2. STUDY ABSTRACT

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Study name: Efficacy and safety of the fixed oral perindopril arginine 5mg/amlodipine 5mg combination compared with amlodipine 5mg alone in patients not adequately controlled with amlodipine 5mg monotherapy.
A randomised, double-blind, 12week study with uptitration after 8 weeks in non-controlled patients.
Protocol number: CL3-05985-016

Coordinator or investigator: [redacted]

Study centres:
22 study centres participated in the study; at least 1 patient was enrolled at each centre. There were a total of 492 patients included.
5 study centres participated in the ABPM sub-study.

Publications (reference documents): Not applicable

Study duration: Start date (first patient's first visit): September 30, 2010 End date (last patient's last visit): June 13, 2011	**Study phase:** Phase III

Objective:

Primary objective:

- To demonstrate a statistically significant greater systolic blood pressure lowering effect (SBP) after 8 weeks of treatment versus baseline with perindopril arginine 5mg/amlodipine 5mg combination than with amlodipine 5mg alone in patients not controlled by amlodipine 5mg monotherapy.

Secondary objectives:

Efficacy

- To demonstrate a statistically significant greater diastolic blood pressure lowering effect (DBP) after 8 weeks of treatment versus baseline with the Per 5/Amlo 5 combination than with Amlo 5 alone in patients not controlled by amlodipine 5mg monotherapy
- To compare the blood pressure normalisation rate and response rate of Per 5/Amlo 5 combination versus Amlo 5 monotherapy treatment alone after 8 weeks of treatment.
- To compare the change from baseline in other blood pressure parameters (Pulse Pressure (PP), Mean Blood Pressure (MBP)) of the Per 5/Amlo 5 combination versus Amlo 5 alone after 8 weeks of treatment.
- To describe the change from baseline in blood pressure parameters (SBP, DBP, PP, MBP, BP normalisation, and response rate) of each treatment strategy (Amlo 5, Amlo 5 titrated Per 5/Amlo 5, Per 5/Amlo 5, Per 5/Amlo 5 titrated to Per 5/Amlo 10) after 12 weeks of treatment.
- To describe change from baseline to W12 in Ambulatory Blood Pressure Monitoring

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(ABPM) parameters in a subgroup of patients from selected study centres.

Safety

To assess the safety and tolerability of each treatment strategy during the 12 weeks of the trial.

- All adverse events occurring during the course of the trial with full documentation
- BP postural changes
- Electrocardiogram abnormalities
- Biochemical and haematological abnormalities, including hyperkalemia and hypokalemia

Methodology:

This study was a multicentre, Chinese, phase III, randomised, double-blind study in two parallel groups over 12 weeks in mild to moderate hypertensive patients. After selection, patients began a 4-week run-in period under Amlo 5 mg, followed by a 12-week, double-blind treatment period.

Patient numbers:

Planned number of included patients: 460 included patients (230 patients per treatment group). In the centres taking part in the ABPM assessment, all patients were to participate in the ABPM assessment, up to 60 patients with ABPM measurements.

Actual number of included patients: 492 included patients, with 247 patients in the perindopril/amlodipine group (Per/Amlo), and 245 patients in the amlodipine group (Amlo). Of these, 66 patients completed 2 ABPM assessments.

Diagnosis and main selection and inclusion criteria:

- Men or women, >= 18 to ≤ 75 years old, with uncomplicated mild to moderate essential hypertension, requiring antihypertensive treatment institution or change due to lack of efficacy or poor tolerability, treated with no more than one antihypertensive drug (excluding amlodipine and/or perindopril).
- Patients were selected for this study if they met the following criteria:
  - 95mmHg ≤ DBP < 110mmHg and 150mmHg ≤ SBP < 180mmHg at selection.
- After four weeks of amlodipine 5 mg treatment, patients were eligible for inclusion if their blood pressure levels were within the following ranges:
  - 90mmHg ≤ DBP < 110 mmHg and 140mmHg ≤ SBP < 180mmHg at inclusion.
  - SBP inclusion < SBP selection.
- Patients were excluded if they had a known history of cerebrovascular stroke or other cerebrovascular disease, unstable angina pectoris, myocardial infarction, coronary revascularization, chronic heart failure, uncontrolled cardiac arrhythmia (such as atrial fibrillation or atrial flutter), level Ⅱ or Ⅲ atrioventricular heart-block, type I diabetes or uncontrolled type 2 diabetes, insufficient renal function, insufficient liver function, symptomatic orthostatic hypotension, history of alcohol or drug abuse or any contra-indication to study drugs.
- Other non-selection criteria were as follows: pregnancy or women of childbearing age without medically accepted form of contraception.

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Study drug:

S05985 –Perindopril/amlodipine combination: Per 5/Amlo 5 - Per 5/Amlo 10 – One capsule per os in the morning before breakfast.

Batch numbers: Perindopril arginine 5mg/amlodipine 5mg: L0035594, L0033544
Perindopril arginine 5mg/amlodipine 10mg: L0035595, L0033540

Comparator:

Amlo 5 – one capsule per os in the morning before breakfast.

Treatment period:

- 4-week run-in period under active drug treatment (from selection to W0, amlodipine 5mg, once daily per os)
- 12-week double-blind active drug treatment period (from W0-W12):
  - First stage (P1, 8 weeks): Amlo 5 or Per 5/Amlo 5, once daily orally;
  - Second stage (P2, 4 weeks): Amlo 5 or Per 5/Amlo 5 (in patients whose BP was controlled at W8, i.e. SBP < 140mmHg and DBP < 90mmHg), once daily orally; Per 5/Amlo 5 or Per 5/Amlo 10 (in patients whose BP was not controlled at W8, i.e. SBP ≥ 140mmHg and/or DBP ≥ 90mmHg), once daily per os

Criteria for evaluation:

Efficacy evaluation:

Primary endpoint:

- Sitting systolic blood pressure

Secondary endpoint:

- Sitting diastolic blood pressure
- Percentage of Normalisation of blood pressure: Definition of BP normalisation was: SBP < 140 mmHg and DBP < 90 mmHg
- Percentage of Response to treatment: Definition of response to treatment was: BP normalisation and/or decrease in SBP ≥ 20 mmHg from baseline and/or decrease in DBP ≥ 10 mmHg from baseline
- Pulse Pressure (PP = SBP – DBP) and Mean Blood Pressure (MBP = 2/3 SBP + 1/3 SBP)
- Ambulatory Blood Pressure Monitoring parameters (ABPM)

Safety assessment:

- Adverse events
- BP postural change
- Vital signs
- Laboratory parameters (haematology, blood chemistry)
- Electrocardiogram (ECG)

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Statistical methods:

Analysis set definition and summary as follows:

Randomisation set (RS): All included patients to whom a therapeutic unit was dispensed.
Full analysis set (FAS): All randomised patients who received at least one dose of study treatment and who had at least one baseline value and one post-baseline value of sitting SBP over 8 weeks.
W8 Per-protocol set (PPS_W8): This set was defined by patients of the Full Analysis Set without relevant deviation(s) which could affect the evaluation of sitting SBP over 8 weeks
W12 Per-protocol set (PPS_W12): This set was defined by patients of the Full Analysis Set without relevant deviation(s) which could affect the evaluation of sitting SBP over 12 weeks
Safety set (SS): All included patients who received at least one dose of study treatment.

Full analysis set - ambulatory blood pressure monitoring subset (FAS-ABPM): This dataset corresponded to all the randomised patients who received at least one dose of study treatment and who had one valid baseline ABPM and one valid W012 ABPM.

Per-protocol set - ambulatory blood pressure monitoring subset (PPS-ABPM): This dataset corresponded to patients in the FAS-ABPM who did not have a protocol deviation that could affect 24-hour mean systolic blood pressure.

Two treatment groups were defined based on patients randomisation at inclusion:
- Perindopril 5mg/amlodipine 5mg combination group (abbreviated as Per/Amlo)
- Amlodipine 5mg monotherapy group (abbreviated as Amlo)

Four treatment strategies were defined, based on uptitrated dose of study drug patient was taking at W008 visit:
- Perindopril 5mg/amlodipine 5mg combination treatment for 12 weeks (abbreviated as P5/A5)
- Uptitrated from perindopril 5 mg/amlodipine 5 mg combination to perindopril 5 mg/amlodipine 10 mg combination (abbreviated as: P5/A5-P5/A10)
- Amlodipine 5 mg monotherapy for 12 weeks (abbreviated as: A5)
- Uptitrated from amlodipine 5 mg monotherapy to perindopril 5 mg/amlodipine 5 mg combination (abbreviated as: A5-P5/A5)

Study outcome:

RS dataset was used to describe demographics, history of hypertension, risk factors, treatment duration, drug administration compliance, patient distribution, reason for withdrawal, deviation from protocol, and concomitant treatment by treatment group and overall.

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Analysis of efficacy:

Primary efficacy endpoint (sitting systolic blood pressure):
The FAS set was used for primary analysis, to demonstrate the superiority of the perindopril 5 mg/amlodipine 5 mg combination compared to amlodipine 5mg monotherapy on the change from baseline to last post baseline sitting systolic blood pressure after 8 weeks of treatment. A general linear model was used studying the treatment effect with baseline and centre (fixed factor) as covariates. The estimate of between group difference, standard error, the 95% confidence interval and superiority test p-values were also provided.
Secondary analysis used the FAS and PPS sets, presented by treatment group and by treatment strategies, and described sitting systolic blood pressure at each follow-up visit, changes from baseline to last post baseline value.

Secondary efficacy endpoints:
Sitting diastolic blood pressure
For sitting diastolic blood pressure, the analysis performed was identical to that for the primary efficacy endpoint.

Treatment response rate and normalised blood pressure rate
For 2 treatment groups, based on W4, W8, and last post baseline BP measurements after the 8-week treatment period, the percentage of patients who responded to treatment and the percentage of patients whose blood pressure was normalised were described. After 8 weeks of treatment the difference between the Per 5 mg/Amlo 5 mg combination and the Amlo 5 mg monotherapy treatment groups and the 95% confidence interval for the difference were described.
The percentage of patients who responded to treatment and the percentage of patients whose blood pressure returned to normal in each treatment strategy were described based on the last post baseline BP measurement over 12-week treatment period.

Pulse Pressure and Mean Blood Pressure
For 2 treatment groups, the Pulse Pressure and Mean Blood Pressure were described for W4, W8, and the last post baseline value over 8 weeks treatment.
After 8 weeks treatment, the change from baseline to last post baseline blood pressure measurement was provided and the difference between the two groups was given, with 95% confidence interval.
For each treatment strategy, the change from baseline in PP and MBP were described based on the last post baseline BP measurement over 12-week treatment period.

Ambulatory Blood Pressure Monitoring (ABPM) parameters
ABPM parameter baseline value, the measured value at W12 and the change from baseline to W12 were described for each treatment strategy.

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Safety analysis:

In safety set, description analysis of adverse events, orthostatic hypotension, laboratory tests, vital signs, and electrocardiogram results were provided. In the safety set, the frequency of adverse event in different treatment groups and strategies was listed by system organ class (SOC) and preferred term (PT). It was also summarized for emergent adverse events, deaths, serious adverse events, study drug-related adverse events, and adverse events leading to withdrawal from the study. Emergent potential clinical significant abnormalities of laboratory parameters were listed.

Results and Discussion

Study outcome

Analysis data set		Per/Amlo	Amlo	Total
Main study				
Randomisation set (RS)	n	247	245	492
Full analysis set (FAS)	n (%)	244 (98.8%)	236 (96.3%)	480 (97.6%)
W8 per-protocol set (PPS_W8)	n (%*)	219 (89.8%)	230 (97.5%)	449 (93.5%)
W12 per-protocol set (PPS_W12)	n (%*)	214 (87.7%)	219 (92.8%)	433 (90.2%)
Safety analysis set (SS)	n (%)	247 (100.0%)	244 (99.6%)	491 (99.8%)

Analysis data set		P5/A5	P5/A5-P5/A10	A5	A5-P5/A5	Total
ABPM sub-study						
Full analysis set – ABPM (FAS-ABPM)	n	7	14	3	26	50
Per-protocol set – ABPM (PPS-ABPM)	n (%#)	4 (57.1%)	11 (78.6%)	3 (100.0%)	23 (88.5%)	41 (82.0%)

n: number of patients; %: percentage in randomisation set of corresponding treatment group; %: percentage in full analysis set of corresponding treatment group; %#: percentage in FAS-ABPM of corresponding treatment group*

Primary baseline characteristics

A total of 492 patients with primary hypertension were randomised into two groups for this study (RS): 247 patients in the Per/Amlo group, 245 patients in the Amlo group. Of these, a total of 112 patients were participated in ABPM assessment, 66 patients completed ABPM assessment both at W000 and W012, and 50 patients had valid ABPM assessments both at W000 and W012(FAS-ABPM).

During the W000-W012 period, a total of 37 patients (7.5%) withdrew from the study, and no patients were lost to follow-up. The primary reason for patients' withdrawal from the study was non-medical reason (11 patients), protocol deviation (11 patients), adverse events (5 patients) and other protocol-defined withdrawal criteria (10 patients); there was no between-group difference. A total of 455 patients (92.5 %) completed W000-W012 of the study: 229 patients (92.7%) in the Per/Amlo group, 226 patients (92.2%) in the Amlo group.

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Results and discussion (cont.)

Main Demographic Data and Disease Characteristics (RS)

			Per/Amlo (N = 247)	Amlo (N = 245)	Total (N = 492)
Age (years)		Mean ± SD	51.1 ± 10.1	52.5 ± 9.1	51.8 ± 9.6
Sex	Male	n (%)	139 (56.3)	135 (55.1)	274 (55.7)
Weight (Kg)		Mean ± SD	73.07 ± 11.46	71.81 ± 10.09	72.44 ± 10.81
Body mass index BMI (kg/m^2)		Mean ± SD	26.14 ± 2.38	25.80 ± 2.54	25.97 ± 2.46
Primary hypertension					
Duration of disease (years)		Mean ± SD	7.7 ± 7.3	8.1 ± 7.4	7.9 ± 7.4
Family history		n (%)	178 (72.4)	170 (69.7)	348 (71.0)
Sitting blood pressure					
SBP (mmHg)		Mean± SD	149.63±6,89	150.53±7.36	150.08±7.13
DBP (mmHg)		Mean± SD	96.89±4.55	96.43±4.39	96.66±4.47

As shown in the table above, the baseline characteristics for the two groups were similar. Other important baseline characteristics between the two groups, such as previous disease history, vital signs, and concomitant drug use, were comparable. Baseline efficacy endpoint assessments between the two groups were comparable.

In RS, mean age was 51.8 ± 9.6 years, a slight majority were male (55.7%), mean weight was 72.44 ± 10.81kg, mean BMI was 25.97 ± 2.46 kg/m². No relevant difference between groups was observed. Included patients were all diagnosed with primary hypertension, the mean disease duration was 7.9 ± 7.4 years, 71.0% of patients had a family history of hypertension.

At inclusion visit, the efficacy endpoint assessments for the two groups were similar. No between-group difference was observed: the mean sitting SBP was 150.08 ± 7.13 mmHg and the mean sitting DBP was 96.66 ± 4.47 mmHg. For patients included in the ABPM assessment, there was no relevant difference among the various treatment groups: the mean 24-hour SBP was 141.61 ± 9.05 mmHg and the mean 24-hour DBP was 91.43 ± 6.06 mmHg.

In RS, total treatment duration was 82.2 ± 12.8 days. Overall treatment compliance was good; 98.8% patients had compliance within 70-130% range. With respect to treatment duration and treatment compliance, there was no between-group difference.

Out of 492 randomised patients, 286 patients were uptitrated due to blood pressure not controlled at W8: 134/247 (54.3%) patients in Per/Amlo group and 152/245 (62.0%) in Amlo group.

Demographic data and main baseline characteristics in FAS and PPS were consistent with RS.

The main demographic and other baseline characteristics of the ABPM subgroup population were close to those of the overall population and no between-group difference was observed.

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Efficacy results

Primary efficacy endpoint: sitting systolic blood pressure

Main Analysis: sitting SBP change from baseline over 8 weeks

The main analytical method for efficacy assessment was based on the difference between groups for the change in sitting SBP from baseline after 8 weeks of treatment in FAS.

W000-W008 period sitting systolic blood pressure (FAS, N = 480)

Sitting systolic blood pressure (mmHg)		Per/Amlo (N = 244)	Amlo (N = 236)
Statistical description			
Baseline value	Mean ± SD	149.6 ± 6.8	150.3 ± 7.1
Last post baseline value	Mean ± SD	138.5 ± 12.2	141.8 ± 12.1
last post baseline value - baseline	Mean ± SD	-11.1 ± 11.9	-8.5 ± 11.1
Statistical analysis:			
Between group difference (last post baseline value - baseline)			
	Estimated value (SE) (1)	-2.7 (1.0)	
	95% CI (2)	[-4.7 ; -0.7]	
	P value (3)	0.0095	

Superiority test of Perindopril/Amlodipine as compared to Amlodipine; Two-sided type I error rate: 0.05.
(1) Estimate (Standard Error) of the difference between baseline and centre adjusted treatment group means: Per/Amlo minus Amlo
(2) 95% Confidence interval of the estimate
(3) General linear model with baseline and centre (fixed effect) as covariates

In FAS, the mean decrease in sitting SBP, between baseline and last post baseline value over 8 weeks was greater in Per/Amlo group compared to the Amlo group (-11.1±11.9 mmHg and -8.5± 11.1mmHg, respectively); the estimated difference between groups was -2.7 mmHg (95% CI: [-4.7; -0.7]), superiority test p = 0.0095. The difference was statistically significant, thereby proving that the Per 5/Amlo 5 combination had superior efficacy in comparison to Amlo 5 monotherapy in patients insufficiently controlled by a first month treatment with Amlo 5 monotherapy.

Secondary Analysis:

In FAS, over 12 weeks treatment duration, the sitting SBP decreased from baseline in the 4 treatment strategies: P5/A5, -17.2 ± 11.4 mmHg; P5/A5-P5A/10, -13.8 ± 11.5 mmHg; A5, was -15.6 ± 12.2 mmHg; A5-P5/A5, -10.0 ± 11.4 mmHg, respectively.

In **FAS**, the patients with poor blood pressure control at W008 and an uptitrated drug dose (P5/A5-P5/A10, A5-P5/A5) achieved further decreases in sitting SBP between W008 and W012: -8.2 mmHg (95% CI: [-10.2; -6.2]) in P5/A5-P5/A10 and -6.1 mmHg (95% CI: [-7.9; -4.2]) in A5-P5/A5; patients whose blood pressure was controlled at W008 and continued with the original drug dose (P5/A5, A5), remained stable in terms of sitting SBP between W008 and W012.

After 8 and 12 weeks of treatment, the sitting SBP analysis results in PPS_W8 and PPS-W12 were consistent with those in FAS.

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Results and discussion (cont.)

Secondary efficacy endpoints

- **Sitting diastolic blood pressure**

The mean decrease in sitting DBP, between baseline and the last post-baseline value over 8 weeks tended to be greater in the Per/Amlo group compared to the Amlo group (-7.3 ± 8.3 mmHg and -6.1 ± 7.1 mmHg, respectively); the estimated difference between groups was -0.9 mmHg (95% CI: [-2.2; 0.4]), superiority test p= 0.1725. Sitting DBP was reduced compared to baseline in the 4 treatment strategies over the 12-week treatment period, as follows:P5/A5, -10.4 ± 8.0 mmHg; P5/A5-P5A/10, -8.3 ± 8.0 mmHg; A5, -11.0 ± 8.7 mmHg; A5-P5/A5, -5,7 ±7.2 mmHg.

In FAS, in patients whose blood pressure was not controlled at W008 and who received an uptitrated drug dose for a continued 4 weeks of treatment, titration to higher dose provides additional decrease in sitting DBP in both titrated strategies (-5.1 mmHg (95% CI: [-6.4; -3.8]) in P5/A5-P5/A10 and -2.9 mmHg (95% CI: [-4.1; -1.8]) in A5-P5/A5, respectively). Patients who continued with the original drug dose (P5/A5 and A5 strategy) over 12 weeks remained stable between W008 and W012 in terms of the DBP mean.

- **Blood pressure normalisation rate**

In FAS, after 8 weeks of treatment, the percentage of normalized blood pressure patients tends to be greater in the Per/Amlo group (39.8%) than in the Amlo group (33.5%). Among the patients who were not controlled after 8 weeks of treatment and were uptitrated, the percentage of patients with blood pressure controlled increased between W8 and W12 from zero to respectively: 42.5% in P5/A5-P5/A10 and 29.6% in A5-P5/A5 .

- **Treatment response rate**

In FAS, after 8 weeks of treatment, the percentage of patients who responded to treatment was greater in the Per/Amlo group (50.8%) than in the Amlo group (40.7%). Among the patients who were not controlled after 8 weeks of treatment, and were uptitrated, more patients were able to respond to treatment after continuing treatment for 4 weeks

- **Pulse Pressure (PP) and Mean Blood Pressure (MBP)**

In FAS, after 8 weeks of treatment, the decrease of PP and MBP was slightly higher in the Per/Amlo group compared to the Amlo group.

- **24-hour ambulatory blood pressure monitoring parameters**

ABPM was performed in a subset (FAS-ABPM, N = 50) of the study population (N = 492) and, as planned by study design, ABPM was performed in 4 different treatment strategies leading to a very small number of patients per strategy (P5/A5= 7 patients, P5/A5-P5/A10 = 14 patients, A5 = 3 patients,A5-P5/A5 = 26 patients). Therefore the interpretation and conclusion from ABPM data should be done cautiously.

Results from 24-hour ambulatory blood pressure monitoring indicated that after 12 weeks of treatment the **mean systolic and diastolic blood pressure** at different nycthemeral intervals (**24 hours, standard daytime, standard nighttime, daytime, nighttime, actual daytime, actual nighttime, last 6 hours before taking drug, and morning**) were lowered to varying degrees in all 4 treatment strategies (cf. Table).

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ABPM - 24 Hour Mean Systolic blood pressure and Diastolic blood pressure (mmHg, FAS-ABPM)

Statistical description		P5/A5 (N = 7)	P5/A5-P5/A10 (N = 14)	A5 (N = 3)	A5-P5/A5 (N = 26)
24 hour mean systolic blood pressure					
Baseline value	Mean ± SD	139.02 ± 9.71	143.65 ± 9.30	148.04 ± 5.77	140.46 ± 8.92
Post baseline (W012)	Mean ± SD	129.77 ± 13.29	130.79 ± 7.39	132.49 ± 6.70	138.21 ± 9.73
Post baseline (W012) – baseline value	Mean ± SD	-9.25 ± 8.45	-12.86 ± 8.62	-15.55 ± 3.03	-2.25 ± 9.31
24 hour mean diastolic blood pressure					
Baseline value	Mean ± SD	89.38 ± 8.56	92.81 ± 5.81	90.39 ± 3.42	91.36 ± 5.79
Post baseline (W012)	Mean ± SD	82.20 ± 9.73	83.37 ± 4.59	80.68 ± 6.14	90.00 ± 5.79
Post baseline (W012) – baseline value	Mean ± SD	-7.18 ± 5.22	-9.44 ± 5.58	-9.71 ± 5.28	-1.36 ± 5.68

Regarding secondary efficacy endpoints, PPS_W8 and PPS_W12 results were consistent with FAS results.

Safety results

The safety analysis set (SS) included 491 patients (247 patients in Per/Amlo group, 244 patients in Amlo group). Treatment duration and drug exposure duration were both similar for the two groups. Based on the drug titration at W008, there were 4 treatment strategies, and the distribution in the SS was: 113 patients in P5/A5 strategy, 134 patients in P5/A5-P5/A10 strategy, 92 patients in A5 strategy, and 152 patients in A5-P5/A5 strategy.

Summary of Emergent Adverse Events (W000-W012, SS)

		P5/A5 (N = 113)	P5/A5-P5/A10 (N = 134)	A5 (N = 92)	A5-P5/A5 (N = 152)	Total (N = 491)
Patients reporting at least 1 EAE	n (%)	41 (36.3%)	51 (38.1%)	21 (22.8%)	57 (37.5%)	170 (34.6%)
Severe EAE	n (%)	3 (2.7%)	2 (1.5%)	1 (1.1%)	2 (1.3%)	8 (1.6%)
EAE related to study drug	n (%)	12 (10.6%)	11 (8. 2%)	3 (3.3%)	4 (2.6%)	30 (6.1%)
EAE induced withdrawal	n (%)	5 (4.4%)	-	-	-	5 (1.0%)
Patients reporting at least 1 serious EAE	n (%)	4 (3.5%)	1 (0.7%)	1 (1.1%)	2 (1.3%)	8 (1.6%)
Serious EAE related to study drug	n (%)	-	-	-	-	-
Death	n (%)	-	-	-	-	-
Serious EAE induced withdrawal	n (%)	2 (1.8%)	-	-	-	2 (0.4%)

Adverse events

In SS, during W000-W008, 80 patients (16.3%) reported **98 emergent adverse event (EAE)**: 49 patients (19.8%) in Per/Amlo group, 31 patients (12.7%) in Amlo group. The main difference between groups was cough (6.1% in Per/Amlo, 1.2% in Amlo). During W8-W12, EAEs reported in the 2 uptitrated strategies were similar: 33 (24.6%) patients in P5/A5-P5/A10，39 (25.7%) patients in A5-P5/A5. During W000-W012, EAE reported in the 4 treatment strategies were, respectively: P5/A5 group 41 patients (36.3%), P5/A5-P5/A10 group 51 patients (38.1%), A5 group 21 patients (22.8%), and A5-P5/A5 group 57 patients (37.5%).

In SS, during the W000-W012 period, the most common affected System Organ Class (SOC) by EAEs in the four treatment strategies (P5/A5, P5/A5-P5/A10, A5, A5-P5/A5) were as follows:

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metabolic and nutritional disorders (12.4%, 11.9%, 7.6%, 15.8%, respectively), infections and infestations (respectively 7.1%, 6.0%, 4.3%, and 7.2%), investigations (2.7%, 7.5%, 6.5%, and 5.9%, respectively) and nervous system disorders (respectively, 1.8%, 3.0%, 2.2%, 5.9%); the most commonly seen EAE was "cough" (8.8%, 8.2%, 0.0%, 3.3%, respectively), "hyperlipidaemia" (10.6%, 8.2%, 6.5%, 11.2%, respectively) and "upper respiratory tract infection" (4.4%, 3.0%, 2.2%, 5.9%, respectively).

The intensity of most EAEs was mild (81.8%) or moderate (14.3%), and a very small minority were severe EAEs (3.9%).

The outcome of most EAEs was "recovery" (53.2%) or "improving" (39.8%).

There were 5 patients in the P5/A5 group who withdrew from the study because of EAEs; of these, 3 patients withdrew from the study because of the adverse event "cough" related to the study drug.

In SS, during W000-W012, 30 patients had EAEs related to the study drug, respectively: P5/A5 group 12 patients (10.6%), P5/A5-P5/A10 group 11 patients (8.2%), A5 group 3 patients (3.3%), A5-P5/A5 group 4 patients (2.6%). The main SOCs were respiratory, thoracic and mediastinal disorders (respectively, 8.8%, 6.7%, 1.1%, and 2.6%), main reports were "cough" (P5/A5 group 10 patients, P5/A5-P5/A10 group 9 patients, A5-P5/A5 group 4 patients) and "oedema peripheral" (P5/A5 group 1 patients, P5/A5-P5/A10 group 1 patient, A5 group 2 patients, and A5-P5/A5 group 1 patient).

In SS, during W000-W012, a total of 8 patients reported 8 **serious emergent adverse events (SEAE)**. Of these, 4 SEAEs occurred during the W000-W008 period (P5/A5 group 3 patients, respectively, ischemic stroke, synovitis, and pregnancy; A5 group 1 patient with lumbar intervertebral disc protrusion) and for 4 patients the SEAE occurred during W008-W012 (P5/A5 group 1 case of acute coronary artery syndrome, P5/A5-P5/A10 group 1 patient had cataract operation, A5-P5/A5 group 1 patient with cerebral infarction and 1 patient with lacunar infarct).

Among these 8 SEAEs, all of other 7 patients recovered except 1 patient improving (1 patient in P5/A5 with ischemic stroke improving). 2 SEAEs (P5/A5 group 1 patient with ischemic stroke and 1 pregnant patient) resulted in the patients withdrawing from the study. Based on the judgment of the investigator, all of the SEAEs described above were unrelated to the study drug.

During the study, 1 patient died during the run-in period (female, 54 years old, died in traffic accident).

Blood biochemistry and haematological parameters

In SS, during the 12-week treatment period, emergent blood biochemical and haematological abnormal values of potential clinical significance were rarely observed. The differences among the treatment strategies were not relevant.

Vital signs and orthostatic hypotension

In SS, during the 12-week treatment period, there was a slight decrease in heart rate in various

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treatment strategies; body weight remained stable. No significant difference was observed among strategies.
In SS, during 8-week treatment period, orthostatic hypotension was occurred in 5 patients (3 patients in Per/Amlo group, 2 patients in Amlo group), and during 4 weeks continuing treatment, there was no onset of orthostatic hypotension.

Electrocardiogram tests
In SS, based on investigator's judgement, 29 patients at baseline and 28 patients at the end of the study had ECG abnormalities with clinically significance, mainly including left ventricular hypertrophy and left ventricular high voltage.

Conclusion

The study was a randomised, double-blind, 12-week study with uptitration after 8 weeks in non-controlled patients. The efficacy and safety of the fixed oral perindopril arginine 5mg/amlodipine 5mg combination were compared with amlodipine 5mg alone in patients not adequately controlled with amlodipine 5mg monotherapy.
The study demonstrated that the perindopril 5mg/amlodipine 5mg combination was superior, with statistical significance, to the continuation of amlodipine 5mg monotherapy in the treatment of hypertensive patients not adequately controlled with amlodipine 5mg monotherapy (change from baseline in sitting SBP after 8 weeks of treatment). In addition, compared to the continuation of the amlodipine 5mg monotherapy, the perindopril 5mg/amlodipine 5mg combination reduced sitting DBP, pulse pressure and mean blood pressure, and increased the proportion of patients with BP normalisation and response-to-treatment over 8 weeks of treatment in patients not adequately controlled with amlodipine 5mg monotherapy.

For patients uncontrolled after 8 weeks of treatment, uptitration to the perindopril arginine 5mg/amlodipine 10mg combination showed an additional effect on reducing sitting SBP/DBP and increasing the proportion of patients with BP normalisation and response to treatment.

No unexpected safety concerns were identified for perindopril arginine 5mg/amlodipine 5mg or perindopril arginine 5mg/amlodipine 10mg.

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