Clinical Therapeutics 47 (2025) 1113–1123

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Original Research

Multicenter, Randomized, Double-Blind, Parallel, Phase 2 Clinical Trial to Compare and Evaluate the Efficacy and Safety of SPC1001 and Monotherapy in Patients With Essential Hypertension

Jinho Shin, MD, PhD[1], SeongHwan Kim, MD, PhD[2], KiHoon Han, MD, PhD[3], MooHyun Kim, MD, PhD[4], YoungKeun Ahn, MD, PhD[5], IlSuk Sohn, MD, PhD[6], KwangIl Kim, MD, PhD[7], DongHun Cha, MD, PhD[8], SoonJun Hong, MD, PhD[9], EunJoo Cho, MD, PhD[10], HaeYoung Lee, MD, PhD[11], WookBum Pyun, MD, PhD[12], HoJoong Youn, MD, PhD[13], WooShik Kim, MD, PhD[14], MooYong Rhee, MD, PhD[15], JunHee Lee, MD, PhD[16], JongWon Ha, MD, PhD[17], JiYong Choi, MD, PhD[18], ByungSu Yoo, MD, PhD[19], JinOk Jeong, MD, PhD[20], WookJin Chung, MD, PhD[21], YeongJin Jeong, MD, PhD[22], ChongJin Kim, MD, PhD[23,*]

[1] *Division of Cardiology, Department of Internal Medicine, College of Medicine, Hanyang University, Seoul, South Korea*
[2] *Department of Cardiology, CHA Gangnam Medical Center, CHA University, Ansan-si, South Korea*
[3] *Department of Cardiology, School of Medicine, University of Ulsan, Asan Medical Center, Seoul, South Korea*
[4] *Department of Cardiology, Dong-A University Hospital, Busan, South Korea*
[5] *Department of Cardiology, Chonnam National University Hospital / Chonnam National University Medical School, Gwangju, South Korea*
[6] *Department of Cardiology, Kyung Hee University Hospital at Gangdong, Seoul, South Korea*
[7] *Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Gyeonggi-do, South Korea*
[8] *Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam-si, South Korea*
[9] *Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea*
[10] *Division of Cardiology, Department of Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea*
[11] *Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea*
[12] *Department of Internal Medicine, Ewha Woman's University Seoul Hospital, Seoul, South Korea*
[13] *Division of Cardiology, Department of Internal Medicine, Seoul Central Medical Center, Seoul, South Korea*
[14] *Division of cardiology, Department of Internal medicine, Kyung Hee University Hospital, Seoul, South Korea*
[15] *Division of Cardiology, Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang-si, South Korea*
[16] *Cardiovascular Center Kangdong Sacred Heart Hospital, Hallym University, Seoul, South Korea*
[17] *Division of Cardiology, Department of Internal Medicine, Severance Hospital, Seoul, South Korea*
[18] *Department of Cardiology, Daegu Catholic University Medical Center, Daegu, South Korea*
[19] *Department of Internal Medicine, Division of Cardiology, Yonsei University Wonju College of Medicine, Wonju-si, South Korea*
[20] *Division of Cardiology, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, South Korea*
[21] *Division of Cardiology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, South Korea*
[22] *Shin Poong Pharm. Co., Ltd., Seoul, South Korea*
[23] *Department of Cardiology, CHA Gangnam Medical Center, CHA University, Seoul, South Korea*

ARTICLE INFO

Key words:
Amlodipine
Blood pressure
Candesartan
Hypertension
Indapamide
Low-dose combination therapy

ABSTRACT

Purpose: Hypertension poses challenges for many patients in achieving adequate blood pressure control, despite using monotherapy or standard treatment regimens. A low-dose triple combination drug has recently been considered for initial hypertension therapy; however, its safety, efficacy, and dose-response relationship remain unclear. We evaluated these aspects for patients with hypertension to determine the optimal combination dose.

* Address correspondence to: ChongJin Kim, Department of Cardiology, CHA Gangnam Medical Center, CHA University, 566, Nonhyeon-ro, Gangnam-gu, Seoul, 06135, South Korea.
E-mail address: chongjinkim@naver.com (C. Kim).

https://doi.org/10.1016/j.clinthera.2025.10.001
Accepted 3 October 2025

Methods: A multicenter, randomized, double-blind, parallel, phase 2 clinical trial was conducted in South Korea. Following a two-week placebo run-in period, 253 patients of SPC1001 were randomized into the High, Mid1, Mid2, and Low groups, which consisted of a fixed-dose triple combination of candesartan, amlodipine, and indapamide at varying doses. The dosages were SPC1001 High (4/2.5/1.25 mg), SPC1001 Mid1 (2.67/1.67/0.83 mg), SPC1001 Mid2 (4/1.25/1.25 mg), SPC1001 Low (2/1.25/0.625 mg), SPC3001 (candesartan 8 mg), SPC4001 (amlodipine 5 mg), SPC4002 (amlodipine 10 mg), and placebo, with the number of participants in the groups at a 1:1:1:1:1:1:1:1:1 ratio. Participants who had been using antihypertensive medication during the screening visit were required to discontinue it at least 4 weeks before the run-in period. The primary endpoint was determined by evaluating how mean sitting systolic blood pressure (MSSBP) varied between the baseline measurement and week 8. Treatment emergent adverse events and clinically significant changes on physical examination, including the assessment of ankle edema, laboratory tests, vital signs, and 12-lead electrocardiography, were also evaluated.
Findings: SPC1001 High and SPC1001 Mid2 were identified as the two groups with the most effective dosages. The least square mean difference (LSMD) of SPC1001 High compared to SPC3001, SPC4001, SPC4002, and placebo was –7.50, –7.68, 0.03, and –16.97 mm Hg, respectively (*P*-values for ANCOVA were 0.04, 0.0473, 0.9929, and <0.0001). The LSMD of SPC 1001 Mid2 compared with that of SPC3001, SPC4001, SPC4002, and placebo was –8.72, –8.72, –1.85, and –18.02 mm Hg, respectively (*P-values* for ANCOVA were 0.0075, 0.0119, 0.5704, and <0.0001). The LSMD of SPC 1001 Mid1 compared to that of SPC3001, SPC4001, SPC4002, and placebo was –4.90, –5.21, 3.03, and –14.44 mm Hg, respectively (*P*-values for ANCOVA were 0.1178, 0.1205, 0.3347, and <0.0001). The LSMD of SPC1001 Low compared to that of SPC3001, SPC4001, SPC4002, and placebo was –0.51, –0.87, 7.30, and –9.88 mm Hg, respectively (*P-values* for ANCOVA were 0.8799, 0.8088, 0.0284, and <0.0047). There were two serious adverse events recorded, in SPC1001 High and SPC3001.
Implications: Low-dose triple combination therapies may be effective for treating hypertension.
Trial Registration: ClinicalTrials.gov identifier: NCT06212648.

Introduction

In alignment with the Korean Society of Hypertension guidelines, individuals are classified as hypertensive if their systolic blood pressure (SBP) is 140 mm Hg or above, or if their diastolic blood pressure (DBP) reaches 90 mm Hg or higher.[1] Elevated blood pressure stands out as a principal contributor to cardiovascular disease and early mortality. High blood pressure tends to be more common among adults in less affluent nations as compared to those from wealthier countries.[2] The control and management of hypertension is regarded as a significant issue for improving public health. The Korean Hypertension Fact Sheet 2022, using nationwide data from 2020, reports that 29.4% of Korean adults aged 20 years and above, equivalent to roughly 12.6 million individuals, are affected by high blood pressure. It also stated that the awareness rate of hypertension was 69.5%, and overall control rate of hypertension was 47.4%.[3]

For individuals diagnosed with grade 1 hypertension, it is recommended to start antihypertensive medication when the SBP reaches 140 mm Hg or higher, or when the DBP is 90 mm Hg or above. Lifestyle modifications and drug therapies are both widely recognized approaches for reducing blood pressure. For patients with grade 2 or 3 hypertension (blood pressure ≥ 160/100 mm Hg), drug therapy should begin immediately after diagnosis, typically with a two-drug combination, rather than waiting to assess the impact of lifestyle modifications. If rapid blood pressure control is necessary due to clinical or practical reasons, immediate treatment can be initiated for all hypertensive cases. Combination therapy is preferred over monotherapy for the initial drug selection, according to ESC guidelines.[4]

Hypertension arises from a complex interplay of mechanisms, and the variability in individual responses to antihypertensive medications makes it challenging to effectively control blood pressure with a single drug.[1] Therefore, fixed dose combination therapy may provide better blood pressure control while minimizing side effects.[5]

A low-dose triple combination drug, in half, third, or quarter doses, has recently been considered for initial hypertension therapy.[6] A clinical trial has reported that patients treated with a low-dose three-drug combination (telmisartan, amlodipine besylate, and chlorthalidone) showed benefits in achieving target blood pressure and controlling mean blood pressure compared to monotherapy, and may be beneficial for initial treatment. The three-drug combination was also well tolerated, with fewer peripheral edema adverse events (AEs) reported compared to the two-drug combination.[7] The most frequently utilized three-drug combination for hypertension management consists of an inhibitor targeting the renin-angiotensin system, a calcium channel blocker, and a diuretic agent.

Although there are some studies that demonstrate the efficacy of combination therapies such as three-drug regimens, the safety, efficacy, and dose-response relationship of low-dose triple combination therapies remain unclear.

Therefore, our 8-week clinical trial aimed to evaluate whether a specific low-dose combination of candesartan cilexetil, amlodipine besylate, and indapamide was more effective than monotherapy. We also attempted to determine the tolerability of this combination.

Participants and Methods

Study Design and Population

The SPC1001 clinical trial was a multicenter, randomized, double-blind, parallel-design phase II study conducted in Korea to evaluate the efficacy and safety of SPC1001 and monotherapy in patients with essential hypertension. The trial enrolled 253 patients who were randomly allocated in equal proportions to receive different dosages of SPC1001, monotherapy, or placebo.

The protocol for this study was implemented after receiving approval from the Ministry of Food and Drug Safety as well as from the Institutional Ethics Review Board of each clinical trial site. The study was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice standards, and all participants provided written informed consent before participating in any study-related procedures.

At the screening visit, participants underwent a comprehensive evaluation, including physical examinations, clinical laboratory tests, and assessments of vital signs, medical history, and concomitant medication use. Sex was defined on the basis of biologic difference without including intersex. Participants were advised to routinely check their blood pressure using a personal blood pressure device and to have it measured by a healthcare provider during clinic visits.

Participants were eligible if they were aged ≥19 and <75 years and, if not receiving antihypertensive drugs, if they had a mean sitting systolic blood pressure (MSSBP) ≥140 mm Hg and <180 mm Hg. If receiving antihypertensive drugs, or if they had diabetes or chronic kidney disease, the MSSBP had to be ≥130 mm Hg and <180 mm Hg. At the

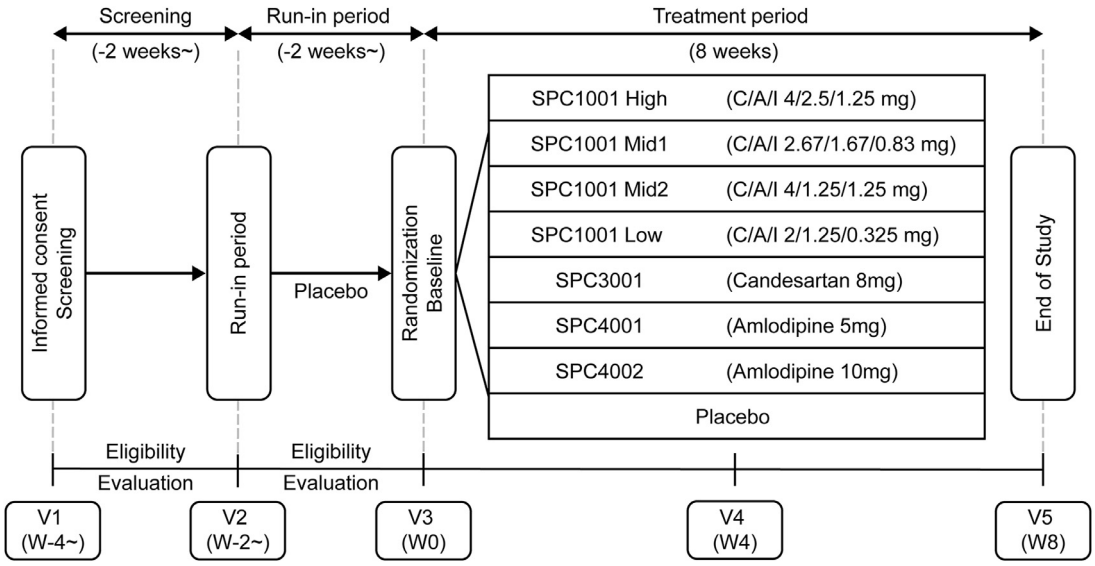

Figure 1. Schematic representation of study designs.

randomization visit, participants were required to have an MSSBP ≥140 mm Hg and <180 mm Hg, with a mean sitting diastolic blood pressure (MSDBP) <110 mm Hg across all groups.

Participants were excluded if the MSSBP difference between arms was greater than 20 mm Hg or if the MSDBP difference was greater than 10 mm Hg. Additional exclusion criteria included specific medical conditions, such as significant electrolyte imbalances (sodium <135 mmol/L or potassium >5.5 mmol/L), uncontrolled diabetes (glycated hemoglobin level >9.0%), severe kidney disease (creatinine level >1.5 fold of the upper limit, creatinine clearance <30 ml/min, or estimated glomerular filtration rate <30 ml/min/1.73 m^2), severe cerebrovascular disease (history of stroke, cerebral infarction, or cerebral hemorrhage within 6 months of screening), serious ocular disease (hypertensive retinopathy with retinal microhemorrhages within 6 months of screening), and autoimmune or inflammatory diseases (Supplemental Table S1).

After the placebo run-in phase, participants who met the eligibility criteria, with an MSSBP ranging from 140 to 180 mm Hg and MSDBP below 110 mm Hg, were assigned to the SPC1001 treatment group (Figure 1).

Study Protocol

This clinical trial received an approval of protocol from the Korean Ministry of Food and Drug Safety on September 7, 2021, and was approved by the Institutional Ethics Review Boards of a total of 24 clinical trial sites. The first subject was recruited on March 25, 2022, and the last subject visit was completed on January 27, 2023.

The study comprised a 2-week screening phase, followed by a 2-week placebo lead-in period, during which participants ceased their prior antihypertensive medications and began taking a daily placebo pill. Throughout this study, participants were encouraged to adopt lifestyle modifications. Upon completion of the run-in phase, participants who met the inclusion criteria were randomly assigned to one of eight groups and administered varying doses of SPC1001, monotherapy, or placebo during an 8-week double-blind treatment period. The groups included SPC1001 High, with a combination of candesartan, amlodipine, and indapamide in 4 mg, 2.5 mg, and 1.25 mg doses, respectively; SPC1001 Mid1, with a combination of candesartan, amlodipine, and indapamide in 2.67 mg, 1.67 mg, and 0.83 mg doses, respectively; SPC1001 Mid2, in 4 mg, 1.25 mg, and 1.25 mg doses, respectively; SPC1001 Low, in 2 mg, 1.25 mg, and 0.625 mg doses, respectively; SPC3001, with 8 mg candesartan; SPC4001, with 5 mg amlodipine; SPC4002, with 10 mg amlodipine; and placebo. Participants were distributed in a 1:1:1:1:1:1:1:1 ratio (Figure 1).

The randomization codes for this clinical trial were generated by an independent statistician using the block randomization method on SAS® (Version 9.4, SAS Institute, Inc., Cary, NC, USA) to ensure equal assignment of subjects across the eight treatment arms. Before the trial commenced, the statistician provided a packaging list to the team of the sponsor, who prepared and distributed the investigational products (IPs) to the study sites accordingly. Eligible subjects were then assigned to each treatment group based on randomization codes, using the Interactive Web Response System.

During the treatment phase, participants took the designated study medication once each morning. Blood pressure measurements were performed at baseline, 4 weeks, and 8 weeks according to the standard BP measurement protocol recommended by the guidelines.[8] Compliance with the treatment protocol was assessed by analyzing the difference between the number of IPs provided to participants and the number returned. This was determined by deducting the quantity of IPs returned from the total dispensed at each visit. The result was then compared to the expected number of IPs based on the dosing schedule. Throughout the run-in phase, participants needed to maintain a compliance rate of at least 75%, which was raised to 80% during the treatment period.

Study Endpoints and Measures

The primary endpoint involved evaluating the changes in MSSBP from baseline to week 8. The secondary endpoints were (1) change in MSSBP from baseline to week 4, (2) changes in MSDBP from baseline to weeks 4 and 8, (3) blood pressure control rate, where “control” was defined as having an MSSBP <140 mm Hg and MSDBP <90 mm Hg for most participants, and MSSBP <130 mm Hg and MSDBP <80 mm Hg for those with diabetes or chronic kidney disease, and (4) SBP or DBP response rate after 4 and 8 weeks, defined as the percentage of participants with a drop in SSBP ≥20 mm Hg and/or SDBP ≥10 mm Hg relative to baseline.

Blood pressure was measured using a validated automated sphygmomanometer. After the patient rested for at least 5 min in a seated position with back supported and feet flat on the floor, three consecutive measurements were taken at intervals of more than 2 min. The first reading was discarded, and the mean of the final two measurements was calculated (rounded to the nearest mm Hg) (refer to Glossary).

Safety evaluations were conducted by monitoring AEs, vital signs, results of clinical laboratory tests, physical examinations, and electrocardiography findings.

Sample Size Determination

This 8-arm parallel design study explored the optimal combination dose by comparing four test groups and four control groups. An exploratory effect size was applied to determine the necessary sample size, as the effect size for individual doses could not be predicted. Additionally, given that this was a phase 2 exploratory study, no adjustments for significance level correction were made to account for multiple comparisons.

The combination drug study was consulted to establish the effect size of MSSBP at 8 weeks compared to baseline in the test and control groups. That clinical trial compared the combination therapy of candesartan 4 mg and amlodipine 2.5 mg, both of which were included in the high dose arm of SPC1001 in this study, with a placebo to assess its efficacy. Therefore, the exploratory goals for the effect of the test and control groups in this study were defined as those used in the previous study.

The results of the combination therapy review showed that the fixed-dose combination therapy of candesartan 4 mg and amlodipine 2.5 mg resulted in a change in MSSBP from baseline to 52 weeks of −16.31 mm Hg, compared to −6.22 mm Hg for the placebo, with standard deviations of 12.35 mm Hg and 12.00 mm Hg, respectively. In addition, since the MSSBP change observed at 52 weeks was similar to that at 8 weeks, the mean MSSBP change from baseline to 8 weeks was set as −16.31 mm Hg in the test group and −6.22 mm Hg in the control group, with a standard deviation of 12.35 mm Hg.[9]

Based on this rationale, a 1:1 ratio between treatments arms was used with a two-sided significance level of 5%. To achieve 80% power, the minimum required sample size was 24 patients per arm. Assuming a 20% dropout rate, which would increase the required patient number by 30 patients per arm, a total of 240 patients would need to be recruited across the eight arms.

Statistical Analysis

The full analysis set (FAS) included all patients who were randomized, received at least one dose of the study drug, and completed at least one evaluation of the primary efficacy endpoints during the treatment period. The per-protocol set was defined as a subset of the FAS, comprising patients who adhered to the study protocol without any significant deviations that could influence efficacy outcomes. Finally, the safety analysis set encompassed all randomized participants who received at least one dose of the study medication.

Efficacy outcomes were analyzed based on the FAS, where missing values were handled through the Last Observation Carried Forward approach. All statistical analyses in this study were conducted using SAS® software.

Efficacy outcomes encompassed the count of participants, along with descriptive statistics such as the mean, standard deviation, median, and the range (minimum to maximum) of values. These were reported for MSSBP measurements at baseline, at 8 weeks, and for the change from baseline to 8 weeks by dose group. Differences in each treatment group and each control group were analyzed using analysis of covariance (ANCOVA), with baseline MSSBP as a covariate. For categorical variables, frequencies and percentages were reported by dose group, and differences in proportions between groups were assessed through Pearson's chi-square test or Fisher's exact test, based on whether more than 20% of the cells had an expected frequency below five.

Safety outcomes included AEs, subject counts, incidence rates, and case counts for treatment-emergent AEs (TEAEs), adverse drug reactions (ADRs), serious AEs (SAEs), and serious ADRs (SADRs). These outcomes were categorized by dose group, coded according to the system organ class and preferred term using the Medical Dictionary for Regulatory Activities, and analyzed with Fisher's exact test for group comparisons.

Laboratory test results were summarized by dose group, including subject counts, mean, standard deviation, median, minimum, and maximum for continuous variables, and frequencies and percentages for categorical variables.

For ankle swelling, subject counts, mean, standard deviation, median, minimum, and maximum values were reported for each dose group. Comparisons of mean changes between treatment and control groups were performed using the Wilcoxon rank-sum test, while the Wilcoxon signed-rank test was used for within-group significance analysis. Although ankle edema is generally reported as a categorical variable, in this study it was assessed on a severity scale and analyzed as a continuous variable, with the purpose of more precisely evaluating individual changes and group differences.

Results

Participant Characteristics

A total of 308 subjects were screened in this trial, and 253 were randomized to participate in the trial after a 2-week run-in period. For the subjects who completed the test, 125 were placed in the test group and 113 in the control group (Figure 2). The demographic information of the subjects who participated in this test is shown in Table 1.

Efficacy Outcomes

All variables showed significant differences compared to placebo unless otherwise indicated. For SPC1001 High and SPC1001 Mid2, the MSSBP changes showed significant reductions compared to SPC3001 and SPC4001 (SPC1001 High: −7.50 ± 3.57 to −7.68 ± 3.79 mm Hg, $P = 0.0400$ to 0.0473; SPC1001 Mid2: −8.72 ± 3.15 to −8.72 ± 3.36 mm Hg, $P = 0.0075$ to 0.0119). However, SPC1001 Mid1 (−4.90 ± 3.09 to −5.21 ± 3.30 mm Hg, $P = 0.1178$–0.1205) and SPC1001 Low (−0.51 ± 3.34 to −0.87 ± 3.58 mm Hg, $P = 0.8799$–0.8088) showed no significant reductions compared to SPC3001 and SPC4001.

The difference in MSSBP change was not significant in SPC1001 High and SPC1001 Mid2 compared to that in SPC4002 (SPC1001 High: 0.03 ± 3.65 mm Hg, $P = 0.9929$; SPC1001 Mid2: −1.85 ± 3.24 mm Hg, $P = 0.5704$). However, SPC1001 Low showed a significantly lower BP reduction compared to SPC4002 (7.30 ± 3.25 mm Hg, $P = 0.0284$) (Table 2).

In terms of MSDBP change, no significant differences were observed between any treatments and SPC3001, SPC4001, or SPC4002, except that SPC1001 High showed a significantly greater BP reduction compared to SPC4001 at week 4 (−3.70 ± 1.42 mm Hg, $P = 0.0121$) (Table 3).

At 4 weeks, BP control rates were significantly higher for SPC1001 High (37.85%, $P = 0.0030$) and SPC1001 Mid2 (35.48%, $P = 0.0051$) compared to SPC3001, whereas no significant differences were observed for SPC1001 Mid1 and SPC1001 Low compared to SPC3001. Similarly, BP control rates were significantly higher for SPC1001 High (37.62%, $P = 0.0040$) and SPC1001 Mid2 (35.25%, $P = 0.0066$) compared to SPC4001, whereas no significant differences were observed for SPC1001 Mid1 and SPC1001 Low compared to SPC4001. At 8 weeks, SPC1001 High and SPC1001 Mid2 continued to show significantly higher BP control rates over SPC3001 and SPC4001, whereas no significant differences were observed for other groups.

Across both 4 and 8 weeks, no significant BP response differences were found between any treatment group and SPC3001, SPC4001, or SPC4002 (Figures 3 and 4).

In an ad-hoc analysis, there were 23 subjects in SPC1001 High, 25 in SPC1001 Mid1, 24 in SPC1001 Mid2, 23 in SPC1001 Low, 20 in SPC3001, 19 in SPC4001, 23 in SPC4002, and 25 in the placebo with

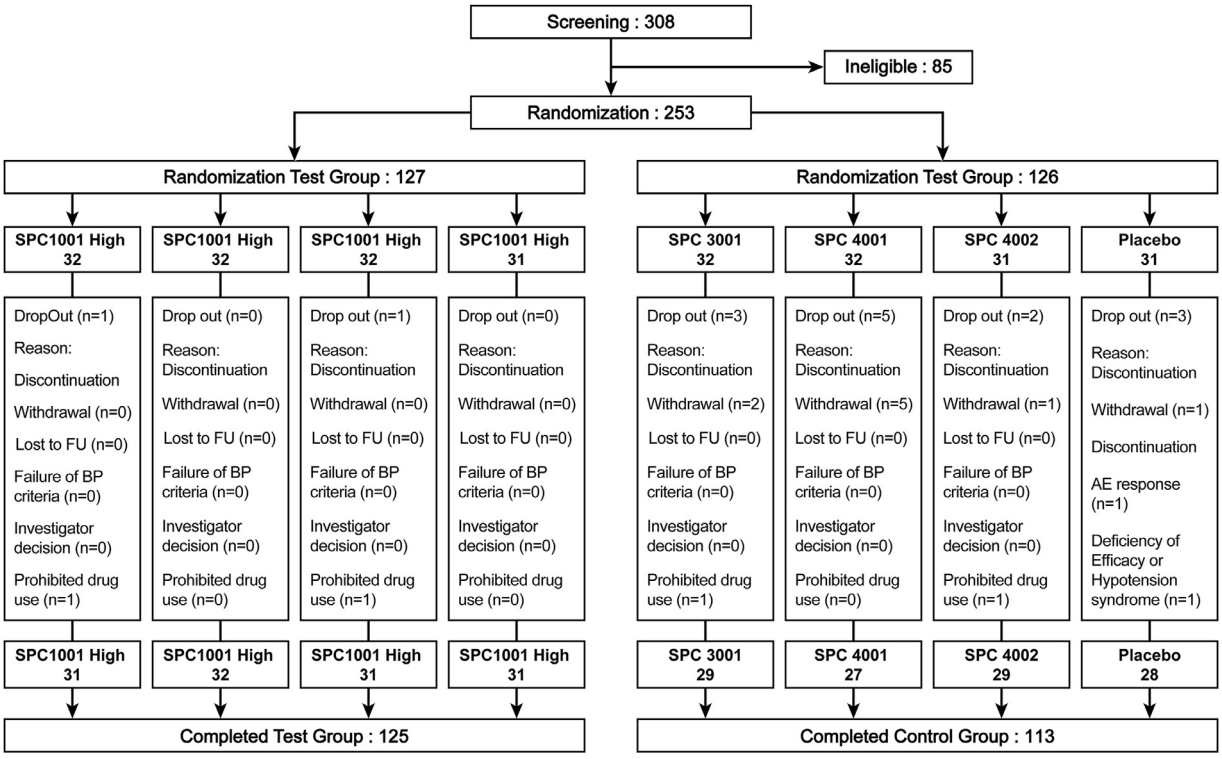

Figure 2. Flow and disposition of participants in all test versus control groups.

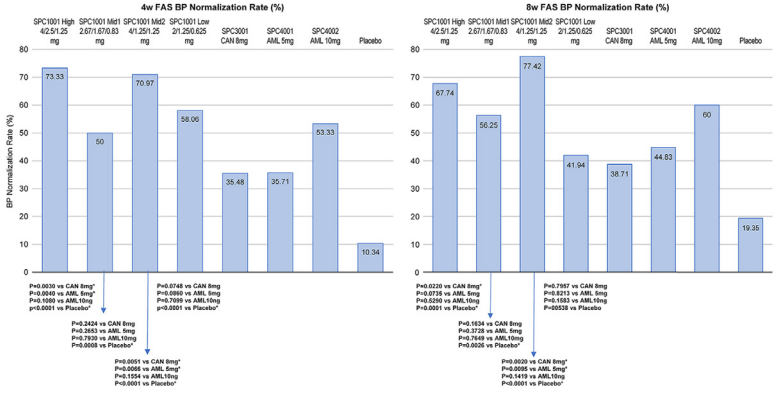

Figure 3. BP control rate at 4-week and 8-week treatment. CAN = Candesartan; AML = Amlodipine.

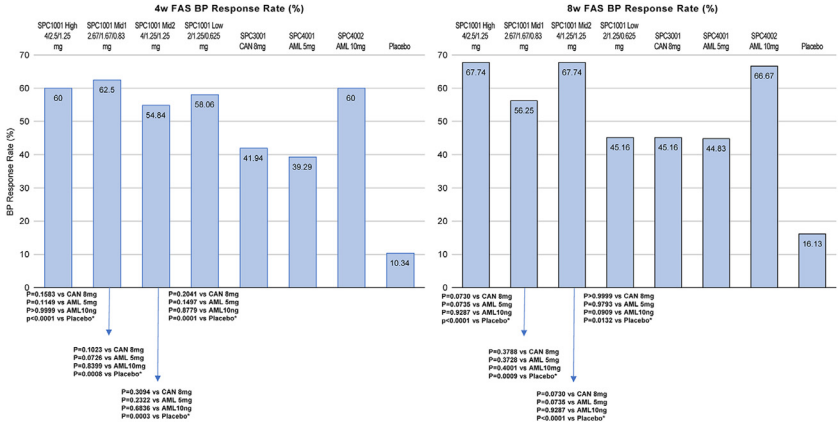

Figure 4. BP response rate at 4-week and 8-week treatment

Table 1
Demographic and baseline characteristics.

	Candesartan/Amlodipine/Indapamide					Monotherapy			
	SPC1001 High, 4/2.5/1.25 mg (N = 32)	SPC1001 Mid 1, 2.67/1.67/0.83 mg (N = 32)	SPC1001 Mid 2, 4/1.25/1.25 mg (N = 32)	SPC1001 Low 2/1.25/0.625 mg (N = 31)	SPC3001, CAN 8 mg (N = 32)	SPC4001 AML 5 mg (N = 32)	SPC4002 AML 10 mg (N = 31)	Placebo (N = 31)	*P*
Sex (Men), n (%)	23 (71.88)	23 (71.88)	21 (65.63)	19 (61.29)	24 (75.00)	25 (78.13)	20 (64.52)	23 (74.19)	0.8225[a]
Age (y), Mean (SD)	61.5 (7.98)	63.6 (7.92)	59.1 (12.43)	62.5 (6.88)	58.3 (10.33)	59.1 (11.68)	57.8 (12.45)	60.8 (9.01)	0.4277[b]
Age ≥ 65 y, n (%)	11 (34.38)	16 (50.00)	13 (40.63)	13 (41.94)	8 (25.00)	10 (31.25)	13 (41.94)	13 (41.94)	0.5726[c]
Smoking, n (%)	7 (21.88)	4 (12.50)	9 (28.13)	4 (12.90)	7 (21.88)	8 (25.00)	9 (29.03)	7 (22.58)	0.6627[c]
BMI (kg/m^2), mean (SD)	23.83 (2.53)	24.83 (2.74)	25.68 (3.23)	25.97 (2.31)	25.90 (2.52)	27.10 (3.849)	25.91 (4.14)	26.40 (3.00)	0.0013[b]
MSSBP (mm Hg), mean (SD)	153.83 (9.99)	154.16 (10.31)	151.42 (10.39)	152.74 (11.50)	152.98 (10.89)	153.40 (10.695)	151.71 (9.39)	153.15 (10.59)	0.9554[b]
MSDBP (mm Hg), mean (SD)	92.40 (9.96)	92.39 (8.48)	91.44 (7.85)	89.44 (9.67)	94.86 (9.48)	91.78 (7.965)	92.29 (8.09)	92.79 (9.20)	0.4903[b]
Duration of essential hypertension (y), mean (SD)	9.583 (6.22)	10.365 (9.40)	8.709 (10.26)	8.984 (6.28)	10.78 (8.96)	8.768 (7.4588)	9.009 (7.59)	9.493 (7.85)	0.8250[b]
Diabetes or CKD, n (%)	7 (21.88)	8 (25.00)	5 (15.63)	7 (22.58)	5 (15.63)	9 (28.13)	10 (32.26)	12 (38.71)	0.3858[c]
diabetes, n (%)	7 (21.88)	8 (25.00)	5 (15.63)	7 (22.58)	5 (15.63)	9 (28.13)	10 (32.26)	12 (38.71)	0.3858[c]
CKD, n (%)	0	0	0	0	0	0	0	0	NA[d]

AML = Amlodipine; BMI = body mass index; CAN = Candesartan; CKD = chronic kidney disease; MSSBP = mean sitting systolic blood pressure; MSDBP = mean sitting diastolic blood pressure; n/N = number of participants; NA = not applicable; SD = standard deviation.
Percentage: Calculate the percentage using the number of participants in each group as the denominator.
Demographic data was collected at Visit 1, however, MSSBP and MSDBP were collected at Visit 3.
Duration of Essential Hypertension (year): 1 year = 365.25 days.
1) Continuous variables: Independent *t*-test or Wilcoxon rank-sum test, 2) Categorical variables: Chi-square test or Fisher's exact test. Statistical significance determined by $p < 0.05$.
[a] ANOVA.
[b] Kruskal–Wallis test, Categorical variables.
[c] Chi-square test.
[d] Fisher's exact test.

Table 2
Change in MSSBP from baseline at weeks 4 and 8.

	Candesartan/Amlodipine/Indapamide				Monotherapy			
	SPC1001 High 4/2.5/1.25 mg (N = 31)	SPC1001 Mid 1 2.67/1.67/0.83 mg (N = 32)	SPC1001 Mid 2 4/1.25/1.25 mg (N = 31)	SPC1001 Low 2/1.25/0.625 mg (N = 31)	SPC3001 CAN 8 mg (N = 31)	SPC4001 AML 5 mg (N = 29)	SPC4002 AML 10 mg (N = 31)	Placebo (N = 31)
MSSBP								
baseline, mean (SD)	153.31 (9.70)	154.16 (10.31)	151.60 (10.52)	152.74 (11.50)	153.31 (10.92)	154.13 (10.78)	151.71 (9.39)	153.15 (10.59)
Week 4, mean (SD)	133.40 (14.93)	133.29 (9.70)	131.98 (16.18)	132.48 (14.88)	138.37 (12.48)	137.07 (11.35)	131.26 (11.26)	149.00 (14.04)
Week 8, mean (SD)	129.77 (16.89)	132.88 (13.12)	127.23 (15.21)	136.51 (13.60)	137.27 (14.336	138.07 (15.98)	128.97 (11.64)	146.62 (15.19)
Change from baseline at week 4								
Mean (SD)	−19.99 (13.66)	−20.87 (12.06)	−19.62 (13.09)	−20.25 (17.20)	−14.93 (10.61)	−16.36 (11.61)	−20.11 (12.08)	−3.21 (11.11)
LSM difference [95% CI][a]	−5.03, [−11.11, 1.05]	−5.49, [−10.55, −0.44]	−5.05, [−11.07, 0.97]	−5.64, [−12.22, 0.93]				
P (ANCOVA)	0.1029	0.0336*	0.0988	0.0912				
LSM difference [95% CI][b]	−3.65, [−10.02, 2.72]	−4.05, [−9.19, 1.10]	−3.80, [−10.17, 2.56]	−4.37, [−11.14, 2.41]				
P (ANCOVA)	0.2557	0.1209	0.2367	0.2018				
LSM difference [95% CI][c]	1.04, [−5.33, 7.40]	1.15, [−4.04, 6.33]	0.56, [−5.75, 6.88]	0.83, [−5.85, 7.51]				
P (ANCOVA)	0.7459	0.6599	0.8591	0.8043				
LSM difference [95% CI][d]	−16.52, [−23.00, −10.04]	−16.76, [−22.30, −11.22]	−16.47, [−22.80, −10.14]	−16.77, [−23.82, −9.72]				
P (ANCOVA)	<0.0001*	<0.0001*	<0.0001*	<0.0001*				
Change from baseline at week 8								
Mean (SD)	−23.54 (15.73)	−21.28 (12.97)	−24.36 (12.24)	−16.23 (15.90)	−16.04 (12.72)	−16.06 (13.58)	−22.40 (14.59)	−6.54 (12.01)
LSM difference [95% CI][a]	−7.50, [−14.65, −0.35]	−4.90, [−11.08, 1.28]	−8.72, [−15.02, −2.42]	−0.51, [−7.18, 6.17]				
P-value (ANCOVA)	0.0400*	0.1178	0.0075*	0.8799				
LSM difference [95% CI][b]	−7.68, [−15.26, −0.10]	−5.21, [−11.82, 1.41]	−8.72, [−15.44, −2.00]	−0.87, [−8.05, 6.30]				
P (ANCOVA)	0.0473*	0.1205	0.0119*	0.8088				
LSM difference [95% CI][c]	0.03, [−7.27, 7.34]	3.03, [−3.20, 9.26]	−1.85, [−8.35, 4.64]	7.30, [0.80, 13.81]				
P (ANCOVA)	0.9929	0.3347	0.5704	0.0284*				
LSM difference [95% CI][d]	−16.97, [−24.07, −9.87]	−14.44, [−20.61, −8.27]	−18.02, [−24.22, −11.82]	−9.88, [−16.62, −3.15]				
P (ANCOVA)	<0.0001*	<0.0001*	<0.0001*	0.0047*				

[a] Compared to SPC3001 (Candesartan 8 mg).
[b] Compared to SPC4001 (Amlodipine 5 mg).
[c] Compared to SPC4002 (Amlodipine 10 mg).
[d] Compared to Placebo.
* $P < 0.05$.

Table 3
Change in MSDBP from baseline at weeks 4 and 8.

	Candesartan/Amlodipine/Indapamide				Monotherapy			
	SPC1001 High 4/2.5/1.25 mg (N = 31)	SPC1001 Mid 1 2.67/1.67/0.83 mg (N = 32)	SPC1001 Mid 2 4/1.25/1.25 mg (N = 31)	SPC1001 Low 2/1.25/0.625 mg (N = 31)	SPC3001 CAN 8 mg (N = 31)	SPC4001 AML 5 mg (N = 29)	SPC4002 AML 10 mg (N = 31)	Placebo (N = 31)
MSDBP								
baseline, mean (SD)	92.07 (9.95)	92.39 (8.48)	91.52 (7.97)	89.44 (9.67)	95.17 (9.47)	91.86 (8.24)	92.29 (8.09)	92.79 (9.20)
Week 4, mean (SD)	82.40 (8.72)	85.38 (9.19)	83.35 (9.39)	81.95 (11.64)	87.27 (10.59)	85.83 (7.84)	83.91 (9.63)	93.08 (7.15)
Week 8, mean (SD)	81.65 (10.34)	84.02 (9.85)	79.88 (9.69)	82.55 (10.86)	87.00 (11.62)	83.70 (9.58)	81.81 (8.75)	91.99 (8.31)
Change from baseline at week 4								
Mean (SD)	−9.97 (6.85)	−7.02 (8.92)	−8.17 (9.44)	−7.49 (7.27)	−7.91 (6.13)	−6.16 (5.170)	−9.01 (5.61)	0.87 (7.48)
LSM difference [95% CI][a]	−2.69, [−5.89, 0.51]	0.18, [−3.59, 3.9]	−1.21, [−5.21, 2.79]	0.01, [−3.57, 3.60]				
P (ANCOVA)	0.0975	0.9261	0.5461	0.9937				
LSM difference [95% CI][b]	−3.70, [−6.55, −0.84]	−0.71, [−4.23, 2.8]	−2.19, [−5.92, 1.53]	−1.68, [−5.00, 1.65]				
P (ANCOVA)	0.0121*	0.6877	0.2436	0.3167				
LSM difference [95% CI][c]	−1.08, [−4.21, 2.05]	1.86, [−1.86, 5.58]	0.48, [−3.44, 4.41]	1.46, [−1.98, 4.90]				
P (ANCOVA)	0.4920	0.3208	0.8058	0.3986				
LSM difference [95% CI][d]	−10.77, [−13.84, −7.70]	−7.79, [−11.42, −4.17]	−9.40, [−13.21, −5.59]	−9.11, [−12.76, −5.47]				
P (ANCOVA)	<0.0001*	<0.0001*	<0.0001*	<0.0001*				
Change from baseline at week 8								
Mean (SD)	−10.42 (8.20)	−8.37 (8.29)	−11.64 (8.64)	−6.90 (7.30)	−8.18 (7.71)	−8.16 (6.81)	−11.11 (6.95)	−0.81 (7.76)
LSM Difference [95% CI][a]	−2.84, [−6.86, 1.18]	−0.69, [−4.73, 3.35]	−4.16, [−8.37, 0.04]	0.61, [−3.37, 4.59]				
P (ANCOVA)	0.1622	0.7327	0.0523	0.7603				
LSM difference [95% CI][a]	−2.20, [−5.97, 1.57]	−0.08, [−3.89, 3.73]	−3.57, [−7.50, 0.36]	0.88, [−2.77, 4.53]				
P (ANCOVA)	0.2467	0.9667	0.0744	0.6305				
LSM difference [95% CI][c]	0.46, [−3.27, 4.19]	2.59, [−1.17, 6.36]	−0.95, [−4.85, 2.95]	3.56, [−0.10, 7.23]				
P (ANCOVA)	0.8076	0.1736	0.6262	0.0565				
LSM difference [95% CI][d]	−9.88, [−13.55, −6.20]	−7.72, [−11.43, −4.00]	−11.35, [−15.18, −7.53]	−7.07, [−10.72, −3.42]				
P (ANCOVA)	<0.0001*	0.0001*	<0.0001*	0.0003*				

[a] Compared to SPC3001 (Candesartan 8 mg).
[b] Compared to SPC4001 (Amlodipine 5 mg).
[c] Compared to SPC4002 (Amlodipine 10 mg).
[d] Compared to Placebo.
* $P < 0.05$.

baseline MSSBP levels <160 mm Hg. The demographic information of the subjects is summarized in Supplemental Table S1.

Regarding the MSSBP changes at week 4, no significant differences were observed among the treatment groups of SPC1001 High, Mid1, Mid2, and Low when compared to SPC3001, SPC4001, and SPC4002. At 8 weeks, SPC1001 Mid2 showed significant differences in MSSBP compared to SPC3001 (−10.60 ± 3.28 mm Hg, $P = 0.0024$) and SPC4001 (−9.90 ± 3.23 mm Hg, $P = 0.0039$) (Supplemental Table S2).

At 4 weeks, SPC1001 High demonstrated a significantly greater BP difference compared to SPC4001. At 8 weeks, SPC1001 Mid2 showed a significantly greater BP reduction compared to SPC3001, whereas SPC1001 Low had a significantly lower BP reduction compared to SPC4002 (Supplemental Table S3).

At 4 weeks, the SPC1001 High (51.82%, $P = 0.0007$), SPC1001 Mid1 (30.00%, $P = 0.0450$), and SPC1001 Mid2 (49.17%, $P = 0.0010$) groups showed significantly higher BP control rates compared to SPC3001. SPC1001 Low (26.52%, $P = 0.0807$) did not show a significant difference compared to SPC3001. SPC1001 High (39.71%, $P = 0.0085$) and SPC1001 Mid2 (37.06%, $P = 0.0125$) demonstrated a significantly greater BP control rate compared to SPC4001. No treatment groups showed significant differences in BP control rate compared to SPC4002. At 8 weeks, SPC1001 High (43.26%, $P = 0.0041$) and SPC1001 Mid2 (48.33%, $P = 0.0010$) demonstrated significant improvements in the BP control rate compared to SPC3001. Compared to SPC4001, SPC1001 Mid2 was significantly different, whereas SPC1001 High, Mid1, and Low were not. SPC1001 High, Mid1, and Mid2 demonstrated significant differences compared to the placebo (Supplemental Figure S1).

At 4 weeks, SPC1001 Mid1 exhibited a significant BP response rate compared to SPC3001 (54.55%, $P = 0.0377$), whereas no significant differences were observed for SPC1001 High, SPC1001 Mid2, or SPC1001 Low. No significant differences in the BP response rate were observed for any treatment group compared to SPC4001 or SPC4002 (Supplemental Figure S2).

Safety Outcomes

A total of 23 AEs occurred before IP administration, whereas 44 TEAEs were reported after administration, with no significant differences in TEAE incidence among treatment groups. The overall incidence of ADRs related to IP administration was 3.97% (14 events in 10 subjects), with no significant differences between dose groups.

The incidence of SAEs was 0.79% (2 events) in SPC1001 High (rib fracture, n = 1) and 3.13% in SPC3001 (sudden hearing loss n = 1), with no SADRs reported. Four dropout-related AEs (1.59%) occurred for palpitations, tuberculosis, dizziness, and headache, with no significant differences among dose groups (Table 4).

No clinically significant abnormal findings were observed in post-baseline laboratory tests, vital signs, or electrocardiograms.

Upon further analysis of the subjects with baseline MSSBP levels below 160 mm Hg, no significant differences in the incidence of ADRs or SADRs were observed between the groups (Supplemental Table S4).

Discussion

The main findings of the present study are as follows: SPC1001 High and SPC1001 Mid2 showed significantly greater BP reductions compared to both SPC3001 and SPC4001; the BP reductions in SPC1001 Mid1 were comparable to those of SPC3001 and SPC4001; and the BP reductions of SPC1001 High, SPC1001 Mid1, and SPC1001 Mid2 were comparable to those of SPC4002.

In terms of BP control rate, SPC1001 Mid2 achieved a better control rate than SPC3001 or SPC4001, whereas the control rate of SPC1001 High was only better than that of SPC3001.

In a prior study comparing a low-dose triple combination regimen (amlodipine, losartan, and chlorthalidone) with a control arm of amlodipine (5 mg and 10 mg) plus losartan (100 mg), similar outcomes were reported. Specifically, the reductions in SBP observed in the half-dose (2.5/25/6.25 mg) and third-dose (1.67/16.67/4.17) groups were −17.2 mm Hg and −19.5 mm Hg, respectively, which are on par with the −18.5 mm Hg decrease seen in the amlodipine 10 mg group. As the third-dose group[6] of that study incorporated the highest diuretic dosage among all arms, it aligns closely with the design of the present study, where the SPC1001 Mid2 group also used the highest dose of diuretics.

In terms of the control rate, given that SBP control rates at week 8 in the amlodipine 10 mg groups were approximately 60% in both the previous and present studies (63.6% vs 60%), the control rate of SPC1001 Mid2 seems to be better (77.42%) than that of the third-dose group in the previous study (60.6%).[6] In a meta-analysis covering seven studies for the low-dose triple and quadruple combination, a low-dose combination was associated with a better control rate at eight weeks than that of monotherapy (66% versus 46%).[10] Such superiority was reported to be maintained until 12 months.[11] In our study, TEAE rates and treatment withdrawal did not differ significantly among any of the study arms, including the placebo group, which aligns with findings from the previous study.

Initial combination therapy that includes the standard dose may be associated with an excessive BP reduction in grade 1 hypertension (blood pressure ranging from 140/90 mm Hg to 160/100 mm Hg). According to the result of the present study, a low-dose triple combination such as SPC1001 High and SPC1001 Mid2 would seem to be an option, considering the results of the ad-hoc group in which SBP < 160 mm Hg. However, given that the sample size of the ad-hoc group was not sufficient for testing the differences among the groups, further studies are warranted.

This study has certain limitations. The 8-week treatment period may not be sufficient to evaluate the long-term sustainability of blood pressure-lowering effects or to identify AEs associated with prolonged treatment. This phase II exploratory study aimed to determine the effectiveness of a low-dose triple combination therapy by assessing its ability to reduce blood pressure relative to a placebo. However, it remains uncertain whether the low-dose triple combination achieves efficacy and tolerability equivalent to monotherapy for each component.

The question of whether initial therapy with a low-dose combination provides better cardiovascular protection through earlier blood pressure control requires further investigation in large-scale, long-term follow-up studies. Additionally, pharmacokinetic and pharmacodynamic analyses of low-dose regimens are necessary to better understand their mechanisms and antihypertensive effects.

The findings suggest a new treatment approach that starts with a quarter-dose triple combination therapy as the initial option and progresses to a third- or half-dose triple combination for maintenance.

Conclusion

In conclusion, this research showed that a low-dose triple combination therapy including candesartan, amlodipine, and indapamide provides effective blood pressure control with a comparable or greater BP reduction compared to monotherapy without increasing adverse effects.

Glossary

ANCOVA (Analysis of Covariance): A statistical method used to compare one or more groups while controlling for the effects of one or more continuous covariates. It adjusts the dependent variable for the influence of the covariates to provide a clearer understanding of the group differences.

Mean sitting systolic blood pressure: The average systolic blood pressure measured while the subject is in a sitting position. Systolic blood pressure is the pressure in the arteries when the heart contracts and pumps blood.

Mean sitting diastolic blood pressure: The average diastolic blood pressure measured while the subject is in a sitting position. Diastolic

Table 4
Overall summary of TEAE.

	Candesartan/Amlodipine/Indapamide					Monotherapy			
	SPC1001 High 4/2.5/1.25 mg (N = 32)	SPC1001 Mid 1 2.67/1.67/0.83 mg (N = 32)	SPC1001 Mid 2 4/1.25/1.25 mg (N = 32)	SPC1001 Low 2/1.25/0.625 mg (N = 32)	SPC3001 CAN 8mg (N = 32)	SPC4001 AML 5mg (N = 31)	SPC4002 AML 10mg (N = 32)	Placebo (N = 31)	*P*-value
TEAEs	7 (21.88) [10]	5 (15.63) [6]	3 (9.38) [3]	3 (10.00) [4]	9 (28.13) [12]	3 (9.68) [6]	7 (21.88) [7]	7 (22.58) [12]	0.3377[a]
Intensity									
mild	7 (21.88) [10]	5 (15.63) [6]	2 (6.25) [2]	3 (10.00) [4]	8(25.00) [11]	3 (9.68) [5]	7 (21.88) [7]	6 (19.35) [11]	NA
Moderate	0 [0]	0 [0]	1 (3.13) [1]	0 [0]	1 (3.13) [1]	1 (3.23) [1]	0 [0]	1 (3.23) [1]	
Severe	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	
SAEs	1 (3.13) [1]	0 [0]	0 [0]	0 [0]	1 (3.13) [1]	0 [0]	0 [0]	0 [0]	>0.9999[b]
ADRs	1 (3.13) [3]	2 (6.25) [2]	1 (3.13) [1]	0 [0]	2 (6.25) [4]	1 (3.23) [1]	0 [0]	3 (9.68) [3]	0.5513[a]
Serious ADRs	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	NA
common TEAEs									
Infections and infestations	2 (6.25) [2]	1 (3.13) [1]	1 (3.13) [1]	2 (6.67) [2]	3 (9.38) [3]	1 (3.23) [1]	4 (12.50) [4]	1 (3.23) [1]	
Nervous system disorders	1 (3.13) [1]	1 (3.13) [1]	1 (3.13) [1]	1 (3.33) [1]	1 (3.13) [1]	1 (3.23) [1]	0 [0]	3 (9.68) [3]	
General disorders and administration site conditions	1 (3.13)) [1]	1 (3.13)) [1]	0 [0]	1 (3.33)) [1]	2 (6.25) [2]	2 (6.45) [2]	0 [0]	1 (3.23)) [1]	
Gastrointestinal disorders	1 (3.13) [1]	1 (3.13) [1]	0 [0]	0 [0]	1 (3.13) [1]	0 [0]	0 [0]	2 (6.45) [2]	
Investigations	2 (6.25) [2]	1 (3.13) [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 (3.13) [1]	1 (3.23) [4]	
Injury, poisoning and procedural complications	2 (6.25) [2]	0 [0]	0 [0]	0 [0]	2 (6.25) [2]	0 [0]	0 [0]	0 [0]	
Musculoskeletal and connective tissue disorders	0 [0]	0 [0]	0 [0]	0 [0]	1 (3.13) [1]	1 (3.23) [1]	1 (3.13) [1]	1 (3.23) [1]	
Cardiac disorders	1 (3.13) [1]	1 (3.13) [1]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	
Ear and labyrinth disorders	0 [0]	0 [0]	0 [0]	0 [0]	1 (3.13) [1]	1 (3.23) [1]	0 [0]	0 [0]	
Eye disorders	0 [0]	0 [0]	0 [0]	0 [0]	1 (3.13) [1]	0 [0]	0 [0]	0 [0]	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 [0]	0 [0]	0 [0]	0 [0]	1 (3.13) [1]	0 [0]	0 [0]	0 [0]	
Respiratory, thoracic and mediastinal disorders	0 [0]	1 (3.13) [1]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	
Vascular disorders	0 [0]	0 [0]	1 (3.13) [1]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	

ADRs = adverse drug reactions; AML = Amlodipine; CAN= Candesartan; n/*N* = number of participants; SAEs = Serious adverse events; SD = standard deviation; TEAEs = Treatment-emergent adverse events.
P values between group comparison via.

[a] Chi-square test.

[b] Fisher's exact test.

Data are presented as 'the number of participants (%), [the number of cases]'

blood pressure is the pressure in the arteries when the heart relaxes between beats.

Full analysis set: A set of participants in a clinical trial that includes all randomized individuals who received at least one dose of the study drug and had at least one post-baseline assessment. This analysis set is used to evaluate the effectiveness of the treatment, following the intention-to-treat principle.

Author contributions

C.J. Kim, M.Y. Rhee designed the study. J Shin, S.H. Kim, K.H. Han, M.H. Kim, Y.K. Ahn, I.S. Sohn, K.I. Kim, D.H. Cha, S.J. Hong, E.J. Cho, H.Y. Lee, W.B. Pyun, H.J. Youn, W.S. Kim, M.Y. Rhee, J.H. Lee, J.W. Ha, J.Y. Choi, B.S. Yoo, J.O. Jeong, WJ. Chung Investigation. C.J. Kim, J Shin Data Curation. J Shin Writing-Original draft. C.J. Kim, J Shin Writing-Review & Editing. J Shin Visualization. C.J. Kim Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

Shinpoong Pharmaceutical Co. Ltd., Seoul, Republic of Korea, provided the funding for this clinical trial and was responsible for the study design, data collection, and analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2025.10.001.

References

1. Kim HC, Ihm SH, Kim GH, et al. 2018 Korean Society of Hypertension Guidelines for the management of hypertension: part I-epidemiology of hypertension. *Clin Hypertens*. 2019;25:16. doi:10.1186/s40885-019-0121-0.
2. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020;16:223–237. doi:10.1038/s41581-019-0244-2.
3. Kim HC, Lee H, Lee H-H, et al. Korea hypertension fact sheet 2022: analysis of nationwide population-based data with a special focus on hypertension in the elderly. *Clin Hypertens*. 2023;29:22. doi:10.1186/s40885-023-00243-8.
4. Williams B, Mancia G, Spiering W, et al. 2023 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *Eur Heart J*. 2018;39:3021–3104. doi:10.1093/eurheartj/ehy339.
5. Heaton J, Johal A, Alshami A, et al. Effect of combination antihypertensive pills on blood pressure control. *J Am Heart Assoc*. 2024;13(23):e036046. doi:10.1161/JAHA.124.036046.
6. Hong SJ, Sung K-C, Lim S-W, et al. Low-dose triple antihypertensive combination therapy in patients with hypertension: a randomized, double-blind, Phase II study. *Drug Des Devel Ther*. 2020;14:5735–5746. doi:10.2147/DDDT.S286586.
7. Rodgers A, Salam A, Schutte AE, et al. Efficacy and safety of a novel low-dose triple single-pill combination of telmisartan, amlodipine and indapamide, compared with dual combinations for treatment of hypertension: a randomised, double-blind, active-controlled, international clinical trial. *Lancet*. 2024;404:1536–1546. doi:10.1016/S0140-6736(24)01744-6.
8. Korean Ministry of Food and Drug Administration. *Guidelines for Clinical Trial Evaluation of Antihypertensive Drugs*. Osong, South Korea: Korean Ministry of Food and Drug Administration; 2022.
9. Rakugi H, Ogihara T, Miyata Y, et al. Evaluation of the efficacy and tolerability of combination therapy with candesartan cilexetil and amlodipine besilate compared with candesartan cilexetil monotherapy and amlodipine besilate monotherapy in Japanese patients with mild-to-moderate essential hypertension: a multicenter, 12-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther*. 2012;34(4):838–848. doi:10.1016/j.clinthera.2012.02.015.
10. Wang N, Rueter P, Atkins E, et al. Efficacy and safety of low-dose triple and quadruple combination pills vs monotherapy, usual care, or placebo for the initial management of hypertension: a systematic review and meta-analysis. *JAMA Cardiol*. 2023;8:606–611. doi:10.1001/jamacardio.2023.0720.
11. Chow CK, Atkins ER, Hillis GS, et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. *Lancet*. 2021;398(10305):1043–1052. doi:10.1016/S0140-6736(21)01922-X.