Online Supplement

Contents

Online-only Data Supplement

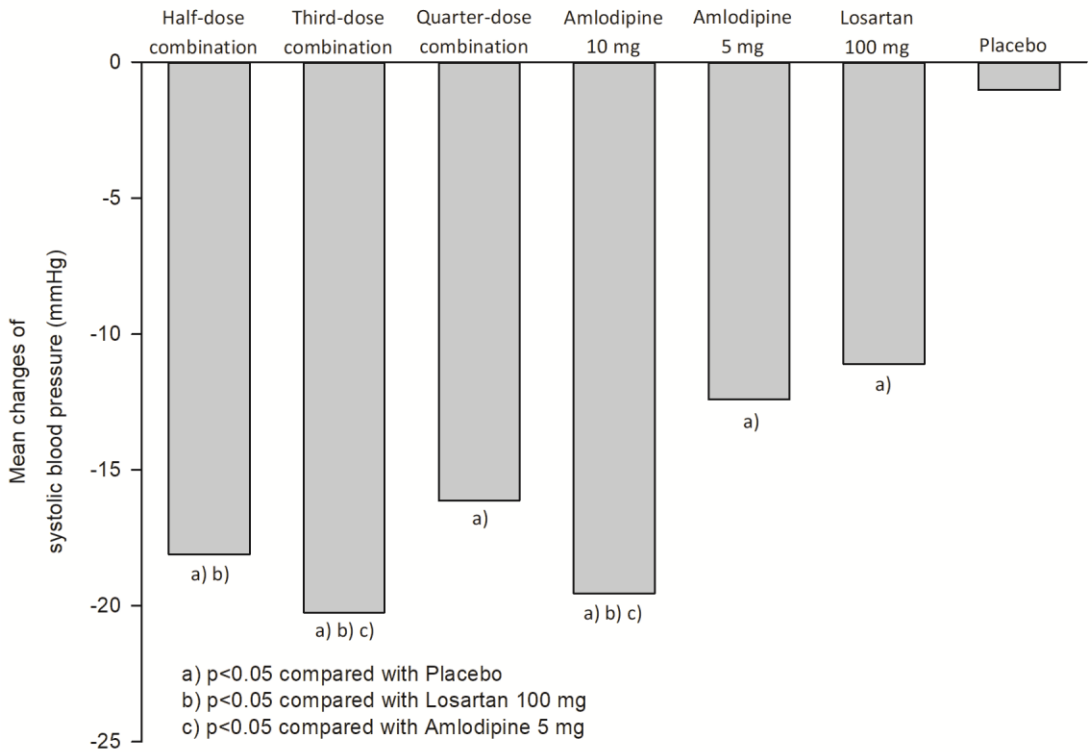
Primary efficacy result

Table S1. Change of sitting systolic blood pressure from baseline at week 8 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Baseline (mmHg)	155.32 (8.67)	153.71 (10.05)	154.36 (10.30)	154.32 (7.43)	154.65 (10.31)	154.57 (9.75)	153.62 (8.86)
Week 8 (mmHg)	137.21 (13.95)	133.15 (15.38)	138.23 (13.61)	134.77 (12.11)	142.25 (15.77)	143.47 (16.02)	152.59 (20.73)
Mean changes from baseline at week 8, mmHg	-18.11 (10.44)	-20.56 (17.87)	-16.13 (13.62)	-19.55 (10.67)	-12.40 (13.13)	-11.10 (15.89)	-1.03 (18.38)
Difference*							
to Placebo (95% CI)	-17.21 (-24.40, -10.00)	-19.49 (-28.19, -10.80)	-14.91 (-22.68, -7.13)	-18.49 (-25.95, -11.00)	-11.32 (-19.17, -3.47)	-9.86 (-18.25, -1.47)	
p value	<0.0001	<0.0001	0.0003	<0.0001	0.0054	0.0220	
to Losartan 100 mg (95% CI)	-6.84 (-13.19, -0.49)	-10.06 (-17.65, -2.47)	-5.13 (-11.88, 1.62)	-8.54 (-15.02, -2.06)	-1.27 (-8.23, 5.69)		
p value	0.0353	0.0102	0.1339	0.0106	0.7163		
to Amlodipine 5 mg (95% CI)	-5.68 (-11.36, 0.01)	-8.64 (-15.91, -1.37)	-3.83 (-10.10, 2.45)	-7.20 (-13.05, -1.35)			
p value	0.0502	0.0205	0.2280	0.0167			
to Amlodipine 10 mg (95% CI)	1.48 (-3.65, 6.60)	-1.42 (-8.12, 5.29)	3.43 (-2.29, 9.16)				
p value	0.5673	0.6745	0.2355				
to Quarter-dose combination (95% CI)	-1.73 (-7.40, 3.93)	-4.88 (-11.80, 2.03)					
p value	0.5441	0.1635					
to Third-dose combination (95% CI)	3.21 (-3.50, 9.91)						
p value	0.3434						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Data are mean (SD). *Least square mean difference in changes by ANCOVA.

Figure S1. Change of sitting systolic blood pressure from baseline at week 8 (full analysis set)



Secondary efficacy results

Table S2. Change of sitting diastolic blood pressure from baseline at week 8 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Baseline (mmHg)	92.43 (8.83)	91.29 (8.70)	94.09 (8.70)	90.68 (11.51)	92.51 (8.28)	89.31 (7.52)	90.47 (8.51)
Week 8 (mmHg)	83.78 (9.43)	82.02 (8.33)	86.10 (9.43)	80.05 (9.71)	84.53 (9.47)	86.54 (10.21)	91.45 (12.86)
Mean changes from baseline at week 8, mmHg	-8.65 (6.88)	-9.27 (7.77)	-7.99 (8.53)	-10.64 (8.65)	-7.99 (6.53)	-2.76 (7.25)	0.98 (9.89)
Difference*							
to Placebo (95% CI)	-9.36 (-13.48, -5.25)	-10.03 (-14.34, -5.71)	-8.17 (-12.71, -3.64)	-11.56 (-15.96, -7.16)	-8.77 (-12.93, -4.61)	-3.70 (-7.96, 0.55)	
p value	<0.0001	<0.0001	0.0006	<0.0001	<0.0001	0.0868	
to Losartan 100 mg (95% CI)	-5.52 (-8.90, -2.13)	-6.02 (-9.48, -2.57)	-4.12 (-7.97, -0.27)	-7.49 (-11.15, -3.84)	-4.97 (-8.37, -1.57)		
p value	0.0018	0.0009	0.0362	0.0001	0.0049		
to Amlodipine 5 mg (95% CI)	-0.69 (-3.84, 2.45)	-1.59 (-4.91, 1.73)	0.44 (-3.10, 3.99)	-3.29 (-6.70, 0.12)			
p value	0.6620	0.3415	0.8033	0.0585			
to Amlodipine 10 mg (95% CI)	2.62 (-0.75, 5.98)	1.63 (-1.85, 5.10)	4.07 (0.33, 7.80)				
p value	0.1253	0.3533	0.0333				
to Quarter-dose combination (95% CI)	-1.18 (-4.68, 2.32)	-2.37 (-6.01, 1.27)					
p value	0.5024	0.1976					
to Third-dose combination (95% CI)	0.95 (-2.34, 4.24)						
p value	0.5657						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Data are mean (SD). *Least square mean difference in changes by ANCOVA.

Figure S2. Change of sitting diastolic blood pressure from baseline at week 8 (full analysis set)

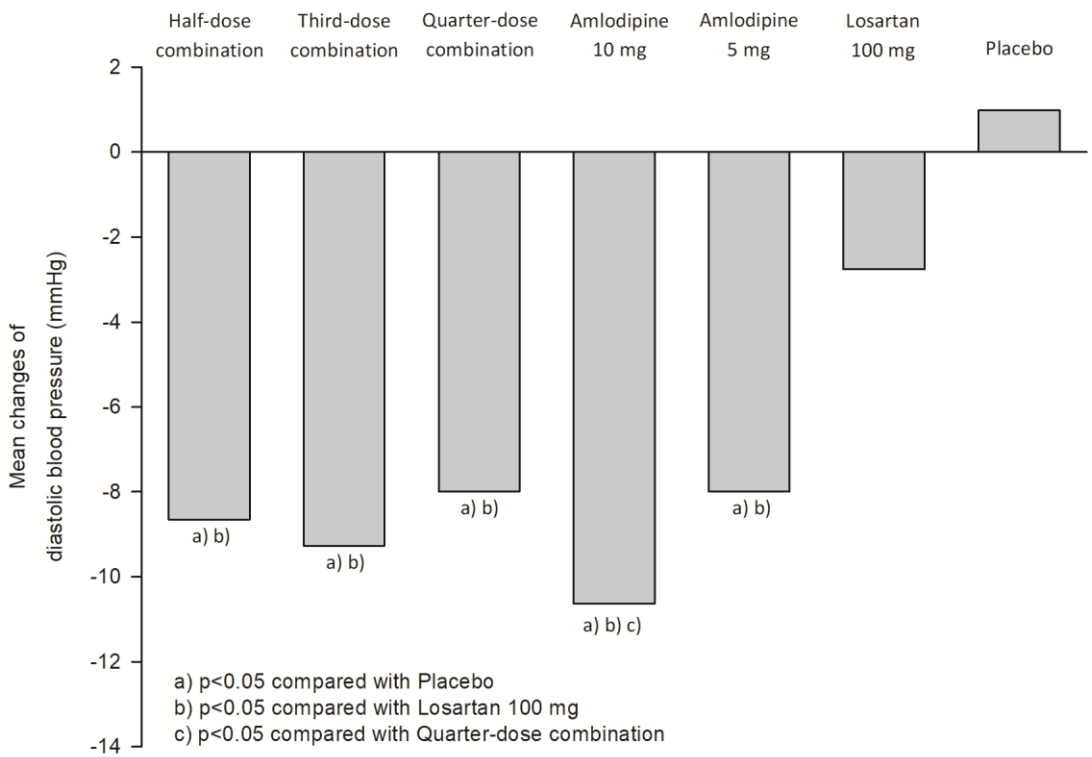


Table S3. Change of sitting systolic blood pressure from baseline at week 4 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Baseline (mmHg)	155.32 (8.67)	153.71 (10.05)	154.36 (10.30)	154.32 (7.43)	154.65 (10.31)	154.57 (9.75)	153.62 (8.86)
Week 4 (mmHg)	136.25 (12.90)	140.73 (12.93)	139.39 (13.96)	134.27 (13.26)	143.87 (10.65)	146.37 (18.87)	157.23 (17.97)
Mean changes from baseline at week 4, mmHg	-19.07 (12.61)	-12.98 (13.53)	-14.97 (14.47)	-20.05 (11.89)	-10.78 (9.30)	-8.21 (16.48)	3.61 (14.49)
Difference*							
to Placebo (95% CI)	-22.47 (-29.04, -15.90)	-16.57 (-23.44, -9.70)	-18.40 (-25.38, -11.40)	-23.69 (-30.26, -17.10)	-14.26 (-20.21, -8.31)	-11.87 (-19.52, -4.23)	
p value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0029	
to Losartan 100 mg (95% CI)	-10.69 (-17.65, -3.73)	-5.06 (-12.33, 2.21)	-6.84 (-14.17, 0.50)	-11.87 (-18.94, -4.79)	-2.56 (-9.00, 3.88)		
p value	0.0031	0.1696	0.0671	0.0014	0.4307		
to Amlodipine 5 mg (95% CI)	-8.02 (-13.04, -3.00)	-2.65 (-7.83, 2.54)	-4.33 (-9.75, 1.09)	-9.37 (-14.43,-4.31)			
p value	0.0022	0.3121	0.1156	0.0005			
to Amlodipine 10 mg (95% CI)	1.32 (-4.48, 7.12)	6.79 (0.78, 12.81)	5.09 (-1.09, 11.28)				
p value	0.6510	0.0275	0.1049				
to Quarter-dose combination (95% CI)	-3.60 (-9.63, 2.43)	1.62 (-4.61, 7.84)					
p value	0.2380	0.6059					
to Third-dose combination (95% CI)	-5.25 (-11.14, 0.65)						
p value	0.0801						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Data are mean (SD). *Least square mean difference in changes by ANCOVA.

Table S4. Change of sitting diastolic blood pressure from baseline at week 4 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Baseline (mmHg)	92.43 (8.83)	91.29 (8.70)	94.09 (8.70)	90.68 (11.51)	92.51 (8.28)	89.31 (7.52)	90.47 (8.51)
Week 4 (mmHg)	82.75 (9.32)	85.77 (9.51)	88.43 (9.98)	80.21 (9.15)	85.82 (8.91)	86.94 (9.87)	92.08 (10.38)
Mean changes from baseline at week 4, mmHg	-9.68 (8.03)	-5.52 (7.51)	-5.66 (8.85)	-10.47 (8.56)	-6.69 (6.28)	-2.37 (7.77)	1.61 (8.20)
Difference*							
to Placebo (95% CI)	-10.72 (-14.51, -6.93)	-6.91 (-10.70, -3.12)	-6.18 (-10.28, -2.08)	-11.99 (-15.71, -8.28)	-7.84 (-11.37, -4.31)	-4.32 (-8.12, -0.51)	
p value	<0.0001	0.0005	0.0037	<0.0001	<0.0001	0.0269	
to Losartan 100 mg (95% CI)	-6.46 (-10.20, -2.73)	-2.70 (-6.40, 1.00)	-1.93 (-6.01, 2.15)	-7.56 (-11.19, -3.92)	-3.69 (-7.16, -0.22)		
p value	0.0010	0.1498	0.3489	<0.0001	0.0374		
to Amlodipine 5 mg (95% CI)	-2.95 (-6.15, 0.24)	1.07 (-2.10, 4.25)	1.52 (-2.03, 5.07)	-4.43 (-7.63, -1.22)			
p value	0.0697	0.5019	0.3957	0.0076			
to Amlodipine 10 mg (95% CI)	1.50 (-1.94, 4.93)	5.26 (1.82, 8.70)	6.24 (2.47, 10.02)				
p value	0.3875	0.0033	0.0016				
to Quarter-dose combination (95% CI)	-4.58 (-8.32, -0.85)	-0.61 (-4.42, 3.20)					
p value	0.0170	0.7514					
to Third-dose combination (95% CI)	-4.00 (-7.42, -0.58)						
p value	0.0227						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Data are mean (SD). *Least square mean difference in changes by ANCOVA.

Table S5. Blood pressure control rate (Proportion of Subjects with sitting systolic blood pressure < 140 mmHg and sitting diastolic blood pressure < 90 mmHg) at week 4 and 8 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Week 4							
Controlled, n (%)	21 (58.33%)	15 (45.45%)	17 (48.57%)	21 (63.64%)	11 (32.35%)	11 (32.35%)	3 (9.09%)
p-value[a)]	<0.0001[†]	0.0009[†]	0.0004[†]	<0.0001[†]	0.0192[†]	0.0192[†]	
p-value[b)]	0.0292[†]	0.2712[†]	0.1702[†]	0.0104[†]	1.0000[†]		
p-value[c)]	0.0292[†]	0.2712[†]	0.1702[†]	0.0104[†]			
p-value[d)]	0.6521[†]	0.1380[†]	0.2111[†]				
p-value[e)]	0.4096[†]	0.7969[†]					
p-value[f)]	0.2847[†]						
Week 8							
Controlled, n (%)	23 (63.89%)	23 (69.70%)	20 (57.14%)	22 (66.67%)	15 (44.12%)	14 (41.18%)	6 (18.18%)
p-value[a)]	0.0001[†]	<0.0001[†]	0.0010[†]	0.0001[†]	0.0221[†]	0.0397[†]	
p-value[b)]	0.0571[†]	0.0189[†]	0.1848[†]	0.0364[†]	0.8063[†]		
p-value[c)]	0.0970[†]	0.0346[†]	0.2793[†]	0.0635[†]			
p-value[d)]	0.8088[†]	0.7916[†]	0.4193[†]				
p-value[e)]	0.5609[†]	0.2832[†]					
p-value[f)]	0.6092[†]						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Compared with: a) Placebo; b) Losartan 100 mg; c) Amlodipine 5 mg; d) Amlodipine 10 mg; e) Quarter-dose combination; f) Third-dose combination.
p-value: [†] Pearson's chi-square test.

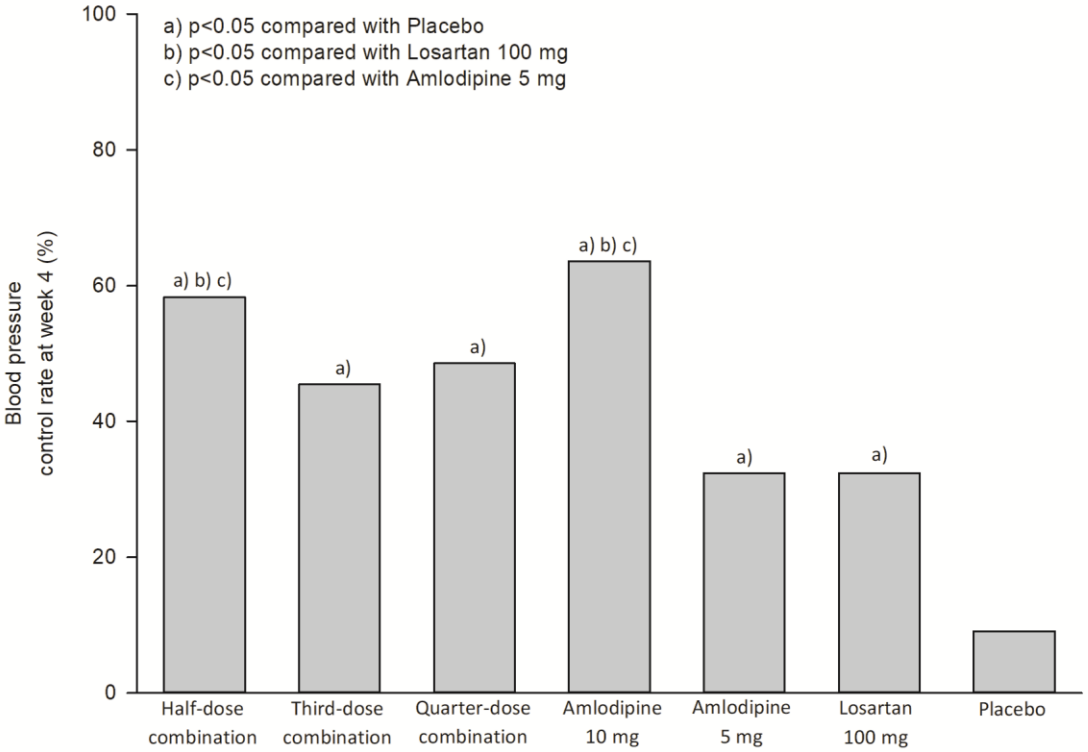
Table S6. Blood pressure response rate (Proportion of subjects, sitting systolic blood pressure ≥20 mmHg and/or sitting diastolic blood pressure ≥10 mmHg lowered from baseline) at week 4 and 8 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Week 4							
Responder, n (%)	19 (52.78%)	11 (33.33%)	18 (51.43%)	20 (60.61%)	11 (32.35%)	10 (29.41%)	2 (6.06%)
p-value[a)]	<0.0001†	0.0053‡	<0.0001†	<0.0001†	0.0065‡	0.0127†	
p-value[b)]	0.0473†	0.7294†	0.0626†	0.0103†	0.7930†		
p-value[c)]	0.0844†	0.9319†	0.1085†	0.0204†			
p-value[d)]	0.5123†	0.0264†	0.4462†				
p-value[e)]	0.9094†	0.1316†					
p-value[f)]	0.1036†						
Week 8							
Responder, n (%)	21 (58.33%)	20 (60.61%)	18 (51.43%)	21 (63.64%)	16 (47.06%)	11 (32.35%)	7 (21.21%)
p-value[a)]	0.0017†	0.0011†	0.0098†	0.0005†	0.0259†	0.3037†	
p-value[b)]	0.0292†	0.0204†	0.1085†	0.0104†	0.2153†		
p-value[c)]	0.3449†	0.2662†	0.7166†	0.1725†			
p-value[d)]	0.6521†	0.7997†	0.3090†				
p-value[e)]	0.5588†	0.4462†					
p-value[f)]	0.8477†						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Compared with: a) Placebo; b) Losartan 100 mg; c) Amlodipine 5 mg; d) Amlodipine 10 mg; e) Quarter-dose combination; f) Third-dose combination.
p-value: † Pearson's chi-square test; ‡ Fisher's exact test.

Figure S3. Blood pressure control and response rate at week 4 (full analysis set)

a) Control rate



b) Response rate

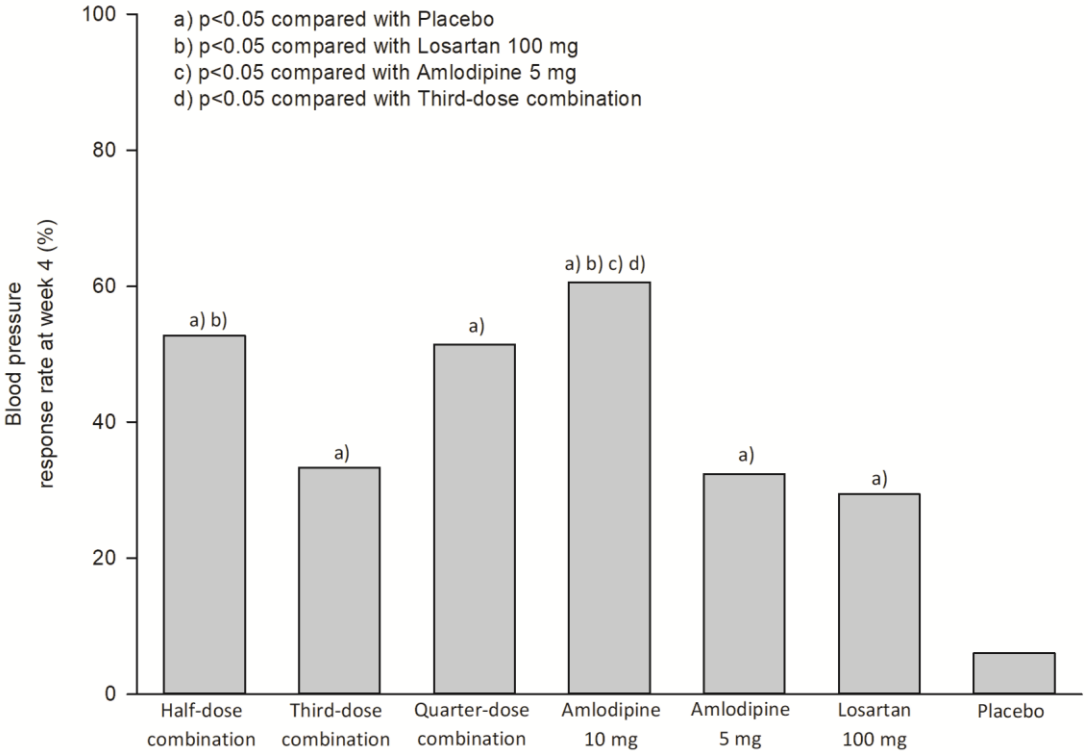


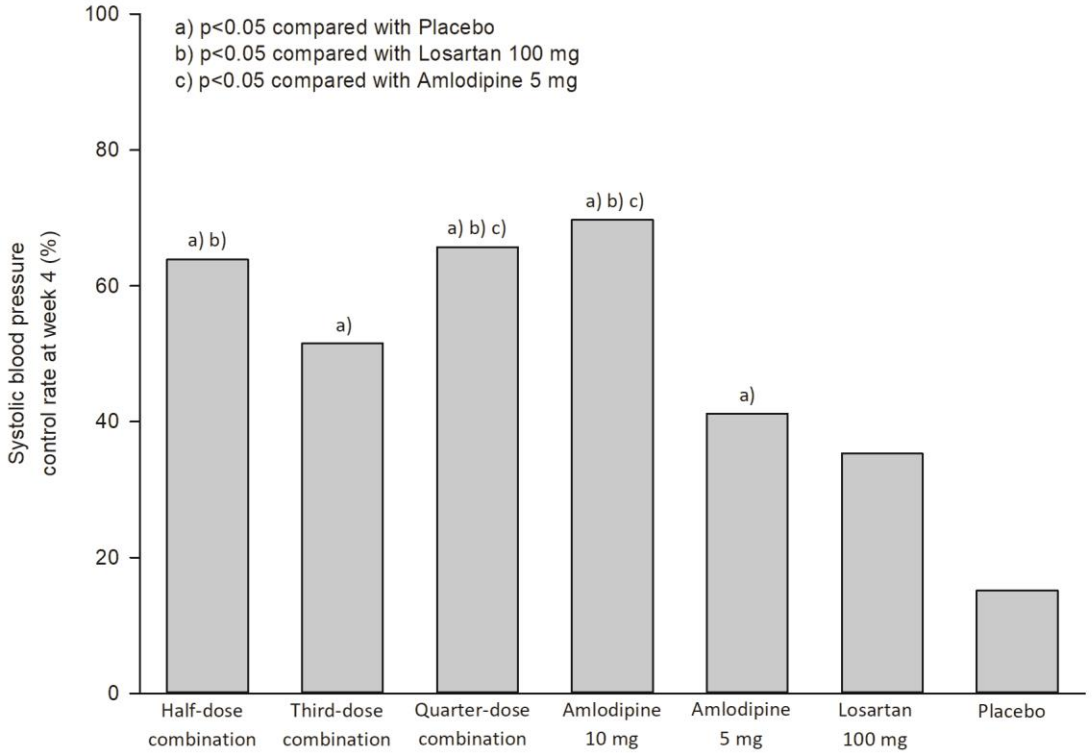
Table S7. Systolic blood pressure control rate (Proportion of Subjects with sitting systolic blood pressure < 140 mmHg) at week 4 and 8 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Week 4							
Controlled, n (%)	23 (63.89%)	17 (51.52%)	23 (65.71%)	23 (69.70%)	14 (41.18%)	12 (35.29%)	5 (15.15%)
p-value[a)]	<0.0001†	0.0017†	<0.0001†	<0.0001†	0.0181†	0.0582†	
p-value[b)]	0.0168†	0.1803†	0.0115†	0.0048†	0.6177†		
p-value[c)]	0.0571†	0.3961†	0.0410†	0.0189†			
p-value[d)]	0.6092†	0.1307†	0.7257†				
p-value[e)]	0.8721†	0.2344†					
p-value[f)]	0.2983†						
Week 8							
Controlled, n (%)	25 (69.44%)	24 (72.73%)	22 (62.86%)	23 (69.70%)	17 (50.00%)	15 (44.12%)	8 (24.24%)
p-value[a)]	0.0002†	0.0001†	0.0014†	0.0002†	0.0293†	0.0867†	
p-value[b)]	0.0323†	0.0176†	0.1186†	0.0346†	0.6270†		
p-value[c)]	0.0970†	0.0563†	0.2814†	0.1003†			
p-value[d)]	0.9818†	0.7857†	0.5513†				
p-value[e)]	0.5574†	0.3846†					
p-value[f)]	0.7640†						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Compared with: a) Placebo; b) Losartan 100 mg; c) Amlodipine 5 mg; d) Amlodipine 10 mg; e) Quarter-dose combination; f) Third-dose combination.
p-value: † Pearson's chi-square test.

Figure S4. Systolic blood pressure control rate (Proportion of Subjects with sitting systolic blood pressure < 140 mmHg) at week 4 and 8 (full analysis set)

a) at week 4



b) at week 8

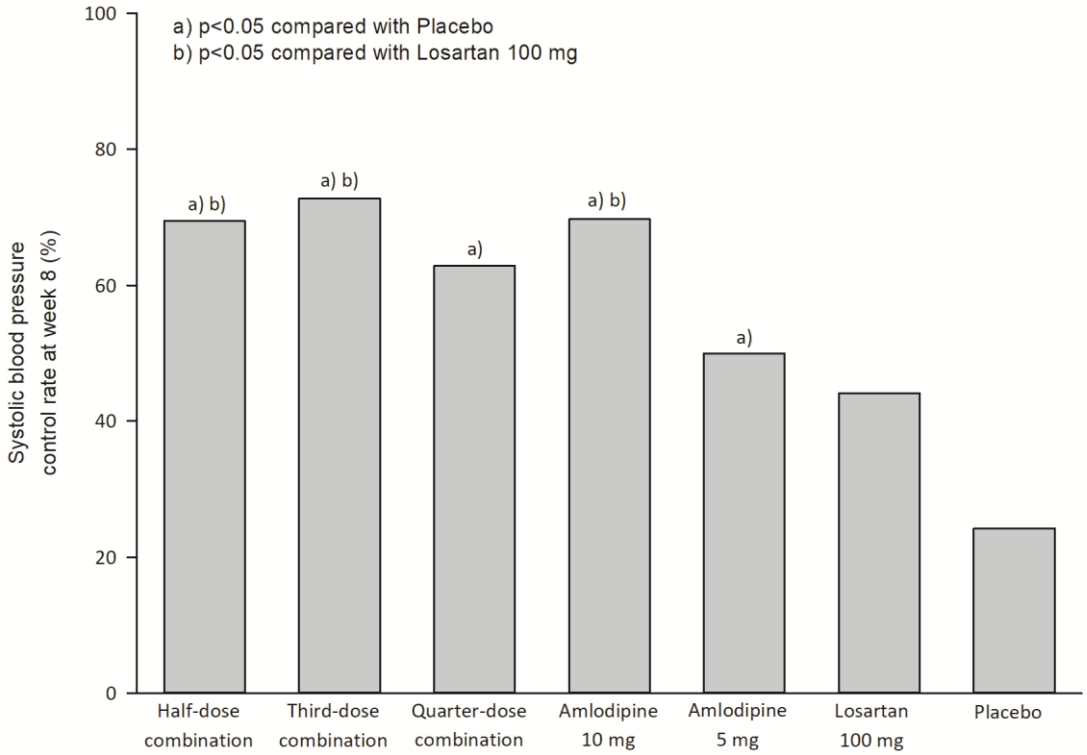

a) p<0.05 compared with Placebo
b) p<0.05 compared with Losartan 100 mg
Systolic blood pressure control rate at week 8 (%)
100
80
60
40
20
0
a) b)
a) b)
a)
a) b)
a)
Half-dose combination
Third-dose combination
Quarter-dose combination
Amlodipine 10 mg
Amlodipine 5 mg
Losartan 100 mg
Placebo

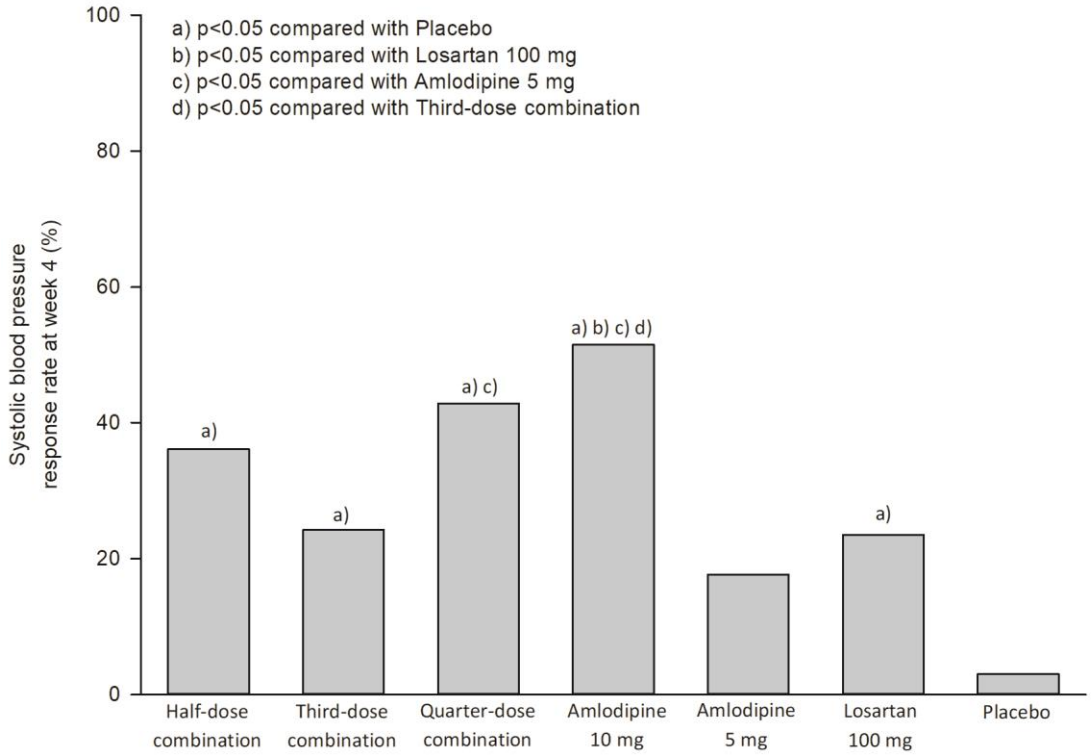
Table S8. Systolic blood pressure response rate (Proportion of subjects, sitting systolic blood pressure lowered ≥20 mmHg lowered from baseline) at week 4 and 8 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Week 4							
Responder, n (%)	13 (36.11%)	8 (24.24%)	15 (42.86%)	17 (51.52%)	6 (17.65%)	8 (23.53%)	1 (3.03%)
p-value[a)]	0.0006[†]	0.0268[‡]	0.0001[†]	<0.0001[†]	0.1054[‡]	0.0272[‡]	
p-value[b)]	0.2509[†]	0.9454[†]	0.0886[†]	0.0179[†]	0.5486[†]		
p-value[c)]	0.0825[†]	0.5068[†]	0.0229[†]	0.0035[†]			
p-value[d)]	0.1973[†]	0.0224[†]	0.4747[†]				
p-value[e)]	0.5609[†]	0.1049[†]					
p-value[f)]	0.2845[†]						
Week 8							
Responder, n (%)	19 (52.78%)	18 (54.55%)	15 (42.86%)	16 (48.48%)	10 (29.41%)	9 (26.47%)	5 (15.15%)
p-value[a)]	0.0010[†]	0.0008[†]	0.0122[†]	0.0036[†]	0.1615[†]	0.2546[†]	
p-value[b)]	0.0247[†]	0.0192[†]	0.1531[†]	0.0625[†]	0.7870[†]		
p-value[c)]	0.0473[†]	0.0370[†]	0.2454[†]	0.1092[†]			
p-value[d)]	0.7216[†]	0.6223[†]	0.6414[†]				
p-value[e)]	0.4028[†]	0.3351[†]					
p-value[f)]	0.8831[†]						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Compared with: a) Placebo; b) Losartan 100 mg; c) Amlodipine 5 mg; d) Amlodipine 10 mg; e) Quarter-dose combination; f) Third-dose combination.
p-value: [†] Pearson's chi-square test; [‡] Fisher's exact test.

Figure S5. Systolic blood pressure response rate (Proportion of subjects, sitting systolic blood pressure lowered ≥ 20 mmHg from baseline) at week 4 and 8 (full analysis set)

a) at week 4



b) at week 8

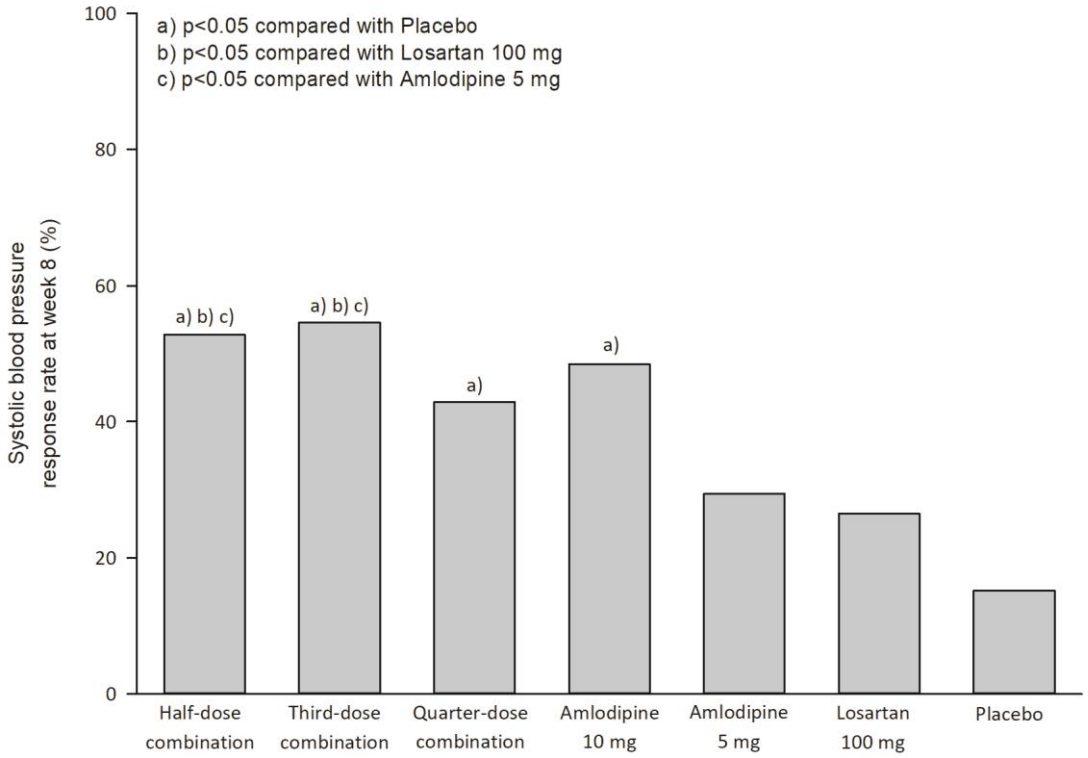

a) p<0.05 compared with Placebo
b) p<0.05 compared with Losartan 100 mg
c) p<0.05 compared with Amlodipine 5 mg
Systolic blood pressure response rate at week 8 (%)
100
80
60
40
20
0
a) b) c)
a) b) c)
a)
a)
Half-dose combination
Third-dose combination
Quarter-dose combination
Amlodipine 10 mg
Amlodipine 5 mg
Losartan 100 mg
Placebo

Table S9. Change of pulse pressure from baseline at week 8 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Baseline (mmHg)	62.89 (9.80)	62.42 (10.39)	60.27 (12.24)	63.64 (10.74)	62.13 (11.87)	65.26 (11.36)	63.15 (11.80)
Week 8 (mmHg)	53.43(11.11)	51.14 (11.66)	52.13 (11.33)	54.73 (11.67)	57.72 (12.78)	56.93 (12.24)	61.14 (16.57)
Mean changes from baseline at week 8, mmHg	-9.46 (8.31)	-11.29 (13.13)	-8.14 (9.56)	-8.91 (6.78)	-4.41 (8.88)	-8.34 (11.38)	-2.02 (13.97)
Difference*							
to Placebo (95% CI)	-7.54 (-12.94, -2.13)	-9.43 (-15.79, -3.07)	-6.85 (-12.48, -1.21)	-6.81 (-12.22, -1.40)	-2.63 (-8.29, 3.03)	-5.75 (-11.78, 0.27)	
p value	0.0071	0.0043	0.0180	0.0145	0.3567	0.0607	
to Losartan 100 mg (95% CI)	-1.88 (-6.41, 2.65)	-3.86 (-9.16, 1.44)	-0.92 (-5.54, 3.69)	-0.96 (-5.31, 3.39)	3.16 (-1.58, 7.90)		
p value	0.4109	0.1503	0.6910	0.6612	0.1874		
to Amlodipine 5 mg (95% CI)	-4.88 (-8.81, -0.95)	-6.71 (-11.79, -1.63)	-4.23 (-8.43, -0.03)	-4.22 (-8.05, -0.40)			
p value	0.0157	0.0104	0.0483	0.0310			
to Amlodipine 10 mg (95% CI)	-0.73 (-4.32, 2.86)	-2.67 (-7.47, 2.13)	0.05 (-3.81, 3.91)				
p value	0.6855	0.2710	0.9801				
to Quarter-dose combination (95% CI)	-0.42 (-4.42, 3.59)	-2.26 (-7.09, 2.58)					
p value	0.8367	0.3548					
to Third-dose combination (95% CI)	2.04 (-2.81, 6.89)						
p value	0.4034						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Data are mean (SD). *Least square mean difference in changes by ANCOVA.

Table S10. Change of pulse pressure from baseline at week 4 (full analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	34	33
Baseline (mmHg)	62.89 (9.80)	62.42 (10.39)	60.27 (12.24)	63.64 (10.74)	62.13 (11.87)	65.26 (11.36)	63.15 (11.80)
Week 4 (mmHg)	53.50 (9.28)	54.95 (10.95)	50.96 (11.59)	54.06 (12.86)	58.04 (10.35)	59.43 (14.51)	65.15 (14.85)
Mean changes from baseline at week 4, mmHg	-9.39 (9.07)	-7.47 (10.16)	-9.31 (10.93)	-9.58 (7.87)	-4.09 (7.12)	-5.84 (12.47)	2.00 (10.81)
Difference*							
to Placebo (95% CI)	-11.51 (-16.06, -6.97)	-9.70 (-14.76, -4.65)	-12.13 (-17.24, -7.02)	-11.49 (-16.05, -6.93)	-6.36 (-10.65, -2.06)	-7.34 (-13.02, -1.66)	
p value	<0.0001	0.0003	<0.0001	<0.0001	0.0044	0.0121	
to Losartan 100 mg (95% CI)	-4.57 (-9.48, 0.34)	-2.52 (-7.93, 2.89)	-4.96 (-10.43, 0.52)	-4.07 (-9.15, 1.01)	0.74 (-4.02, 5.50)		
p value	0.0675	0.3553	0.0753	0.1144	0.7572		
to Amlodipine 5 mg (95% CI)	-5.01 (-8.38, -1.63)	-3.27 (-7.15, 0.61)	-5.77 (-9.71, -1.83)	-5.10 (-8.60, -1.61)			
p value	0.0042	0.0974	0.0048	0.0049			
to Amlodipine 10 mg (95% CI)	-0.10 (-3.95, 3.75)	1.75 (-2.63, 6.14)	-0.67 (-5.17, 3.83)				
p value	0.9585	0.4274	0.7680				
to Quarter-dose combination (95% CI)	1.11 (-3.09, 5.30)	2.63 (-1.90, 7.17)					
p value	0.5998	0.2505					
to Third-dose combination (95% CI)	-1.67 (-5.81, 2.46)						
p value	0.4216						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Data are mean (SD). *Least square mean difference in changes by ANCOVA.

Table S11. Change of sitting systolic blood pressure from baseline at week 8 (full analysis set, patients with sitting systolic blood pressure < 160 mmHg at baseline)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5 mg	Losartan 100 mg	Placebo
N	27	24	26	25	26	25	25
Baseline (mmHg)	151.31 (5.06)	148.71 (5.73)	149.23 (5.42)	151.02 (4.90)	149.81 (5.20)	149.70 (5.24)	149.92 (6.42)
Week 8 (mmHg)	132.85 (10.31)	132.92 (15.02)	135.88 (12.91)	131.40 (10.17)	137.73 (14.92)	143.32 (14.36)	149.54 (16.91)
Mean changes from baseline at week 8, mmHg	-18.46 (9.82)	-15.79 (16.31)	-13.35 (12.51)	-19.62 (10.52)	-12.08 (14.21)	-6.38 (13.09)	-0.38 (16.09)
Difference*							
to Placebo (95% CI)	-17.77 (-25.23, -10.30)	-16.11 (-25.35, -6.88)	-13.13 (-21.28,-4.97)	-18.86 (-26.63, -11.10)	-11.71 (-20.33, -3.10)	-6.01 (-14.44, 2.42)	
p value	<0.0001	0.0010	0.0022	<0.0001	0.0087	0.1582	
to Losartan 100 mg (95% CI)	-11.94 (-18.50, -5.38)	-9.94 (-18.38, -1.50)	-7.02 (-14.30, 0.26)	-12.93 (-19.79, -6.08)	-5.70 (-13.48, 2.08)		
p value	0.0006	0.0220	0.0586	0.0004	0.1474		
to Amlodipine 5 mg (95% CI)	-6.07 (-12.90, 0.77)	-4.42 (-13.01, 4.16)	-1.40 (-8.92, 6.12)	-7.10 (-14.21, 0.01)			
p value	0.0806	0.3053	0.7100	0.0503			
to Amlodipine 10 mg (95% CI)	1.29 (-4.28, 6.87)	1.71 (-5.89, 9.32)	5.44 (-1.11,11.98)				
p value	0.6427	0.6524	0.1013				
to Quarter -dose combination (95% CI)	-4.46 (-10.77, 1.86)	-2.83 (-10.82, 5.17)					
p value	0.1624	0.4807					
to Third-dose combination (95% CI)	-0.75 (-8.18, 6.68)						
p value	0.8407						

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Data are mean (SD). *Least square mean difference in changes by ANCOVA.

Safety Results

Table S12. Changes of ankle circumference from baseline at week 4 and 8 (full analysis set)

	Combination treatment group	Amlodipine treatment group
N	104	67
Baseline (mm)	222.38 (17.46)	216.30 (16.84)
Week 4 (mm)	221.19 (16.63)	217.36 (17.14)
Week 4 - Baseline	-1.11 (6.73)	1.06 (7.20)
Wilcoxon Signed-Rank test to baseline, p value		
p value	0.0399	0.0854
Wilcoxon Rank Sum test between treatment groups		
Difference of changes, 95% CI	-2.17 (6.92), (-4.31, -0.02)	
p-value	0.0047	
Week 8 (mm)	221.54 (16.94)	218.78 (18.78)
Week 8 - Baseline	-0.76 (6.33)	2.48 (8.79)
Wilcoxon Signed-Rank test to baseline		
p value	0.2668	0.0150
Wilcoxon Rank Sum test between treatment groups		
Difference of changes, 95% CI	-3.23 (7.39), (-5.53, -0.94)	
p-value	0.0033	

Combination treatment group: Half-dose combination (amlodipine/losartan/chlorthalidone 2.5/25/6.25mg) + Third-dose combination (amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg) + Quarter-dose combination (amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg); Amlodipine treatment group: Amlodipine 5mg + Amlodipine 10 mg.
Data are mean (SD). It was analyzed based on full-analysis set, and last observation carried forward(LOCF) was applied for subjects with missing value.

Table S13. Treatment-emergent adverse events (safety analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5mg	Losartan 100 mg	Placebo	Total
N	36	33	35	33	34	35	35	241
Serious AE	2 (5.56%) [3]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	3 (1.24%) [4]
Any TEAE	7 (19.44%) [18]	2 (6.06%) [5]	4 (11.43%) [5]	1 (3.03%) [2]	5 (14.71%) [5]	5 (14.29%) [5]	6 (17.14%) [8]	30 (12.45%) [48]
Mild	5 (13.89%) [10]	2 (6.06%) [5]	4 (11.43%) [5]	1 (3.03%) [2]	3 (8.82%) [3]	5 (14.29%) [5]	5 (14.29%) [5]	25 (10.37%) [35]
Moderate	3 (8.33%) [6]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	2 (5.88%) [2]	0 (0.00%) [0]	2 (5.71%) [2]	7 (2.90%) [10]
Severe	2 (5.56%) [2]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	3 (1.24%) [3]
Leading to withdrawal	1 (2.78%) [3]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	2 (5.71%) [2]	3 (1.24%) [5]
Preferred term								
Atrial fibrillation	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	1 (0.41%) [1]
Bradycardia	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (3.03%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Constipation	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.94%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Dry mouth	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (3.03%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Dyspepsia	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	1 (0.41%) [1]
Nausea	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Oesophagitis	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Tooth loss	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Toothache	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Oedema peripheral	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.94%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Conjunctivitis	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Herpes zoster	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Influenza	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Nasopharyngitis	1 (2.78%) [1]	1 (3.03%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	2 (5.71%) [2]	0 (0.00%) [0]	1 (0.41%) [1]
Pneumonia	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Concussion	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	1 (0.41%) [1]
Contusion	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Ligament injury	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.94%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Skin abrasion	0 (0.00%) [0]	1 (3.03%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Traumatic haematoma	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	1 (0.41%) [1]
Blood potassium increased	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Blood pressure increased	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Arthralgia	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	1 (0.41%) [1]
Back pain	0 (0.00%) [0]	1 (3.03%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.94%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	2 (0.83%) [2]
Bone pain	0 (0.00%) [0]	1 (3.03%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Limb discomfort	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]

Muscle spasms	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Musculoskeletal pain	2 (5.56%) [2]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	2 (0.83%) [2]
Neck pain	0 (0.00%) [0]	1 (3.03%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Osteoarthritis	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Rotator cuff syndrome	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Dizziness	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Headache	2 (5.56%) [2]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	3 (8.57%) [3]	5 (2.07%) [5]
Cough	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	1 (0.41%) [1]
Pruritus	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	2 (0.83%) [2]
Rash	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Skin lesion	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.94%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Urticaria	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	1 (0.41%) [1]
Study drug related AE	1 (2.78%) [2]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	2 (5.88%) [2]	1 (2.86%) [1]	1 (2.86%) [1]	5 (2.07%) [6]
Preferred term								
Oedema peripheral	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.94%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Dizziness	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]
Headache	1 (2.78%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	2 (0.83%) [2]
Pruritus	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.86%) [1]	0 (0.00%) [0]	1 (0.41%) [1]
Skin lesion	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	1 (2.94%) [1]	0 (0.00%) [0]	0 (0.00%) [0]	1 (0.41%) [1]

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.
Data are number (%) of patients [number of events].
MedDRA term.

Table S14. Changes of laboratory values from baseline at week 8 (safety analysis set)

	Half-Dose Combination	Third-Dose Combination	Quarter-Dose Combination	Amlodipine 10 mg	Amlodipine 5mg	Losartan 100 mg	Placebo
N	36	33	35	33	34	35	35
AST, IU/L							
Baseline	24.44 (8.08)	26.12 (21.45)	26.54 (9.00)	24.39 (8.85)	25.53 (11.20)	22.14 (5.28)	22.09 (5.89)
Week 8	25.61 (8.51)	25.79 (14.74)	25.45 (13.38)	25.50 (13.14)	26.74 (13.53)	21.63 (5.97)	21.37 (5.28)
Mean changes from baseline at week 8	1.17 (7.24)	-0.33(13.61)	-1.09 (13.36)	0.97 (9.28)	1.03 (11.82)	-0.50 (4.38)	-0.44 (4.96)
Difference of changes compared to placebo	1.61 (-1.63, 4.85)	0.11 (-5.42, 5.64)	-0.65 (-6.08, 4.79)	1.41 (-2.57, 5.40)	1.48 (-3.42, 6.37)	-0.06 (-2.49, 2.38)	
p value	0.5443‡	0.4199‡	0.3988‡	0.4264‡	0.6440‡	0.5976‡	
ALT, IU/L							
Baseline	25.69 (15.21)	20.03 (7.87)	24.14 (13.84)	19.15 (6.85)	22.53 (10.64)	19.29 (7.73)	20.80 (9.41)
Week 8	27.31 (16.15)	21.91 (9.86)	22.82 (14.49)	19.94 (7.82)	25.26 (15.02)	21.94 (12.55)	19.93 (9.06)
Mean changes from baseline at week 8	1.61 (11.31)	1.88 (6.16)	-0.61 (14.12)	0.59 (5.70)	2.13 (13.51)	1.72 (12.26)	-1.33 (6.62)
Difference of changes compared to placebo	2.94 (-1.94, 7.83)	3.21 (-0.10, 6.52)	0.73 (-5.19, 6.64)	1.93 (-1.28, 5.14)	3.46 (-2.27, 9.19)	3.05 (-2.22, 8.33)	
p value	0.1256‡	0.0323‡	0.7820‡	0.2278‡	0.6446‡	0.3679‡	
Creatinine, mg/dL							
Baseline	0.89 (0.15)	0.92 (0.22)	0.90 (0.16)	0.89 (0.23)	0.83 (0.14)	0.92 (0.20)	0.92 (0.18)
Week 8	0.89 (0.18)	0.95 (0.25)	0.89 (0.16)	0.86 (0.18)	0.83 (0.15)	0.96 (0.22)	0.90 (0.17)
Mean changes from baseline at week 8	0.00 (0.10)	0.03 (0.08)	-0.00 (0.07)	-0.03 (0.11)	-0.01 (0.07)	0.04 (0.10)	-0.01 (0.08)
Difference of changes compared to placebo	0.01 (-0.04, 0.06)	0.04 (-0.01, 0.08)	0.01 (-0.03, 0.05)	-0.03 (-0.08, 0.02)	-0.00 (-0.04, 0.04)	0.05 (-0.00, 0.10)	
p value	0.8078‡	0.1065‡	0.8059‡	0.2897‡	0.8088‡	0.1185‡	
BUN, mg/dL							
Baseline	14.17 (3.18)	16.42 (4.03)	14.80 (4.29)	15.94 (4.35)	15.56 (3.33)	15.26 (2.73)	15.91 (4.18)
Week 8	16.11 (4.39)	18.03 (5.71)	15.42 (3.71)	15.22 (4.22)	15.16 (4.38)	15.19 (4.17)	15.52 (4.37)
Mean changes from baseline at week 8	1.94 (3.43)	1.61 (3.86)	0.52 (3.91)	-0.63 (2.95)	-0.48 (4.10)	0.06 (3.40)	-0.37 (3.42)
Difference of changes compared to placebo	2.31 (0.57, 4.06)	1.98 (0.07, 3.88)	0.46 (-1.24, 2.17)	-0.25 (-1.91, 1.41)	-0.19 (-2.12, 1.73)	0.28 (-1.50, 2.06)	
p value	0.0225‡	0.0618‡	0.5883†	0.8242‡	0.8426†	0.7540†	
Uric acid, mg/dL							
Baseline	5.82 (1.33)	5.64 (1.44)	5.63 (1.75)	5.68 (1.35)	5.49 (1.33)	5.67 (1.11)	5.60 (1.34)
Week 8	5.86 (1.22)	5.81 (1.43)	5.43 (1.37)	5.00 (1.29)	5.17 (1.38)	5.52 (0.94)	5.81 (1.55)
Mean changes from baseline at week 8	0.04 (0.82)	0.17 (1.16)	-0.08 (1.34)	-0.63 (0.73)	-0.36 (0.71)	-0.24 (0.71)	0.21 (0.85)
Difference of changes compared to placebo	-0.17 (-0.60, 0.25)	-0.04 (-0.58, 0.49)	-0.30 (-0.89, 0.30)	-0.84 (-1.25, -0.43)	-0.57 (-0.98, -0.16)	-0.45 (-0.86, -0.05)	
p value	0.9280‡	0.7436‡	0.6717‡	0.0002‡	0.0037‡	0.0300‡	
Serum sodium, mmol/L							

Baseline	140.72 (1.75)	141.33 (2.04)	141.00 (2.47)	140.39 (2.24)	140.62 (1.86)	141.29 (1.58)	141.20 (1.91)
Week 8	140.14 (1.33)	140.42 (1.98)	140.45 (2.50)	140.00 (2.14)	141.23 (1.65)	141.19 (1.94)	141.11 (2.44)
Mean changes from baseline at week 8	-0.58 (1.50)	-0.91 (2.16)	-0.61 (2.01)	-0.41 (2.17)	0.58 (1.84)	-0.06 (1.88)	-0.15 (1.49)
Difference of changes compared to placebo	-0.60 (-1.32, 0.13)	-0.74 (-1.66, 0.19)	-0.46 (-1.39, 0.48)	-0.53 (-1.48, 0.42)	0.54 (-0.31, 1.38)	0.08 (-0.80, 0.97)	
p value	0.1035†	0.1163†	0.3731‡	0.2710†	0.2108†	0.8502†	
Serum potassium, mmol/L							
Baseline	4.43 (0.45)	4.41 (0.39)	4.27 (0.33)	4.39 (0.42)	4.38 (0.34)	4.29 (0.37)	4.39 (0.36)
Week 8	4.21 (0.35)	4.29 (0.41)	4.15 (0.30)	4.23 (0.36)	4.26 (0.33)	4.32 (0.30)	4.33 (0.32)
Mean changes from baseline at week 8	-0.22 (0.35)	-0.12 (0.36)	-0.13 (0.28)	-0.14 (0.40)	-0.14 (0.32)	0.02 (0.39)	-0.03 (0.28)
Difference of changes compared to placebo	-0.15 (-0.28, -0.02)	-0.06 (-0.22, 0.09)	-0.09 (-0.24, 0.05)	-0.10 (-0.25, 0.05)	-0.09 (-0.23, 0.05)	0.05 (-0.13, 0.23)	
p value	0.0245†	0.4027†	0.4030‡	0.1758†	0.1904†	0.3803‡	
Fasting blood glucose, mg/dL							
Baseline	109.00 (18.70)	95.85 (12.57)	98.00 (13.75)	100.67 (18.94)	98.53 (15.44)	102.51 (21.44)	100.09 (15.62)
Week 8	114.89 (25.54)	104.21 (18.59)	105.39 (19.05)	103.34 (31.89)	105.32 (26.12)	106.19 (26.77)	104.48 (25.47)
Mean changes from baseline at week 8	5.89 (19.65)	8.36 (13.56)	9.18 (14.66)	3.91 (26.69)	8.13 (22.06)	2.41 (19.88)	5.15 (19.53)
Difference of changes compared to placebo	0.74 (-9.24,10.72)	3.22 (-5.36,11.79)	4.03 (-4.81,12.87)	-1.24 (-13.6,11.16)	2.98 (-8.05,14.01)	-2.74 (-13.1, 7.58)	
p value	0.2347‡	0.0317‡	0.0335‡	0.8312‡	0.2715‡	0.4692‡	
Total cholesterol, mg/dL							
Baseline	177.31 (36.39)	167.73 (35.53)	176.80 (32.37)	185.85 (42.28)	179.47 (44.73)	175.17 (39.72)	177.06 (32.15)
Week 8	183.44 (39.01)	170.70 (32.78)	186.33 (33.76)	185.53 (44.26)	182.03 (38.05)	173.09 (37.61)	180.85 (50.81)
Mean changes from baseline at week 8	6.14 (22.46)	2.97 (26.94)	9.36 (25.44)	-1.50 (34.72)	6.29 (33.15)	-1.19 (20.57)	8.26 (35.70)
Difference of changes compared to placebo	-1.88 (-16.70, 12.94)	-6.19 (-22.21, 9.84)	1.10 (-14.7, 16.93)	-9.76 (-28.2, 8.64)	-1.17 (-18.64, 16.30)	-9.27 (-24.16, 5.63)	
p value	0.8003†	0.4427†	0.9053‡	0.0941‡	0.8940†	0.2178†	
Triglyceride, mg/dL							
Baseline	194.72 (111.3)	195.76 (262.9)	161.03 (75.26)	165.91 (143.2)	170.12 (142.3)	167.63 (87.81)	144.74 (73.63)
Week 8	190.94 (133.1)	168.61 (130.8)	184.15 (90.97)	137.22 (70.72)	158.10 (80.53)	183.75 (120.4)	150.63 (103.6)
Mean changes from baseline at week 8	-3.78 (87.06)	-27.15 (251.8)	23.70 (68.09)	-32.16 (156.8)	-10.52 (111.2)	14.47 (85.72)	6.19 (54.44)
Difference of changes compared to placebo	-8.27 (-47.94, 31.39)	-33.34 (-132,65.65)	18.35 (-14.43, 51.13)	-38.34 (-102,25.15)	-16.70 (-63.9,30.48)	8.28 (-30.0,46.55)	
p value	0.6780†	0.9881‡	0.2669†	0.1300‡	0.7670‡	1.0000‡	

Half-dose combination: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg; Third-dose combination: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg; Quarter-dose combination: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg.

p value: †ANCOVA and ‡Wilcoxon rank sum test, compared to placebo group.

Table S15. Summary of serious adverse events (safety analysis set)

	Adverse events	Study drug allocated	intensity	Relationship to study drug	Action take with study drug	Outcome
1	Pneumonia	Half-dose combination	Severe	No	Does not changed	Recovered
2	Headache and dizziness	Half-dose combination	Moderate	Yes	Drug withdrawn	Recovered
3	concussion	Placebo	Severe	No	Drug withdrawn	Recovered

Study centers and IRB approval numbers

	Hospital	IRB approval number
1	Dongguk University Ilsan Hospital	DUIH 2018-12-008
2	The Catholic University of Korea, Bucheon ST. Mary's Hospital	HC18MDDS0110
3	Kangbuk Samsung Hospital	2018-12-003
4	Korea University Anam Hospital	2018AN0438
5	Seoul National University Hospital	2018-3269
6	Severance Hospital	4-2018-1189
7	Hanyang University Medical Center	2018-12-009
8	Korea University Guro Hospital	2019GR0053
9	Pusan National University Hospital	1812-006-084
10	Seoul Medical Center	2018-12-002
11	Ajou University Hospital	MED-CT2-18-447
12	Cha University Bundang Medical Center	2018-12-008
13	Seoul Metropolitan Government Seoul National University Boramae Medical Center	20190326 / 30-2019-22 /043
14	KyungHee University Medical Center	KHUH 2019-06-013
15	Seoul National University Bundang Hospital	B-1907/550-407
16	Chungnam National University Hospital	CNUH 2019-08-036

Exclusion Criteria

1) Subjects with differences between two arms greater than 20 mmHg for mean sitSBP or 10 mmHg for mean sitDBP at Visit 1.
2) Subjects with a difference in mean sitSBP > 15 mmHg between Visit 1 and Visit 2.
3) Subjects with mean sitSBP ≥ 180 mmHg or mean sitDBP ≥ 110 mmHg at Visit 1 and Visit 2.
4) Subjects with confirmed or suspected secondary hypertension (coarctation of the aorta, primary aldosteronism, renal artery stenosis, renal hypertension, pheochromocytoma, or Cushing's syndrome, among others.)
5) Subjects who have taken an antihypertensive drug within 2 weeks of Visit 1 or those who will need to take contraindicated medication during the trial period (refer to Section 8.2: Concomitant and Contraindicated Medication).
6) Subjects with type 1 diabetes or uncontrolled type 2 diabetes (HbA1c ≥ 9% at Visit 1)
7) Subjects with the following medical history:
   - Serious cerebrovascular disease (for example, cerebral infarction, cerebral hemorrhage), hypertensive encephalopathy, or transient ischemic attack (TIA) within 6 months of Visit 1.
   - Ischemic heart disease (myocardial infarction or angina pectoris) within 6 months of Visit 1.
   - Angioplasty or coronary artery bypass graft (CABG) surgery within 6 months of Visit 1.
   - Serious heart disease [heart failure (NYHA class III or IV)].
   - Hypertrophic obstructive cardiomyopathy, severe obstructive coronary artery disease, aortic stenosis, hemodynamically significant aortic or mitral valve stenosis, or peripheral vascular disease.
   - Clinically significant ventricular tachycardia, atrial fibrillation, atrial flutter, or any other form of arrhythmia determined to be clinically significant by the investigator.
8) Subjects with moderate or malignant retinopathy within 6 months of Visit 1 (moderate is defined as retinopathy symptoms such as bleeding, microaneurysm, cotton-wool spot, hard exudate, or a combination of such symptoms; malignant is defined as symptoms appearing from moderate retinopathy accompanied by edema of the optic nerve disc).
9) Subjects with wasting, autoimmune, or connective tissue disease.
10) Subjects with any form of immune disease or chronic inflammatory disease that requires chronic anti-inflammatory therapy (patients who must take steroids, or non-steroidal anti-inflammatory drugs (NSAIDs) or cytotoxic agents for ≥ 7 days; patients who require immunotherapy).
11) Subjects with hereditary angioedema or those with a history of angioedema during treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker.
12) Subjects with symptomatic orthostatic hypotension.
13) Subjects with clinically significant hyponatremia, hypokalemia, hyperkalemia, or hypercalcemia.
14) Subjects with hyperparathyroidism.
15) Subjects taking digitalis agent, glucocorticosteroid, or adrenocorticotropic hormone (ACTH).
16) Subjects with symptomatic hyperuricemia (history of gout or uric acid stone).
17) Subjects with untreated Addison's disease.
18) Subjects with shock.
19) Subjects with anuria.
20) Subjects with clinically significant kidney or liver disease or those with clinically significant hematological findings at Visit 1 (serum creatinine ≥ 2 mg/dL or AST or ALT level which is three-times more than normal upper limit).
21) Subjects with a history of hypersensitivity to amlodipine, losartan, chlorthalidone, dihydropyridines, angiotensin II receptor blockers, thiazide diuretics, or sulphonamide derivatives.
22) Subjects with genetic disorders, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.
23) Subjects with surgical or internal disease, or a history of surgery that could significantly alter drug absorption, distribution, metabolism, and excretion (including major gastrointestinal surgery, such as gastrectomy, gastro-enterostomy, bowel resection, gastrointestinal bypass surgery, gastrointestinal stapling, or gastrointestinal banding; a history of active inflammatory bowel syndrome within the prior 12 months; active gastritis, ulcers, or gastrointestinal/rectal bleeding; and urinary obstruction determined to be clinically significant by the investigator).
24) Subjects with a history of untreated malignant tumor, recurrence or metastasis of malignant tumor within 5 years of Visit 1 (except for thyroid cancer, basal cell carcinoma, or squamous cell carcinoma)
25) Subjects with a history of alcohol or drug abuse within 12 months of Visit 1.
26) Subjects who have received any other drug in a clinical trial within 12 weeks of Visit 1.

27) Pregnant or lactating females, and fertile males and females who are not using proper contraception (defined as hormonal contraception, intrauterine device, vasectomy, bilateral tubal ligation, or the combined use of male or female condoms, cervical cap, diaphragm, and birth control sponge).
28) Fertile females with a positive pregnancy test performed at Visit 1 (except for females at least 1 year after menopause or those who have received contraceptive surgery).
29) Subjects deemed inadequate by the investigator for inclusion in the clinical trial due to clinically significant test results and/or disease or non-adherence to clinical trial requirements (contact, medication, etc.)

Withdrawal Criteria

Completion of the clinical trial by each subject will be recorded. If the drug or observation is discontinued, the reason(s) will be recorded in the electronic case report form (eCRF) and source documents. Where possible, subjects who withdraw from the clinical trial will undergo tests scheduled at the final visit.
Subjects may voluntaryly withdraw from the study or be withdrawn by the investigator, under the following conditions:

1) Subjects who do not meet the inclusion/exclusion criteria.
2) Subjects who present hypersensitivity to the IP or control drug.
3) Subjects who have difficulties to continue the trial because of the occurrence of a serious AE (SAE)/adverse drug reaction (ADR).
4) Subjects who wish to receive no further treatment.
5) Subjects who do not comply with the instructions given by the investigator.
6) Subjects who are determined by the investigator that continued participation in the clinical trial may be harmful to the subject; for example, in the event of a SAE, such as aplastic anemia, necrotizing vasculitis, pulmonary edema, pancreatitis, agranulocytosis, acute renal failure (interstitial nephritis, etc.), or toxic epidermal necrolysis (Lyell syndrome).
7) Subjects with major protocol violation.
8) Subjects who use contraindicated medication that may seriously impact the clinical trial outcome.
9) Female subjects who are confirmed to be pregnant during the clinical trial.
10) Subjects with mean sitSBP $\geq$ 180 mmHg or mean sitDBP $\geq$ 110 mmHg at any visit after randomization.
11) Subjects with mean a sitSBP < 100 mmHg or mean sitDBP < 60 mmHg at any visit during the study
12) Subjects who are determined by the investigator that the clinical trial should not continue for any reasons.