

# Efficacy and Safety of S-Amlodipine 2.5 and 5 mg/d in Hypertensive Patients Who Were Treatment-Naive or Previously Received Antihypertensive Monotherapy

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## Abstract

The aim of the present study was to evaluate the efficacy and safety of S-amlodipine 2.5 and 5 mg/d in patients with hypertension who were treatment-naive or previously received antihypertensive monotherapy. During the 8-week treatment period, all patients received S-amlodipine 2.5 mg/d for the first 4 weeks, followed by S-amlodipine 5 mg/d for the second 4 weeks. For efficacy assessments, ambulatory and office blood pressure (BP) measurements were performed during the baseline, fourth-week, and eighth-week visits. For safety assessments, all adverse events and abnormal laboratory findings were recorded. This study is registered with ClinicalTrials.gov (NCT03038451). Of 43 patients evaluated at the screening visit, 33 were enrolled. In the treatment-naive arm, significant reductions in both office and ambulatory systolic BP (SBP) and diastolic BP (DBP) were observed with S-amlodipine 2.5 mg/d and additional significant reductions were achieved with dose titration (S-amlodipine 5 mg/d). At the end of the study, the rate of the treatment-naive patients with BP under control (SBP/DBP <140/90 mm Hg) was 53% with S-amlodipine 2.5 mg and increased to 78% with S-amlodipine 5 mg. For the noninferiority evaluation, S-amlodipine 2.5 and 5 mg/d treatments were generally noninferior to both office and ambulatory BP levels achieved with the medications that the patients received before participating in the study. Five nonserious adverse events likely to be associated with the study drug were observed. No serious adverse event was encountered. Consequently, S-amlodipine can be suggested as an effective and safe treatment option for patients with hypertension.

## Keywords

S-amlodipine, hypertension, efficacy, safety

## Introduction

Hypertension is the leading cause of preventable premature deaths worldwide and is associated with an economic burden of billion dollars per year. Blood pressure (BP) is under control only in half of patients having this critical health problem, which involves 1 of every 3 people.<sup>1,2</sup> Uncontrolled hypertension leads to significant complications such as heart diseases, stroke, renal failure, and death.<sup>3</sup> It has been reported that hypertension accounts for at least 45% of the deaths from heart diseases and 51% of the deaths from stroke.<sup>3</sup>

Hypertension is generally defined as a systolic BP (SBP) of  $\geq 140$  mm Hg and/or diastolic BP (DBP) of  $\geq 90$  mm Hg.<sup>3</sup> The goal of the treatment of hypertension is to keep the BP below these levels. In addition, patients with specific health conditions (such as diabetes) benefit from a lower target BP levels. The beneficial effects of reducing BP in preventing cardiovascular diseases and death have been well documented.<sup>4,5</sup> It has been reported that 10 mm Hg reduction in SBP and 5 mm Hg reduction in DBP decrease the incidence of coronary events by 22% and stroke by 41%.<sup>6</sup> It has also been reported that the

treatment of hypertension is effective in preventing left ventricle hypertrophy and congestive heart failure in addition to stroke and myocardial infarction.<sup>7</sup>

Risk factor-oriented lifestyle regulation (reducing/quitting smoking and alcohol consumption, regular exercise, salt restriction, healthy diet) is essential in the prevention and treatment of hypertension.<sup>3</sup> The drugs used to control BP include calcium channel blockers, diuretics, angiotensin converting

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enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors, and  $\beta$  blockers.<sup>3,8</sup> Amlodipine is a member of the dihydropyridine class of calcium channel blockers and can be used as monotherapy or in combination with other antihypertensive drugs for the treatment of hypertension.<sup>9</sup> S-amlodipine is a vasoactive enantiomer of amlodipine. Clinical trials have demonstrated the efficacy of S-amlodipine in the treatment of hypertension.<sup>10</sup> Almost all of the clinical studies with S-amlodipine were conducted on Far Eastern and Asian populations. In this sense, the present study is one of the first studies to evaluate the efficacy and safety of S-amlodipine 2.5 and 5 mg/d in hypertensive patients in a different population, who were treatment-naïve or previously received antihypertensive monotherapy.

## Methods and Materials

### Patients

Among adult ( $\geq 18$ -year-old) patients with hypertension (SBP  $\geq 140$  to  $< 160$  mm Hg, DBP  $\geq 90$  to  $< 100$  mm Hg), those who were treatment-naïve or had previously received antihypertensive monotherapy were enrolled. Patients with secondary hypertension or patients who were followed for the following diseases within the last 12 months before the initiation of the study were excluded: severe hypertension (SBP  $\geq 180$  mm Hg to DBP  $\geq 110$  mm Hg), myocardial infarction, heart failure (stage 2-4 according to the New York Heart Association), history of cerebrovascular disease, history of ischemic attack, encephalopathy, percutaneous coronary intervention or coronary artery bypass surgery, second- or third-degree heart block without pacemaker or symptomatic arrhythmia, clinically significant cardiac valve disease, unstable angina pectoris, type 1 diabetes mellitus, and atrial fibrillation. In addition, pregnant or nursing female patients or those with childbearing potential but not using any effective contraceptive method and patients with allergy against dihydropyridine, uncontrolled type 2 diabetes mellitus, severe liver disease (with baseline alanine aminotransferase and aspartate aminotransferase  $> 2 \times$  upper limit of normal, esophagus varices, portacaval shunt), severe kidney diseases (glomerular filtration rate  $< 60$  mL/min according to the Cockcroft-Gault formula), volume depletion, pancreatic disease, gastrointestinal disease affecting absorption, drug/substance or alcohol abuse, or central nervous system disease were also excluded.

### Study Design

The present study was a local, 8-week, open labeled, phase IV clinical trial evaluating the efficacy and safety of S-amlodipine 2.5 and 5 mg in patients with hypertension who were treatment-naïve or had previously received antihypertensive monotherapy. The present study was approved by the clinical research ethics committee of Istanbul Medical Faculty Clinical Research, and the permission of Turkish Medicine and Medical Device Agency was obtained. All participants gave written

informed consent. The study was conducted in accordance with the Declaration of Helsinki and good clinical practice. This study is registered with ClinicalTrials.gov (NCT03038451).

During the 8-week treatment period, all patients received S-amlodipine besylate 2.5 mg once daily for the first 4 weeks, followed by S-amlodipine besylate 5 mg once daily for the second 4 weeks. The drug was taken at 08:00 o'clock in the morning with a glass of water via oral route. The use of medications that might affect the safety, tolerability, and/or efficacy assessments were not allowed over the course of study.

The patients were evaluated during the visits performed at baseline (day 0 and day 1) and on the fourth week (day 27 and day 28) and eighth week (day 55 and day 56). For efficacy assessments, ambulatory and office BP measurements (24 hours) were performed during the baseline, fourth-week, and eighth-week visits. For safety assessments, all adverse events and abnormal laboratory findings observed and/or reported over the study course were recorded. In addition to BP measurements, pulse rate, concomitant medications, and compliance with study treatment were recorded at all visits. For safety chemistry and hematology laboratory tests, blood samples were collected at the baseline and eighth-week visits. Electrocardiography was also performed at the baseline and eighth-week visits. Besides, protocol deviations were recorded in the case report forms. Patients with major protocol deviations were excluded from the study.

### Primary and Secondary End Points

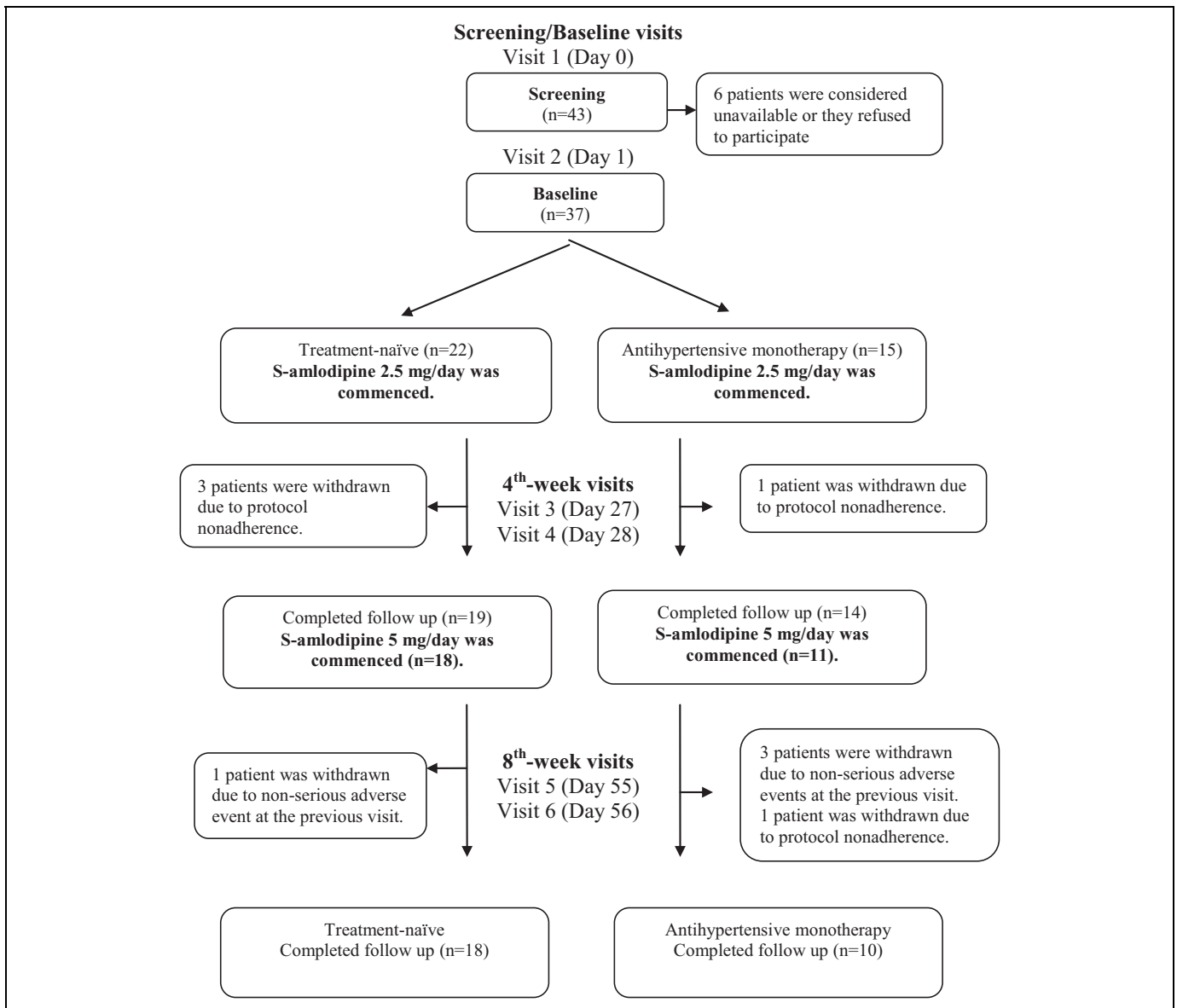
The primary end point of the present study was the change in SBP from the baseline (day 1) to fourth week (day 28). The secondary end points of the study were the change in DBP from the baseline (day 1) to fourth week (day 28), the change in SBP and DBP from the baseline (day 1) to eighth week (day 56), the change in SBP and DBP from the fourth week (day 28) to eighth week (day 56), and the evaluation of BP control rates.

### Measurements

Office BP measurement was performed using a clinical-trial-use approved, validated, and calibrated oscillatory BP measurement device (Omron 7051T, Kyoto, Japan). Three measurements were performed in sitting position at 1- to 2-minute intervals after 5-minute resting, and the arithmetic mean of 3 measurements was calculated.<sup>11</sup>

Ambulatory BP measurement was performed by Holter monitors (Schiller, BR-102 Plus) attached to the patients at the baseline (day 0), on day 27, and on day 55. Holter monitors were removed during the visit on the next day, and recordings were evaluated. Whole-day (24 hours) mean BP as well as daytime and nighttime mean BPs were calculated.

The biochemical analyses performed during the baseline and final visits were as follows: fasting plasma glucose, serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, sodium,



**Figure 1.** Study flow chart.

potassium, calcium, chloride, uric acid, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, creatine kinase, complete blood count, and urinalysis (microalbuminuria and microscopic urine analysis).

### Statistical Analysis and Sample Size

Statistical analysis software program was used for the statistical analysis. Descriptive statistics were expressed as mean, standard deviation (SD), median, minimum, and maximum for the numerical variables and as number and percentage for the categorical variables. For numerical variables, before-after analyses were performed using paired *t* test in case condition for normal distribution was provided, whereas the Wilcoxon signed-rank test was used in case the condition for normal

distribution was not provided. The level of statistical significance was considered  $P < .05$ .

For treatment-naïve patients, it was estimated that at least 24 patients were required to include with a predicted change of  $8 \pm 1$  mm Hg with S-amlodipine treatment with a power of 80% within 95% confidence interval. For the patients who had previously received antihypertensive monotherapy, it was estimated that at least 18 patients were required to include with a power of 80% within 95% confidence interval with the accepted value for noninferiority margin of 3 mm Hg and with the predicted SD of 2 units.

Although the number of enrolled patients was lower than the estimated number, the results reached to a power of 80% for the primary end point (the change in SBP from the baseline [day 1] to fourth week [day 28]) and for almost all objectives in the

**Table 1.** General Characteristics of the Patients Who Completed the First 4 Weeks of the Study.<sup>a</sup>

Characteristics	Treatment Naive (n = 19)	Antihypertensive Monotherapy (n = 14)
Age, year	51.9 (10.8)	51.9 (6.2)
Gender		
Female	6 (31.6)	7 (50.0)
Male	13 (68.4)	7 (50.0)
Height, m	1.69 (0.09)	1.67 (0.14)
Body weight, kg	82.8 (13.8)	85.1 (15.7)
Body mass index	28.8 (3.6)	30.6 (5.1)
Current smoker	8 (42.1)	6 (42.9)
Alcohol consumption	5 (26.3)	6 (42.9)

<sup>a</sup>The values are demonstrated as mean (SD) or number (%), where appropriate.

treatment-naive arm. Noninferiority analysis of the second arm of the study was discussed at the discussion section as well.

**Results**

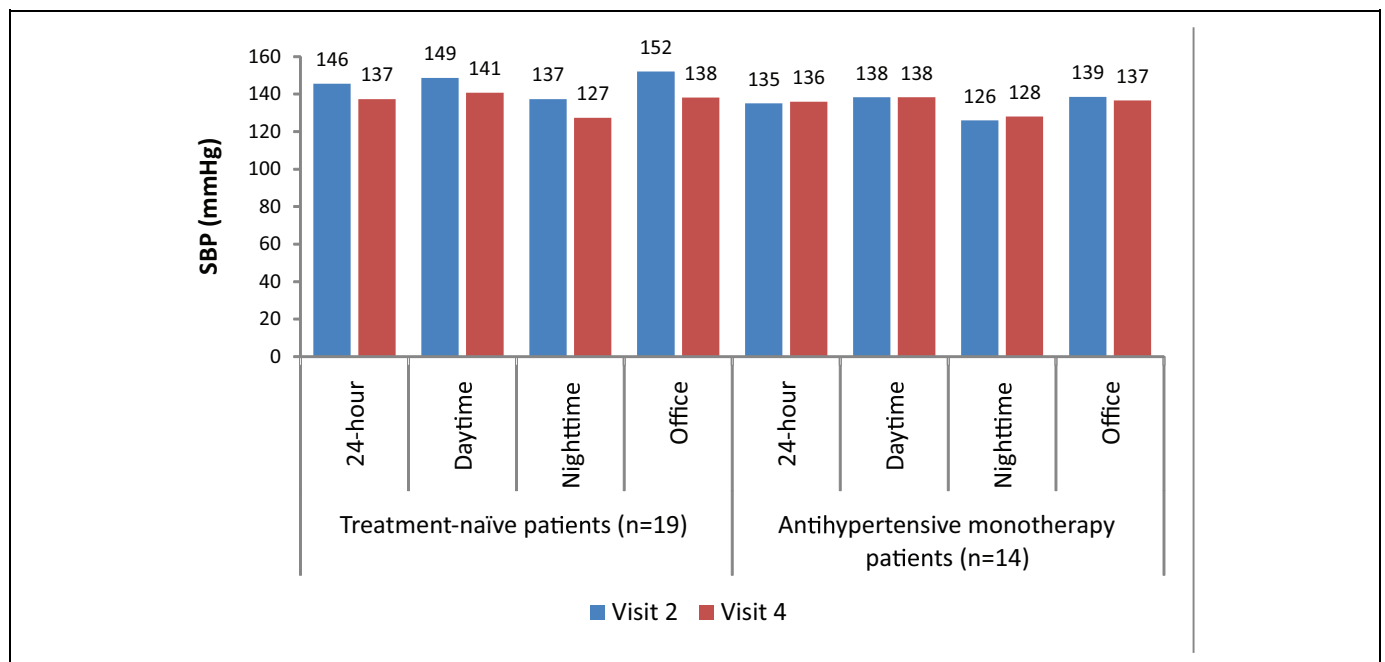
Of 43 patients evaluated at the screening visit, 33 were enrolled and 28 of these patients completed the study. The study flow-chart is illustrated in Figure 1. General characteristics of 33 patients who completed the first 4 weeks of the study are summarized in Table 1. The present study was designed as an uncontrolled study without a run-in period. We evaluated both the office and ambulatory BP levels to confirm the diagnosis of hypertension. We also compared the office SBP and DBP levels between visit 1 (day 0) and visit 2 (day 1; 1 day untreated period) in the treatment-naive arm, and there was no significant

**Table 2.** Systolic Blood Pressure Changes After 4 Weeks of Treatment With S-Amlodipine 2.5 mg/d.<sup>a</sup>

Parameter	Baseline (Second Visit)	Fourth Week (Fourth Visit)	Difference (Fourth Week-Baseline)	P
Treatment-naive patients (n = 19)				
Ambulatory SBP	Mean (SD), Median (Min-Max)	Mean (SD), Median (Min-Max)	Mean (SD), Median (Min-Max)	
24-hour SBP	145.5 (7.6), 146 (134-161)	137.4 (7.6), 138 (123-148)	-8.2 (7.5), -9.0 (-21 to 10)	<b>.0002</b>
Daytime SBP	148.6 (8.3), 149 (133-162)	140.7 (9.7), 143 (125-157)	-7.9 (8.7), -10 (-24 to 13)	<b>.0002</b>
Nighttime SBP	137.3 (8.9), 136 (123-159)	127.3 (7.7), 127 (115-144)	-10 (9.8), -12 (-23 to 11)	<b>.0003</b>
Office SBP	152.1 (10.2), 149 (137-172)	138.2 (8.2), 138 (120-150)	-13.9 (7.9), -13 (-38 to -4)	<b>&lt;.0037</b>
Antihypertensive monotherapy patients (n = 14)				
Ambulatory SBP				
24-hour SBP	135.1 (8.3), 132 (125-153)	135.9 (8.5), 133.5 (120-151)	0.8 (7.6), 2.5 (-12 to 11)	.681
Daytime SBP	138.3 (7.7), 135.5 (129-155)	138.3 (9.6), 139.5 (117-152)	0 (8.9), 3 (-18 to 16)	1.000
Nighttime SBP	126.0 (11.9), 123 (109-151)	128.0 (12.4), 127 (109-156)	2 (10.2), 1.5 (-20 to 25)	.475
Office SBP	138.5 (9.9), 137.5 (124-155)	136.7 (9.7), 133.5 (123-158)	-1.8 (5.9), -1 (-12 to 7)	<b>&lt;.0037</b>

<sup>a</sup>Boldface values denote significance at *p* < .05.

Abbreviations: Min-Max, minimum-maximum; SBP, systolic blood pressure; SD, standard deviation.



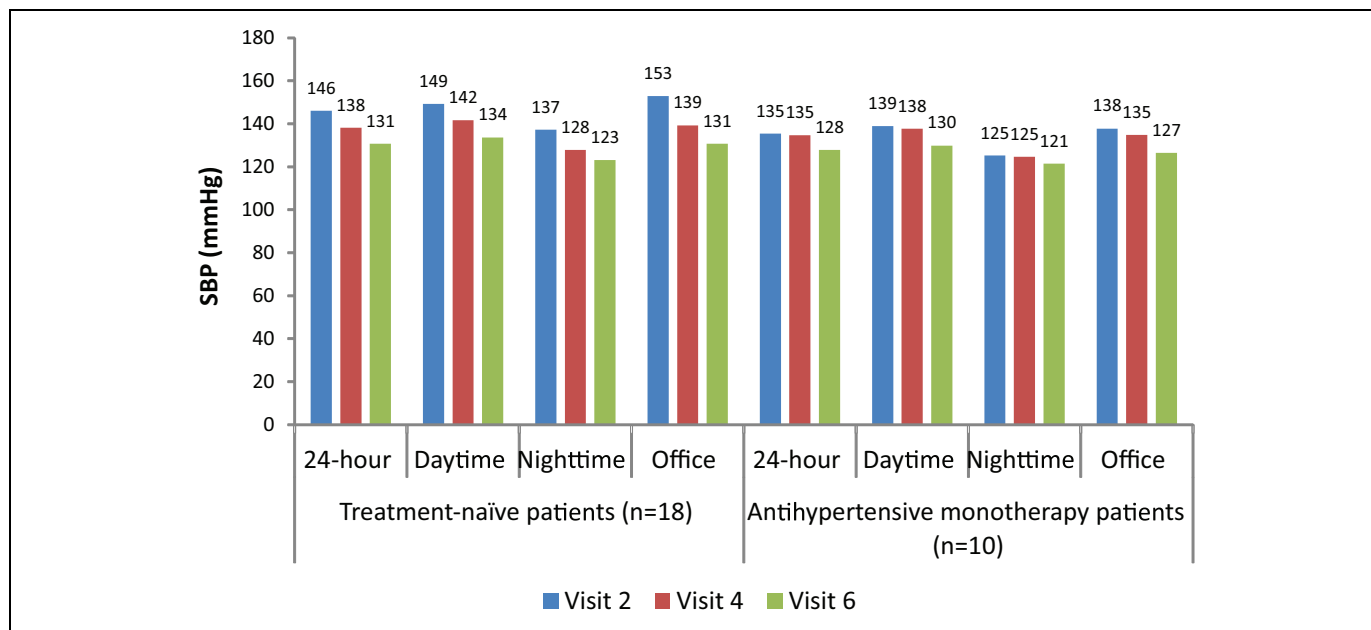
**Figure 2.** Changes in systolic blood pressures (SBP) after 4 weeks of treatment with S-amlodipine 2.5 mg/d.

**Table 3.** Systolic Blood Pressure Changes After 4 Weeks of Treatment With S-Amlodipine 5 mg/d.<sup>a</sup>

Parameter	Baseline (Second Visit)	Fourth Week, (Fourth Visit)	Eighth Week, (Sixth Visit)	Difference,		P
				(Eighth Week-Baseline)	(Eighth Week-Fourth Week)	
Treatment naive (n = 18)						
Ambulatory SBP	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	
24-hour SBP	146.1 (7.5), 146 (134-161)	138.2 (6.9), 138 (126-148)	130.7 (8.2), 130 (117-145)	-15.3 (7.6), -14.5 (-28 to -4)]	-7.4 (7.4), -6 (-24 to 4)	<b>.0005</b>
Daytime SBP	149.3 (7.9), 149.5 (133-162)	141.6 (9.1), 143 (127-157)	133.6 (9.8), 133 (118-148)	-15.8 (8.8), -16 (-31 to 0)	-8 (9.5), -6.5 (-33 to 5)	<b>.0005</b>
Nighttime SBP	137.3 (9.1), 134.5 (123-159)	127.9 (7.5), 127 (115-144)	123.2 (11.5), 125 (97-148)	-14.1 (9.9), -12 (-36 to 3)	-4.7 (10.7), -6 (-24 to 19)	.078
Office SBP	152.9 (9.7), 150.5 (140-172)	139.2 (7.2), 139 (122-150)	130.7 (7.6), 132 (120-142)	-22.2 (8.0), -22 (-38 to -10)	-8.4 (6.7), -7 (-21 to 0)	<b>.0001</b>
AH monotherapy patients (n = 10)						
Ambulatory SBP	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	
24-hour SBP	135.4 (9.5), 132 (125-153)	134.7 (7.3), 133.5 (122-144)	127.8 (3.8), 128 (121-135)	-7.6 (10.6), -5.5 (-25 to -3)	-6.9 (6.1), -5 (-17 to 1)	<b>.006</b>
Daytime SBP	139.0 (8.4), 135.5 (129-155)	137.7 (8.9), 139.5 (117-150)	129.9 (5.5), 130 (121-138)	-9.1 (11.1), -8 (-26 to 6)	-7.8 (7.5), -6.5 (-21 to 4)	<b>.009</b>
Nighttime SBP	125.2 (13.7), 122 (109-151)	124.7 (10.5), 125.5 (109-147)	121.4 (6.4), 123.5 (107-130)	-3.8 (12.5), -1.5 (-27 to 8)	-3.3 (11.3), -4.5 (-11 to 12)	.382
Office SBP	137.8 (10.3), 137.5 (124-155)	134.9 (6.9), 133.5 (123-146)	126.5 (5.5), 125.5 (118-136)	-11.3 (10.2), -18.6 (-32 to 3)	-8.4 (7.1), -13.5 (-20 to 4)	<b>.0024</b>

<sup>a</sup>Boldface values denote significance at p < .05.

Abbreviations: min-max, minimum-maximum; SBP, systolic blood pressure; SD, standard deviation.



**Figure 3.** Changes in systolic blood pressures (SBP) after 4 weeks of treatment with S-amlodipine 5 mg/d.

difference (SBP levels were 153.21 and 152.11 mm Hg at visit 1 and visit 2, respectively,  $P = .46$ ; DBP levels were 90 and 89 mm Hg at visit 1 and visit 2, respectively,  $P = .18$ ).

Changes in SBP after 4 weeks of treatment with S-amlodipine 2.5 mg/d are demonstrated in Table 2 and in Figure 2. Moreover, SBP changes after 4 weeks of treatment with S-amlodipine 5 mg/d are presented in Table 3 and in Figure 3.

According to the results of the study, a significant reduction was observed in the SBP level of the treatment-naïve patients in the first 4 weeks of treatment with S-amlodipine 2.5 mg. Likewise, a reduction in the SBP level with S-amlodipine 5 mg was also significant. Significant additional SBP decreases were achieved with dose titration.

Noninferiority evaluation in the antihypertensive monotherapy group revealed that the office and ambulatory SBP levels achieved with S-amlodipine 2.5 and 5 mg treatments were generally noninferior to those achieved with the medications that the patients had received before participating in the study.

Changes in the DBP levels of the patients are demonstrated in Table 4 and in Figures 4 and 5. According to the results of the present study, a significant reduction was observed in the DBP level with S-amlodipine treatment and noninferiority of S-amlodipine was demonstrated in the patients who had received monotherapy before.

At the end of the study, the rate of the treatment-naïve patients with BP under control (SBP/DBP <140/90 mm Hg) was 53% (10/19) with S-amlodipine 2.5 mg treatment and it increased to 78% (14/18) with S-amlodipine 5 mg treatment.

All of the patients participated in the study ( $n = 43$ ) were included in the safety assessment. In the patients completing the study ( $n = 28$ ), as compared with baseline, the changes in the biochemical parameters did not significantly differ after 8

weeks of treatment (Table 5). In addition, the changes in the hematological parameters, except for hematocrit levels, did not significantly differ after 8 weeks of treatment as compared with baseline (Table 5). Over the study course, among 43 patients, a total of 5 adverse events (uncontrolled hypertension, headache, pretibial edema [ $n = 2$ ], redness, and sensation of warmth in the neck and over the clavicle) likely to be associated with the study drug were observed. All of these adverse events, which were seen in 3 patients in the antihypertensive monotherapy group and in 2 patients in the treatment-naïve group, were categorized as “nonserious” (Table 6). One case of pretibial edema, one case of headache, and one case of sensation of warmth in the neck and over the clavicle were detected at the fourth-week visit, and one case of pretibial edema was detected at the final visit. One patient visited the study site after 10 days of S-amlodipine 5 mg dose titration was performed (the patient’s ambulatory SBP/DBP and pulse rate were 151/90 mm Hg and 70 bpm, respectively, at the fourth-week visit). According to the patient’s self-report, the patient visited a hospital’s emergency 3 days ago with the complaint of high BP after having measured his/her BP at a pharmacy and obtaining an SBP of approximately 170 mm Hg and was given sublingual tablet without hospitalization and prescribed ramipril 5 mg/d in addition to the daily treatment by the physician of the emergency department. The patient was evaluated as uncontrolled hypertension. Accordingly, the patient was prescribed a new treatment and was excluded from the study. All events were reported to the ethics committee and the Turkish Medicine and Medical Device Agency. No other significant safety issue was determined during the baseline and final visits. There was no problem neither in ambulatory (nighttime, daytime, and mean) and office pulse rates nor in body temperature measured over the study course.

**Table 4.** Changes in the Diastolic Blood Pressure With S-Amlodipine Treatment.<sup>a</sup>

Parameter	Baseline, (Visit 2)	Fourth Week, (Visit 4)	Eighth Week, (Visit 6)	Difference, (Eighth Week-Baseline)		Difference, (Eighth Week-Fourth Week)		P
				Mean (SD), Median (min-max)	P	Mean (SD), Median (min-max)	P	
Treatment-naïve patients (n = 18)								
Ambulatory DBP	87.1 (8.7), 88 (73-106)	82.7 (6.2), 82.5 (72-97)	77.7 (6.6), 74.5 (68-92)	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)		
24-hour DBP	89.4 (8.7), 89 (77-110)	85.2 (7.2), 84.5 (73-101)	79.8 (7.9), 78.5 (69-96)					<b>.0002</b>
Daytime DBP	81.1 (10.5), 78 (63-99)	75.8 (6.4), 76 (65-92)	71.4 (7.1), 70 (56-83)					<b>.0003</b>
Nighttime DBP	89.2 (5.1), 90 (78-98)	83.8 (4.8), 84 (74-90)	79.8 (4.4), 78 (72-90)					<b>.013</b>
Office DBP								<b>.0019</b>
Antihypertensive monotherapy patients (n = 10)								
Ambulatory DBP	82.8 (7.3), 81.5 (75-97)	82.5 (7.0), 82.5 (67-90)	78 (4.7), 78.5 (70-88)					<b>.008</b>
24-hour DBP	85.6 (7.4), 83.5 (78-99)	84.1 (7.5), 84.5 (67-93)	79.7 (4.4), 80 (71-89)					<b>.019</b>
Daytime DBP	75.4 (8.7), 74.5 (63-90)	77.7 (7.9), 76 (69-93)	73.7 (7.4), 75.5 (63-84)					.131
Nighttime DBP	85.1 (7.2), 84 (76-100)	80.9 (3.6), 80 (76-88)	78.4 (4.3), 79.5 (70-83)					.1147
Office DBP								

<sup>a</sup>Boldface values denote significance at  $p < .05$ .

Abbreviations: DBP, Diastolic blood pressure; min-max, minimum-maximum; SD, Standard deviation.

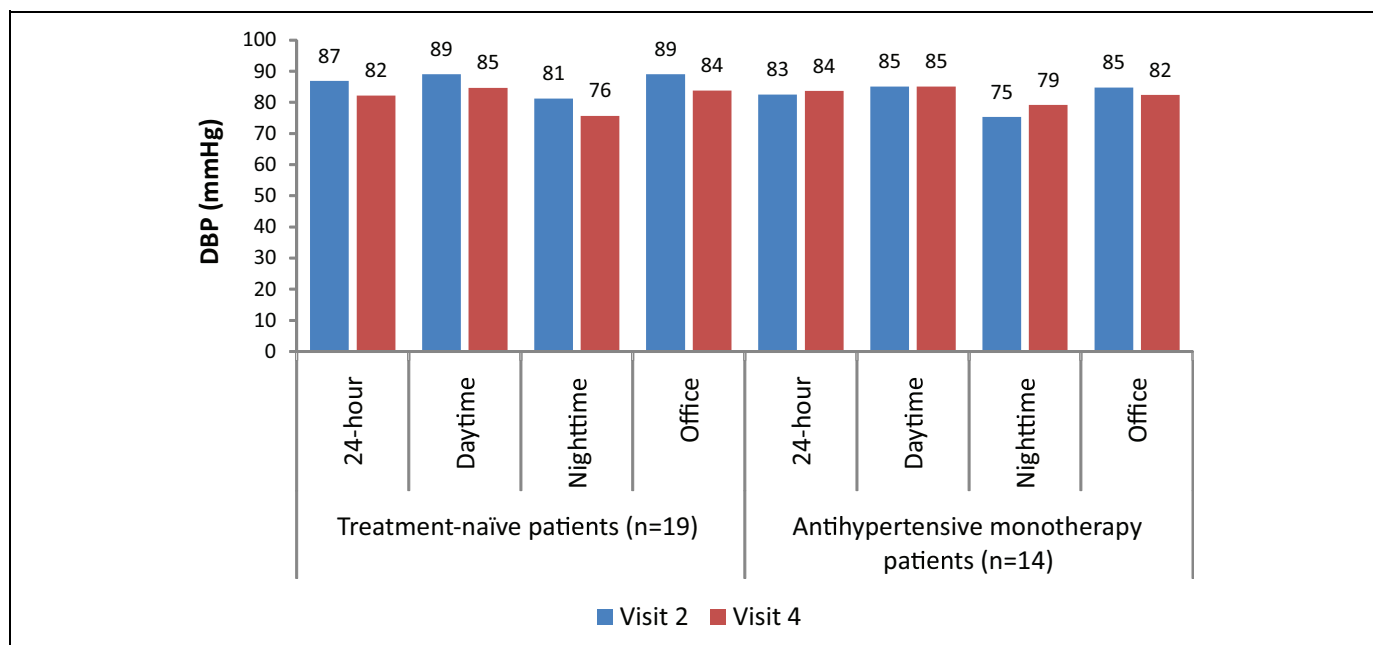


Figure 4. Changes in diastolic blood pressures (DBP) after 4 weeks of treatment with S-amlodipine 2.5 mg/d.

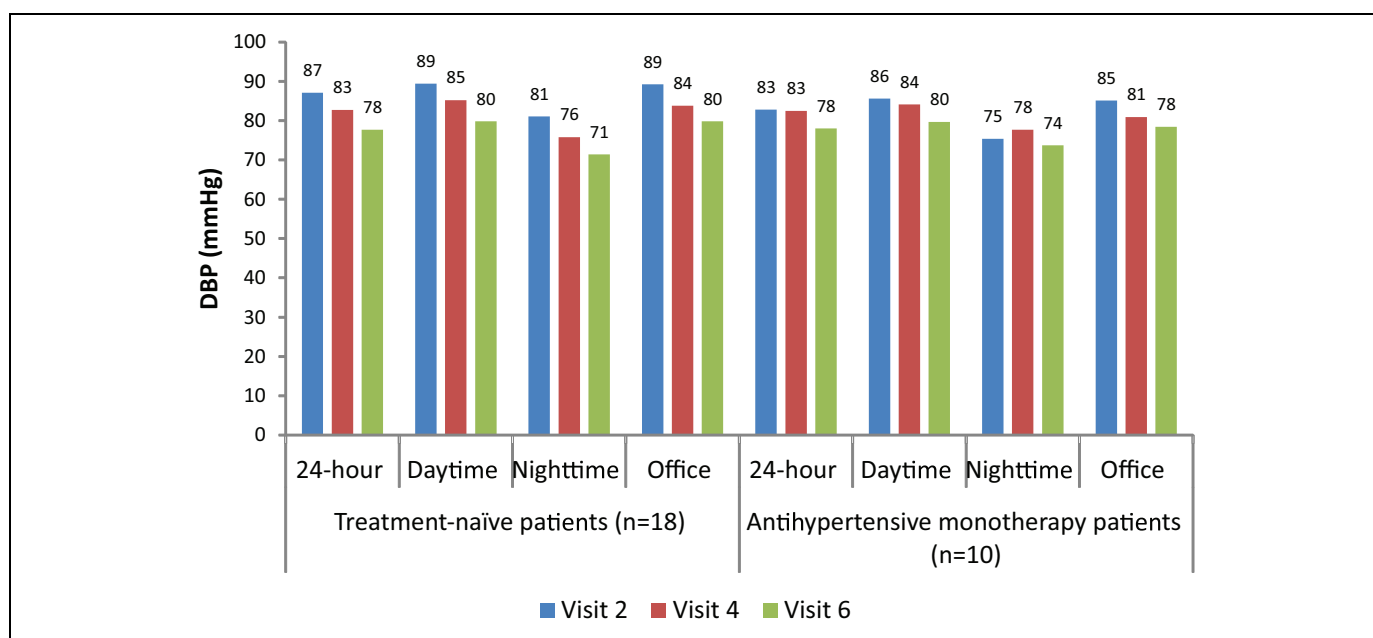


Figure 5. Changes in diastolic blood pressures (DBP) after 4 weeks of treatment with S-amlodipine 5 mg/d.

**Discussion**

Calcium channel blockers used in the treatment of hypertension inhibit voltage-dependent L-type calcium channels in vascular smooth muscle and myocardial cell membrane. They reduce entry of Ca<sup>2+</sup> into the vascular smooth muscle and myocardial cells and accordingly impair excitation–contraction relationship by lowering cytosolic Ca<sup>2+</sup> level; consequently, vasodilatation occurs and peripheral resistance decreases.<sup>12</sup> Antihypertensive mechanism of action of amlodipine depends

on direct spasmolytic effect on the vascular smooth muscle. The definite mechanism of action of amlodipine in relieving angina pectoris is unclear; however, amlodipine reduces total ischemic load in 2 ways. First, amlodipine reduces total peripheral resistance that the heart is exposed to (afterload) by dilating peripheral arterioles. As the heart beat rate remains stable, decreased cardiac load reduces myocardial energy consumption and oxygen requirement. Second, dilatation of the main coronary arteries and the arterioles both in normal and ischemic regions enhances myocardial oxygen



**Table 5.** Hematological and Biochemical Test Results of the Patients Completing the Study.<sup>a,b</sup>

Parameter	Baseline (Second Visit)	Eighth Week (Sixth Visit)	P
	Mean (SD), Median (min-max)	Mean (SD), Median (min-max)	
<b>Hematological parameters</b>			
Platelet, $\times 10^3/\mu\text{L}$	252.5 (55.8), 248.0 (144.0-353.0)	261.75 (58.1), 242.0 (160.0-367.0)	.11
Hemoglobin, g/dL	13.9 (1.6), 13.9 (10.6-17.4)	13.8 (1.9), 13.5 (9.0-18.9)	.87
Hematocrit, %	42.4 (4.3), 42.7 (33.9-53.4)	41.1 (4.7), 41.0 (30.3-56.4)	.007
MCV, fL	87.4 (5.6), 87.5 (74.0-96.0)	86.6 (5.4), 86.5 (75.0-95.0)	.08
MCH, pg	28.7 (2.3), 28.2 (23.0-32.9)	28.9 (2.6), 29.3 (22.1-33.3)	.12
MCHC, g/dL	32.5 (2.2), 32.3 (28.3-39.0)	33.5 (2.6), 33.6 (27.8-38.9)	.47
<b>Biochemical parameters</b>			
Glucose, mg/dL	101.6 (21.8), 95.0 (76.0-174.0)	108.93 (33), 101.5 (79.0-253.0)	.09
BUN, mg/dL	13.9 (4.0), 13.6 (7.0-26.2)	15.08 (4.15), 14.45 (9.3-25.2)	.08
Uric acid, mg/dL	5.4 (1.4), 5.6 (2.40-8.50)	5.0 (1.3), 5.05 (2.80-8.00)	.10
Creatinine, mg/dL	0.959 (0.19), 0.93 (0.65-1.39)	0.964 (0.15), 0.92 (0.76-1.24)	.50
Sodium, mEq/L	137.1 (2.7), 138.0 (130.0-142.0)	136.7 (3.2), 136.0 (130.0-144.0)	.67
Potassium, mEq/L	4.3 (0.4), 4.3 (3.7-5.3)	4.1 (0.3), 4.2 (3.4-4.6)	.14
Chloride, mEq/L	101.5 (5.8), 100.0 (93.0-117.0)	99.9 (4.8), 98.0 (93.0-112.0)	.20
Calcium, mg/dL	9.44 (0.64), 9.4(8.4-11.2)	9.36 (0.49), 9.4(8.6-10.40)	.52
ALT, U/L	29.7 (14.0), 26.0 (13.0-69.0)	28.9 (12.6), 33.8 (12.0-72.0)	.70
AST, U/L	25.9 (9.6), 23.5 (16.0-66.0)	26.6 (9.8), 24.0 (15.0-52.0)	.64
Creatine kinase, UI/L	107.4 (51.6), 94.0 (51.0-247.0)	107.1 (93.7), 81.5 (40.0-538.0)	.09
Total cholesterol, mg/dL	228.3 (44.8), 230.5 (125.0-336.0)	229.3 (30.8), 228.0 (153.0-308.0)	.97
LDL cholesterol, mg/dL	135.9 (34.1), 141.5 (76.0-209.0)	135.32 (30.0), 137.5 (59.0-188.0)	.94
HDL cholesterol, mg/dL	60.24 (19.9), 58.0 (32.0-112.0)	60.1 (18.2), 55.0 (33.0-94.0)	.7
Triglyceride, mg/dL	155.3 (79.1), 146.0 (54.0-327.0)	171.4 (83.4), 161.0 (58.0-395.0)	.29

<sup>a</sup>Boldface values denote significance at  $p < .05$ .

<sup>b</sup>N = 28.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; min-max, minimum-maximum; SD, standard deviation.

**Table 6.** Adverse Events.

Dosage	Treatment Naive	Antihypertensive Monotherapy
S-amlodipine 2.5 mg	Headache (n = 1)	Uncontrolled hypertension (n = 1), Pretibial edema (n = 1), Redness and sensation of warmth in the neck and over the clavicle (n = 1)
S-amlodipine 5 mg	Pretibial edema (n = 1)	

supply in patients with coronary artery spasm (Prinzmetal's or variant angina).<sup>13</sup>

As a racemic mixture, amlodipine comprises R- and S-amlodipine isomers. R-amlodipine is 1000 times less effective; moreover, it is considered to cause adverse effects. S-amlodipine is responsible for antihypertensive and antianginal actions.<sup>13</sup> Pharmacokinetic and pharmacodynamic features and safety profiles of S-amlodipine and racemic amlodipine were compared in many studies.<sup>14-22</sup> Randomized clinical studies have reported that S-amlodipine 2.5 mg and S-amlodipine 5 mg are bioequivalent in terms of absorption and elimination and that they are similar in controlling BP and in tolerability.<sup>18,19,21,22</sup> Similar outcomes have been obtained in the studies comparing S-amlodipine 5 mg and racemic

amlodipine 10 mg.<sup>16,17</sup> In addition, in China, S-amlodipine was demonstrated to be cost-effective as compared to racemic amlodipine.<sup>23</sup>

A single dose of S-amlodipine 2.5 mg is recommended as the starting dose in the treatment of hypertension, and the dose can be titrated to maximum 5 mg/d depending on the patient's response.<sup>13</sup> In the present study, which was performed to evaluate efficacy and safety of S-amlodipine at a daily dose of 2.5 (low) and 5 mg (high) on BP control in adult hypertensive patients, significant reductions were observed both in SBP and DBP levels in the treatment-naive patients after 4 weeks of treatment with S-amlodipine 2.5 mg/d. Afterward, the patients received S-amlodipine 5 mg/d between the fourth and eighth weeks; the reductions in office and ambulatory BPs at the eighth week with respect to the baseline was found to be significant. Additional significant reductions were achieved in office and ambulatory BPs with dose titration (difference between eighth week and fourth week). Considering overall study outcomes within this context, it was concluded that S-amlodipine is an effective therapeutic option at the doses of 2.5 and 5 mg in the treatment of hypertensive patients.

In the study by Chen et al,<sup>24</sup> low-dose (2.5 mg/d) or high-dose (5 mg/d) S-amlodipine was randomly administered to the patients with mild or moderate hypertension for 8 weeks. In the low-dose group (n = 263), 24-hour ambulatory SBP/DBP value

decreased from  $131.5 \pm 15.0/82.1 \pm 10.7$  mm Hg at the baseline to  $126.0 \pm 13.5/78.5 \pm 9.5$  mm Hg at the eighth week. These values were  $133.6 \pm 13.7/83.1 \pm 9.9$  mm Hg at the baseline and  $125.0 \pm 12.0/78.2 \pm 8.9$  mm Hg at the eighth week in the high-dose group ( $n = 260$ ). Similar trends were also observed for daytime and nighttime ambulatory and clinical BP levels. Adverse events were found to be similar between the low-dose and high-dose groups.<sup>24</sup>

In the present study, noninferiority analysis performed in the antihypertensive monotherapy group revealed that office and ambulatory BPs achieved with S-amlodipine 2.5 mg and S-amlodipine 5 mg were generally noninferior to the drugs that the patients had received before participating in the study. Moreover, S-amlodipine 5 mg showed superiority in some parameters. Nevertheless, the number of patients was considered relatively low for arriving at a definite conclusion. Our findings, however, can be considered as preliminary outcomes for further comparative studies.

In the present study, in the patients completing the study ( $n = 28$ ), hematological and biochemical parameters revealed no significant change from baseline to 8 weeks of treatment, except for the hematocrit levels. The reason for the significant change for hematocrit levels could be attributed to the small sample size, and there was no safety concern due to laboratory test results; nevertheless, safety of S-amlodipine should be evaluated in future larger studies. In this study, a total of 5 adverse events (uncontrolled hypertension, headache, pretibial edema [ $n = 2$ ], and redness and sensation of warmth in the neck and over the clavicle) likely to be associated with the study drug were encountered over the study course. No serious adverse event was observed in the study. Leg edema is a side effect encountered with the use of dihydropyridine calcium channel blockers and may require dose reduction or drug discontinuation. Nevertheless, it has been reported that leg edema is less prevalent with S-amlodipine compared with racemic amlodipine.<sup>20,25</sup> In the present study, pretibial edema was determined in 2 patients (one at a dose of 2.5 mg/d and one at a dose of 5 mg/d).

The main limitation of the present study might be the relatively low number of patients; however, the results reached a power of 80% for the primary end point (the change in SBP from the baseline [day 1] to fourth week [day 28]) and for almost all objectives in the treatment-naïve arm. It was indicated that the number of treatment-naïve patients was sufficient to demonstrate the efficacy of S-amlodipine. On the other hand, as we mentioned above, the noninferiority analysis can be considered as a pilot evaluation for further comparative studies. Moreover, in the present study, high BP control rates were achieved by S-amlodipine 2.5 and 5 mg/d; this might be due to the low baseline BP levels of the study population comprising mostly patients with stage I hypertension. In addition, almost all of the studies with S-amlodipine were conducted on Far Eastern and Asian populations. Accordingly, it can be said that the present study is valuable in terms of evaluating and demonstrating the efficacy and safety of S-amlodipine in a different population. Nevertheless, it should be taken into

account that the promising results of the present single-center study were obtained in a small and highly selected population, and the patients were followed up for a short treatment period of 4 to 8 weeks. Therefore, for the results to be generalized to the universe of patients with hypertension, the efficacy and safety of S-amlodipine should be confirmed in more compelling and definitive controlled multicenter, long-term follow-up studies in a more diverse broadly representative population.

## Conclusion

In conclusion, a significant reduction in BP level was observed with S-amlodipine 2.5 mg/d and significant reductions both in office and ambulatory BPs were achieved with dose titration (5 mg/d). Moreover, both office and ambulatory BP levels obtained in the antihypertensive monotherapy group with S-amlodipine 2.5 mg and S-amlodipine 5 mg were generally noninferior to the drugs that the patients had received before participating in the study. In addition, it can be concluded that S-amlodipine has a good safety profile at both low and high doses because no serious adverse event was encountered.

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## Authors Contribution

S.Ş. contributed to conception and design, acquisition, analysis, and interpretation and drafted manuscript. M.D. contributed to conception and design, analysis, and interpretation. Z.Y. contributed to conception and interpretation. A.Y.Ü. contributed to conception and design, acquisition, analysis, and interpretation and drafted manuscript. All authors critically revised manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.


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