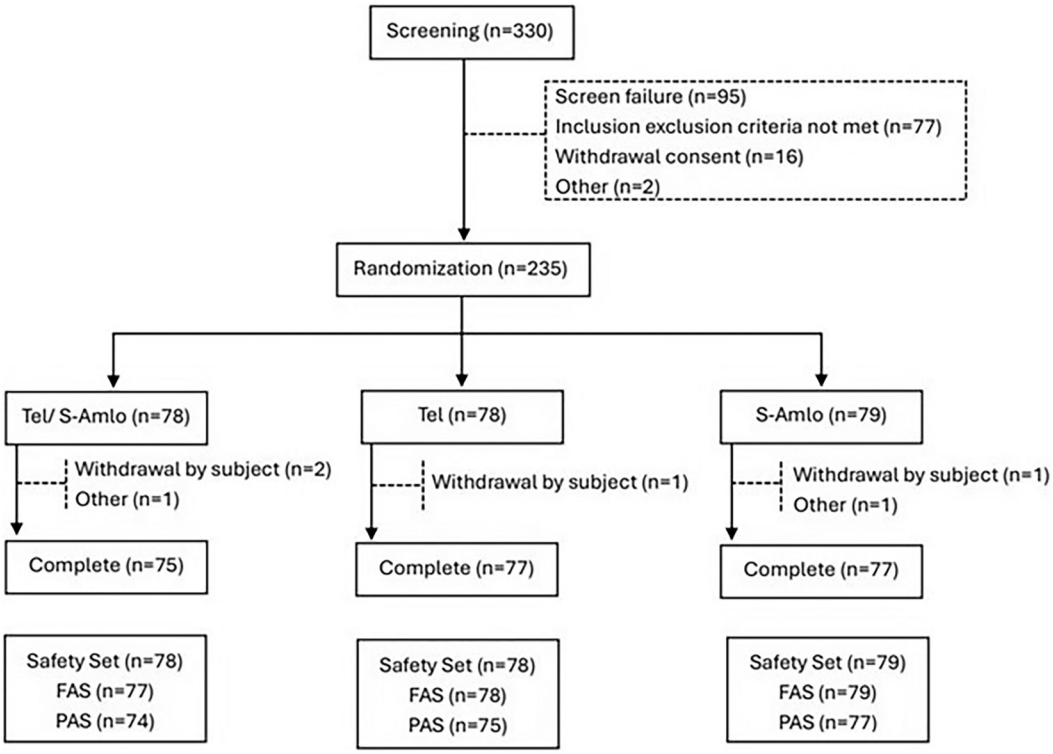


Figure 2. Flowchart describing subject disposition. Tel/S-Amlo: telmisartan 20 mg/S-amlodipine 1.25 mg combination therapy, Tel: telmisartan 20 mg single therapy, S-Amlo: s-amlodipine 1.25 mg single therapy.

Table 1
Demographic.

	Tel/S-Amlo (n = 77)	Tel (n = 78)	S-Amlo (n = 79)	Total (n = 234)
Age(Years)				
Mean (SD)	57.09 (11.80)	57.55 (13.45)	56.15 (13.76)	56.93 (13.00)
P-value*				0.6932[K]
Elderly, n (%)				
<65 years	56 (72.73)	45 (57.69)	49 (62.03)	150 (64.10)
≥65 years	21 (27.27)	33 (42.31)	30 (37.97)	84 (35.90)
P-value†				0.1333[C]
Gender, n (%)				
Male	47 (61.04)	43 (55.13)	45 (56.96)	135 (57.69)
Female	30 (38.96)	35 (44.87)	34 (43.04)	99 (42.31)
P-value[2]				0.7480[C]
Hypertension duration (Years)				
N	77	78	79	234
Mean (SD)	5.76 (6.07)	6.78 (7.70)	5.02 (5.82)	5.85 (6.59)
Median	3.91	3.55	2.78	3.63
Min, Max	0.00, 23.95	0.00, 25.85	0.00, 28.56	0.00, 28.56
P-value*				0.8297[K]
msSBP				
N	77	78	79	234
Mean (SD)	150.25 (8.90)	150.65 (9.03)	151.10 (8.87)	150.67 (8.90)
Median	147.7	147.7	149.3	148
Min, Max	140.00, 175.00	140.00, 179.00	140.30, 176.70	140.00, 179.00
P-value*				0.6939[K]
msDBP				
N	77	78	79	234
Mean (SD)	94.16 (8.36)	91.70 (7.29)	93.07 (8.18)	92.97 (7.99)
Median	94.30	91.70	93.30	93.00
Min, Max	71.70, 109.00	77.00, 108.30	73.30, 107.70	71.70, 109.00
P-value*				0.1579[A]

Tel/S-Amlo: telmisartan 20 mg/S-amlodipine 1.25 mg combination therapy, Tel: telmisartan 20 mg single therapy, S-Amlo: s-amlodipine 1.25 mg single therapy

* Test results for comparisons between treatment groups (Analysis of Variance (A) or Kruskal-Wallis Test (K))

† Test results for comparisons between treatment groups (Chi-square test (C) or Fisher's exact test (F) or Monte Carlo exact test estimate)

Table 2
Mean change of msSBP and msDBP at 4 and 8 weeks of treatment.

		Tel/S-Amlo (n = 77)	Tel (n = 78)	S-Amlo (n = 79)
msSBP				
Baseline	Mean (SD)	150.25 (8.90)	150.65 (9.03)	151.10 (8.87)
Week 4	Mean (SD)	132.70 (12.16)	137.47 (11.34)	139.43 (12.19)
Week 8	Mean (SD)	132.48 (10.75)	136.50 (13.71)	138.91 (11.08)
Change from baseline to week 4	LS-Mean (SE)	–20.06 (1.39)	–15.71 (1.39)	
		–19.88 (1.48)		–14.03 (1.47)
Difference in change between arms at week 4	LS-Mean Diff (SE)		–4.35 (1.70)	–5.85 (1.79)
	[95% CI]*		[–7.70, –1.00]	[–9.39, –2.31]
	P-value†		0.0114	0.0014
Change from baseline to week 8	LS-Mean (SE)	–20.04 (1.46)	–16.44 (1.46)	
		–21.12 (1.33)		–15.58 (1.32)
Difference in change between arms at week 8	LS-Mean Diff (SE)		–3.60 (1.78)	–5.53 (1.61)
	[95% CI]*		[–7.13, –0.08]	[–8.72, –2.35]
	P-value†		0.0451	0.0008
msDBP				
Baseline	Mean (SD)	94.16 (8.36)	91.70 (7.29)	93.07 (8.18)
Week 4	Mean (SD)	85.62 (8.72)	86.63 (8.69)	88.62 (10.08)
Week 8	Mean (SD)	85.39 (9.10)	84.97 (9.32)	87.80 (10.22)
Change from baseline to week 4	LS-Mean (SE)	–7.76 (0.93)	–5.13 (0.92)	
		-8.02 (0.94)		–4.21 (0.93)
Difference in change between arms at week 4	LS-Mean Diff (SE)		-2.63 (1.14)	–3.81 (1.14)
	[95% CI]*		[–4.89, –0.38]	[–6.06, –1.56]
	P-value†		0.0224	0.0010
Change from baseline to week 8	LS-Mean (SE)	–7.54 (0.98)	–6.27 (0.98)	
		–8.17 (0.97)		–4.92 (0.95)
Difference in change between arms at week 8	LS-Mean Diff (SE)		–1.27 (1.20)	–3.24 (1.17)
	[95% CI]*		[–3.65, 1.11]	[–5.55, –0.94]
	P-value†		0.2926	0.0062

Tel/S-Amlo: telmisartan 20 mg/S-amlodipine 1.25 mg combination therapy, Tel: telmisartan 20 mg single therapy, S-Amlo: s-amlodipine 1.25 mg single therapy, msSBP: mean sitting systolic blood pressure, msDBP: mean sitting diastolic blood pressure

* 95% Confidence Interval for the difference in LS-Means between treatment groups

† ANCOVA results for the comparison of LS-Means between treatment groups (Covariate: baseline msSBP (① 140mm Hg ≤ msSBP < 160mm Hg or ② msSBP ≥ 160mm Hg))

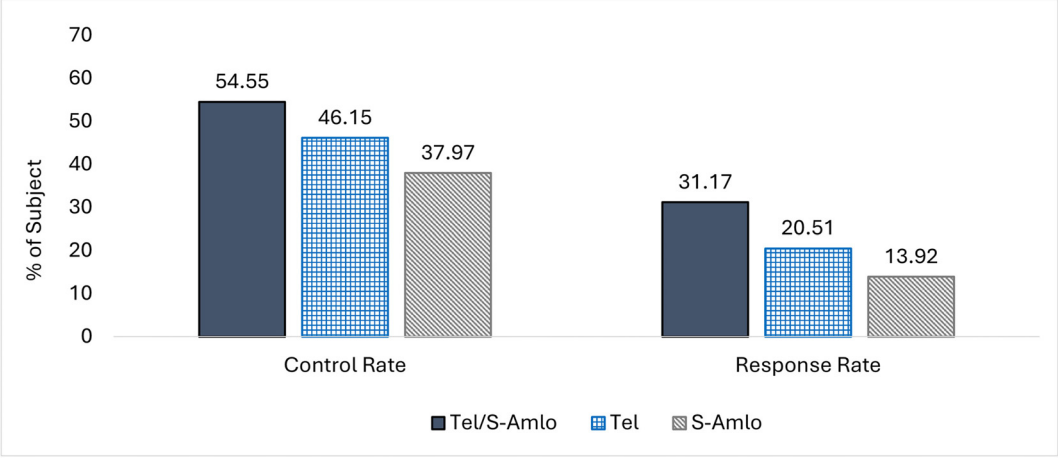


Figure 3. (A) Achievement rate of the BP target (msSBP/msDBP <140/90 mm Hg) at 8 weeks of treatment. (B) Response rate of the BP at 8 weeks or treatment. Tel/S-Amlo: telmisartan 20 mg/S-amlodipine 1.25 mg combination therapy, Tel: telmisartan 20 mg single therapy, S-Amlo: s-amlodipine 1.25 mg single therapy, msSBP: mean sitting systolic blood pressure, msDBP: mean sitting diastolic blood pressure.

Safety

Safety analysis was performed on subjects who took at least one dose of the investigational drug. Among the 235 subjects in the safety analysis set, 18 subjects (7.66%) experienced 22 treatment-emergent adverse events (TEAE). In the Tel/S-Amlo group, 9 subjects (11.54%, 10 cases) were reported, 5 (6.41%, 7 cases) in the Tel group and 4 (5.06%, 5 cases) in the S-Amlo group. There was no significant difference among the 3 groups (*P*-value = 0.2747). Most of the 22 cases were mild in severity (20 mild and 2 moderate). The moderate AEs were "Nasopharyngitis" and "Blood uric acid increased" in S-Amlo group. Only 3 subjects (1.28%) experienced 3 ADRs after treatment (Table 3). In the Tel/S-amlo group, 2 subjects (2.56%, 2 cases) were reported, 1 (1.28%, 1 case) in the Tel group, and there was no ADR in the S-Amlo group. There was no significant difference among the 3 groups (*P*-value = 0.3277). All AEs were reported only once, and no AE occurred more than twice. The reported ADRs were "Cholestasis" and "Dizziness" in Tel/S-Amlo group, and "Petechiae" in Tel group. "Cholestasis" and "Dizziness" reported in Tel/S-Amlo group have already been identified as AE associated with previously approved telmisartan and amlodipine. There was

Table 3
Summary of adverse events.

	Tel/S-Amlo (n = 78) n (%) [case]	Tel (n = 78) n (%) [case]	S-Amlo (n = 79) n (%) [case]	*p*-value*
Adverse event (AE)	9 (11.54) [10]	5 (6.41) [7]	4 (5.06) [5]	0.2747[C]
Adverse drug reaction (ADR)	2 (2.56) [2]	1 (1.28) [1]	-	0.3277[F]
Cholestasis	1 (1.28) [1]	-	-	0.6638[F]
Dizziness	-	1 (1.28) [1]	-	0.6638[F]
Petechiae	1 (1.28) [1]	-	-	0.6638[F]
Serious adverse event (SAE)	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	-
Adverse events leading to study drug discontinuation	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	-

* Chi-square test (C) or Fisher's exact test (F) for comparison of between treatment groups.

no serious AE and AE which induced discontinuation of investigational product.

Discussion

This was a randomized, double-blind, multicenter, therapeutic confirmatory, phase III study designed to confirm the efficacy and safety of low-dose combination therapy with telmisartan and s-amlodipine in patients with hypertension. The LS mean (SE) change in msSBP from baseline to 8 weeks of treatment were significantly decreased in the Tel/S-Amlo group compared to the Tel and S-Amlo groups, respectively. Furthermore, the control rate and response rate of BP were also greater than in Tel and S-Amlo groups during the 8-week follow-up.

In the present study, the Tel/S-Amlo group demonstrated LS mean change in msSBP from baseline of approximately −20 mm Hg after 8 weeks of treatment. A 20 mm Hg reduction in systolic blood pressure (SBP) is clinically significant, correlating with approximately a 40% lower cardiovascular disease (CVD) risk.[11,12]

Although direct head-to-head comparisons present methodological challenges, this LS mean reduction in msSBP observed in the present study (approximately –20 mm Hg) was greater than the LS mean reductions reported with standard-dose monotherapy of either telmisartan (–15.4 mm Hg) or amlodipine (–14.8 mm Hg), and even high-dose telmisartan monotherapy (–15.4 mm Hg) in previous study.[13] In addition to the present study, another non-inferiority trial was conducted to develop the lowest-dose combination therapy of telmisartan and s-amlodipine. The non-inferiority study aimed to evaluate to efficacy and safety of the combination therapy compared with amlodipine 5 mg, which is the standard initial dose of amlodipine. The combination of telmisartan 20 mg and s-amlodipine 1.25 mg not only met the criteria for non-inferiority but also demonstrated superiority in reducing msSBP compared to amlodipine 5 mg (LS-mean difference: –3.25 mm Hg, *P*-value = 0.0091). Therefore, this combination may be considered a potential alternative to amlodipine 5 mg. Based on these findings, the low-dose telmisartan/s-amlodipine combination seems to be as effective as, or more effective compared to standard-dose monotherapy with either agent alone. Epidemiologic evidence shows that every 2-mm Hg reduction in SBP reduces stroke mortality by ~10% and ischemic heart disease mortality by ~7%. Thus, an additional 4–5 mm Hg reduction achieved with combination therapy could translate into a meaningful reduction in long-term cardiovascular risk.[12]

The combination of ARB and CCB is one of the recommended combination therapies of antihypertensive agents, and previous studies have demonstrated the efficacy and tolerability of combination therapy with telmisartan and either s-amlodipine or amlodipine.[14] Telmisartan, an ARB with a unique pharmacokinetic profile - including high receptor affinity, long receptor-binding duration, and high lipophilicity-has demonstrated sustained blood pressure lowering and cardiovascular risk reduction.[15] S-amlodipine, a long-acting dihydropyridine CCB, effectively reduces peripheral vascular resistance through inhibition of calcium influx into vascular smooth muscle cells.[16] However, no prior studies have evaluated the efficacy and safety of the lowest-dose combination therapy consisting of telmisartan 20 mg and s-amlodipine 1.25 mg, in comparison to low-dose of monotherapy with each agent. This clinical study is the first to demonstrate superior blood pressure reduction with the combination of telmisartan 20 mg and s-amlodipine 1.25 mg versus respective monotherapies (telmisartan 20 mg or s-amlodipine 1.25 mg).

Additionally, combination therapy can offer advantages not only in efficacy but also in safety due to the complementary mechanisms. In particular, the combination of telmisartan and amlodipine is associated with a notably lower risk of peripheral edema, as it allows for lower doses of amlodipine to be used while maintaining effective blood pressure control.[17] Peripheral edema is a well-known dose-dependent adverse event induced by amlodipine; therefore, its incidence can be reduced at lower dose of amlodipine. Furthermore, s-amlodipine has been shown to carry a lower risk of peripheral edema compared to the conventional racemic formulation. In a previous meta-analysis of amlodipine, the incidence rate of peripheral edema in patients receiving dose of 5 mg or less was approximately 6%.[18,19] However, in the present study, peripheral edema was not observed in either the Tel/S-Amlo and S-Amlo group, both of which received a low dose of s-amlodipine. While the short trial duration and small sample size limit definitive conclusions regarding peripheral edema risk, it can be expected to reduce the risk of peripheral edema risk by taking a low-dose combination of telmisartan and s-amlodipine.

Furthermore, aside from the absence of edema, other safety analysis revealed comparable tolerability profiles across all groups (Tel/S-Amlo, Tel, and S-Amlo group), with no major safety concerns identified in the combination arm. Therefore, these results suggest that low-dose combination with telmisartan and s-amlodipine may be considered a safe option while maintaining therapeutic efficacy.

There are a few limitations to this study. A relatively small number of Korean patients were enrolled. Thus, this study limits the generalizability of these results to prolonged treatment periods and other ethnic groups. Despite these limitations, the data show that Tel/S-amlo for 8 weeks in hypertensive patients significantly improved BP without safety concerns. Thus, a SPC of telmisartan 20 mg and s-amlodipine 1.25 mg could represent an effective and safe first-step treatment option for patients with hypertension.

Conclusions

Combination therapy with low-dose telmisartan and s-amlodipine was superior in lowering BP compared to either agent alone. No significant difference was observed between the combination and either agent alone in safety evaluation; thus, the combination with low-dose telmisartan and s-amlodipine can be safely administered. Therefore, the combined administration of low-dose telmisartan and s-amlodipine can effectively control BP as an initial therapy in hypertensive patients.

CRediT Authorship Contribution Statement

Sang Hyun Lee and Jinho Shin wrote and revised the manuscript. Jinho Shin contributed to the study design and, Jinho Shin, Sang Hyun Lee, Kyungil Park, Ki Hong Lee, Yoonhaeng Cho, Dae-Hee Kim, Sungmin Lim, Seong Bo Yoon, Jae-Sik Jang, Hong-Seok Lim, Joon-Hyung Doh, Dae-Young Kim, Il Suk Sohn, Dae Young Cheon, Myung Hwan Bae, Sung Hea Kim, Yonggu Lee, Sang Hyun Ihm, Rak Kyeong Choi, Hun-Jun Park, Wook Bum Pyun, Seonghoon Choi contributed to data collection and analysis.

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Declaration of competing interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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