2. STUDY ABSTRACT

Sponsor: **Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)**	**Separate study form serves as one part of this document**	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: **Perindopril/Amlodipine (S05985)**	**Page(s):**	

Study name: Efficacy and safety of the fixed oral perindopril arginine 5 mg/ amlopidine 5 mg combination compared with perindopril tert-butylamine 4 mg alone in patients not adequately controlled with perindopril tert-butylamine 4 mg monotherapy.
A randomised, double-blind, 12-week study with up-titration after 8 weeks in non-controlled patients
Protocol code: CL3-05985-017

Coordinator or investigator: [redacted]

Study centres:
21 centres participated in the study and included at least one patient, for a total inclusion of 353 patients.
7 centres participated in the ABPM sub-study.

Publications (reference documents): Not applicable

Study duration:	**Study phase:**
Start date (first patient's first visit): October 11, 2010 End date (last patient's last visit): June 20, 2011	Phase III

Objectives:

Primary objective:

- To demonstrate a statistically significant greater systolic blood pressure lowering effect (SBP) after 8 weeks of treatment versus baseline with perindopril arginine 5 mg/amlodipine 5 mg (Per 5/Amlo 5) combination than with perindopril tert-butylamine 4 mg alone in patients not controlled by perindopril tert-butylamine 4 mg (Per 4) monotherapy.

Secondary objectives:

Efficacy

- To demonstrate a statistically significant greater diastolic blood pressure lowering effect (DBP) after 8 weeks of treatment versus baseline with Per 5/Amlo 5 combination than with perindopril tert-butylamine 4 mg alone in patients not controlled by Per 4 monotherapy.
- To compare the blood pressure normalisation rates and response rates of the Per 5/Amlo 5 combination group versus the Per 4 monotherapy treatment group 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 perindopril 5 mg/amlodipine 5 mg combination group versus the perindopril tert-butylamine 4 mg monotherapy treatment group after 8 weeks of treatment.

Sponsor: **Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)**	**Separate study form serves as one part of this document**	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: **Perindopril/Amlodipine (S05985)**	**Page(s):**	

- To describe the change from baseline in blood pressure parameters [systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean blood pressure (MBP), blood pressure normalisation rate, and response rate] of each treatment strategy (perindopril tert-butylamine 4 mg, uptitrated from perindopril tert-butylamine 4 mg to perindopril 5 mg/amlodipine 5 mg combination; perindopril 5 mg /amlodipine 5 mg combination, uptitrated from perindopril 5 mg/amlodipine 5 mg combination to perindopril 10 mg/amlodipine 5 mg combination) after 12 weeks of treatment.
- To describe change from baseline to W12 in ambulatory blood pressure monitoring (ABPM) parameters in a subgroup of patients.

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 change
- Electrocardiogram abnormalities
- Biochemical and haematological abnormalities, including hyperkalemia and hypokalemia

Methodology:

This study was a multicentre, 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, receiving perindopril tert-butylamine 4 mg therapy, followed by the 12-week double-blind treatment period.

Number of patients:

Planned number of patients included: 280 patients included (140 patients per treatment group), of which approximately 60 patients taking part in the ABPM assessment.

Actual number of patients included: 353 patients were included, with 178 patients in the perindopril/amlodipine group (Per/Amlo group) and 175 patients in the perindopril group (Per). Of these, there were 41 patients who completed two ABPM assessments.

Diagnosis and main selection and inclusion criteria:

- Men or women, ≥ 18 to ≤ 75 years, mild to moderate primary hypertensive patients without complications, who require antihypertensive or replacement treatment strategy because of poor efficacy or tolerability, currently taking no more than one antihypertensive treatment (not including amlodipine and/or perindopril). Fixed combinations at sub-therapeutic doses were allowed.
- Patients who met the following criteria were selected for this study:
  - At selection, 95 mmHg ≤ DBP < 110 mmHg and 150 mmHg ≤ SBP< 180 mmHg.
- After taking perindopril 4 mg treatment for four weeks, participants with blood pressure levels within the following ranges were eligible for inclusion:
  - At inclusion, 90 mmHg ≤ DBP < 110 mmHg and 140 mmHg ≤ SBP < 180 mmHg.

Sponsor: Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)	Separate study form serves as one part of this document	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: Perindopril/Amlodipine (S05985)	**Page(s):**	

- SBP at inclusion < SBP at selection.

- Patients were excluded if they had a known history of cerebrovascular stroke or other cerebrovascular disease, unstable angina pectoris, myocardial infarction, coronary revascularisation, congestive heart failure, uncontrolled cardiac arrhythmia (such as atrial fibrillation or atrial flutter), level II or III atrioventricular heart-block, type 1 diabetes or uncontrolled type 2 diabetes, insufficient renal function, insufficient liver function, symptomatic orthostatic hypotension, history of alcohol or drug abuse or any other drugs contraindicated with the study.
- Other non-selection criteria were: pregnancy or women of childbearing age who were not taking a medically accepted contraceptive.

Study drug:
S05985 – Perindopril/amlodipine combination: Per 5 mg/Amlo 5 mg - Per 10 mg/Amlo 5 mg. One capsule or one capsule and one tablet taken orally before breakfast.
Batch numbers: Perindopril arginine 5mg/amlodipine 5mg: L0033545, L0035679
Perindopril arginine 10mg/amlodipine 5mg: L0033466, L0035504

Control drug:
Perindopril tert-butylamine 4 mg – one capsule taken orally before breakfast. Matching placebo tablet of Per 10 mg/Amlo 5 mg and matching placebo capsule of Per 5 mg/Amlo 5 mg taken orally before breakfast.

Treatment period:
- 4-week run-in period, active drug treatment (from selection to W0; perindopril tert-butylamine 4mg, one capsule once daily, orally)
- 12-week double-blind active drug treatment period (from W0 - W12):
  - First stage (P1, 8 weeks): perindopril tert-butylamine 4mg or perindopril 5mg/amlodipine 5mg, one capsule once daily orally
  - Second stage (P2, 4 weeks): perindopril tert-butylamine 4mg or perindopril 5mg/amlodipine 5mg, one capsule once daily; perindopril 5mg/amlodipine 5mg or perindopril 10mg/amlodipine 5mg (patients whose blood pressure was not controlled at W8, i.e. SBP ≥ 140mmHg and/or DBP ≥ 90 mmHg), one tablet and one capsule once daily orally

Criteria for evaluation:

Efficacy:
Primary efficacy endpoint:
- Sitting systolic blood pressure (SBP)

Secondary efficacy endpoint:
- Sitting diastolic blood pressure (DBP)
- Pencentage of normalisation of blood pressure: Definition of BP normalisation was: SBP < 140 mmHg and DBP < 90 mmHg

Sponsor: **Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)**	**Separate study form serves as one part of this document**	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: **Perindopril/Amlodipine (S05985)**	**Page(s):**	

- Pencentage 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 DBP + 1/3 SBP)
- Ambulatory Blood Pressure Monitoring (ABPM) parameters

Safety:
- Adverse events
- BP postural changes
- Vital signs
- Laboratory parameters (haematology, biochemistry)
- Electrocardiogram (ECG)

Sponsor: **Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)**	**Separate study form serves as one part of this document**	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: **Perindopril/Amlodipine (S05985)**	**Page(s):**	

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 a 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 protocol deviations 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 protocol deviations 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 a valid baseline ABPM and a 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 protocol deviations that could affect assessment of 24-hour mean SBP.

Two treatment groups were defined, based on patient randomisation:
- Perindopril 5mg/Amlodipine 5mg combination group (abbreviated as Per/Amlo)
- Perindopril tert-butylamine 4mg monotherapy group (abbreviated as Per)

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 5mg/Amlodipine 5mg combination to Perindopril 10mg/Amlodipine 5mg combination (abbreviated as P5/A5-P10/A5)
- Perindopril tert-butylamine 4mg monotherapy for 12 weeks (abbreviated as P4)
- Uptitrated from Perindopril tert-butylamine 4mg monotherapy to Perindopril 5mg/Amlodipine 5mg (abbreviated as P4-P5/A5)

Study outcome:

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

Sponsor: Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)	Separate study form serves as one part of this document	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: Perindopril/Amlodipine (S05985)	**Page(s):**	

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 5mg/Amlodipine 5mg combination compared to perindopril tert-butylamine 4mg monotherapy on the change from baseline to last post baseline sitting SBP after 8 weeks of treatment.
A general linear model studying treatment effect with baseline and study centre (fixed factors) as covariates was used. The estimate of between group difference, standard error, 95% confidence interval, and superiority test p-values were also provided.
Secondary analysis used the FAS and PPS, presented by treatment group and by treatment strategy, and described sitting SBP at each follow-up visit, and changes from baseline to last post-baseline measurement.

Secondary efficacy endpoints:
Sitting DBP
For sitting DBP, the analysis performed was identical to that for the primary efficacy endpoint.
Percentage of response to treatment and normalisation of blood pressure
The percentage of responders/normalised at W004, W008 and on last post-baseline value over 8 weeks were described for each treatment group. The differences between Per 5/Amlo 5 combination and Per 4 on last post-baseline value over 8 weeks will be given, as well as their 95% confidence intervals.
The percentage of responders/normalised on the last value during the study were described by strategy over 12 weeks.
Pulse pressure and mean blood pressure
Pulse pressure and mean blood pressure were described at W4, W8 and the last post-baseline value over 8 weeks of treatment by treatment group.
For the change from baseline value to last post-baseline value over 8 weeks, differences between Per 5/Amlo 5 combination and Per 4 were described, and 95% confidence intervals given. Pulse Pressure and Mean Blood Pressure values and the change from baseline to last value were described over 12 weeks by strategy.
ABPM parameters:
All ABPM parameters were described at W0 and W12, as well as the change from baseline to W12 value were presented by strategy.

Safety analysis:
In safety set, description analysis of adverse events, orthostatic hypotension, laboratory tests, vital signs, and electrocardiogram over 12 weeks were provided by treatment strategy. 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,

Sponsor: Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)	Separate study form serves as one part of this document	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: Perindopril/Amlodipine (S05985)	**Page(s):**	

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 set		Per/Amlo	Per	Total
Main study				
Randomisation set (RS)	n	178	175	353
Full analysis set (FAS)	n (%)	173 (97.2%)	173 (98.9%)	346(98.0%)
W8 per-protocol set (PPS_W8)	n (%*)	159 (91.9%)	157 (90.8%)	316(91.3%)
W12 per-protocol set (PPS_W012)	n (%*)	159 (91.9%)	154 (89.0%)	313(90.5%)
Safety set(SS)	□ (%)	178 (100.0%)	175 (100.0%)	353(100.0%)

Analysis data set		P5/A5	P5/A5-P10/A5	P4	P4-P5/A5	Total
ABPM sub-study						
Full analysis set –ABPM subset (FAS-ABPM)	n	8	11	5	10	34
Per-protocol set – ABPM subset (PPS-ABPM)	n (%#)	7 (87.5%)	9 (81.8%)	5(100.0%)	8 (80.0%)	29 (85.3%)

n: Number of patients; % : Percentage of randomisation set comprised by the corresponding treatment group;
% : Percentage referring to the Full Analysis Set for the corresponding treatment group;*
%# : Percentage referring to the FAS-ABPM for the corresponding treatment group

Primary baseline characteristics

A total of 353 patients with primary hypertension were randomised for this study (RS): 178 patients in the Per/Amlo group, 175 patients in the Per group. Of these, 67 patients were included in the ABPM assessment, 41 patients completed both ABPM assessments at W000 and W012, and 34 of these patients had two valid ABPM assessments (FAS-ABPM).

During the W000-W012 period, 21 patients (5.9%) withdrew from the study, and no patient was lost to follow-up. The main reasons for patient withdrawal from the study were non-medical reasons (8 patients), protocol deviation (5 patients), adverse events (5 patients), and other protocol withdrawal criteria (3 patients), there was no between-group difference. 332 patients (94.1%) completed W000-W012 of the study: 169 in the Per/Amlo group (94.9%), 163 in the Per group (93.1%).

Sponsor: **Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)**	**Separate study form serves as one part of this document**	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: **Perindopril/Amlodipine (S05985)**	**Page(s):**	

Main Demographic Data and Disease Characteristics (RS)

		Per/Amlo (N =178)	Per (N =175)	Total (N =353)
Age (years)	Mean ± SD	53.7 ± 9.0	52.7 ± 9.0	53.2 ± 9.0
Sex	Male n (%)	103 (57.9)	91 (52.0)	194 (55.0)
Bodyweight (Kg)	Mean ± SD	70.17 ± 10.10	69.76 ± 10.18	69.97 ± 10.13
Body mass index (BMI, Kg/m^2)	Mean ± SD	25.23 ± 2.33	25.17 ± 2.56	25.20 ± 2.45
Primary hypertension				
Disease duration (years)	Mean ± SD	7.7 ± 7.6	6.3 ± 7.4	7.0 ± 7.5
Family history	n (%)	100 (56.2)	98 (56.0)	198 (56.1)
Sitting blood pressure				
SBP (mmHg)	Mean ± SD	150.74 ± 6.84	150.02 ± 6.82	150.38 ± 6.83
DBP(mmHg)	Mean ± SD	97.62 ± 4.98	97.68 ± 4.66	97.65 ± 4.82

The primary baseline characteristics for the two groups were similar. In terms of other significant baseline characteristics for the two groups, such as previous disease history, vital signs, concomitant medicines, all were comparable. Baseline efficacy endpoints were comparable between the two groups.

In RS, patient age was 53.2 ± 9.0 years, males were a slight majority (55.0%), bodyweight was 69.97 ± 10.13 kg, body mass index was 25.20 ± 2.45 kg/m^2. No between-group difference was observed. Patients included in the study were all diagnosed with primary hypertension, mean duration of disease was 7.0 ± 7.5 years, and 56.1% of patients had a family history of hypertension.

At the inclusion visit, efficacy endpoint assessments for the two groups were similar: mean sitting SBP was 150.38 ± 6.83 mmHg, mean sitting DBP was 97.65 ± 4.82 mmHg.

In terms of patients included in the ABPM assessment, there were no relevant differences among the various treatment strategies: 24-hour mean SBP was 146.48 ± 9.00 mmHg, 24-hour mean DBP was 93.81 ± 6.92 mmHg.

In RS, for the W000-W012 period, total treatment duration was 83.1 ± 13.4 days. Overall treatment compliance was good: 98.9% of patient compliance was in the range of 70% ~ 130%. With respect to treatment duration and treatment compliance, there was no between-group difference.

Among 353 randomised patients, 187 patients (53.0%) uptitrated due to blood pressure not controlled at W8: 76/178 (42.7%) patients in Per/Amlo group and 111/175 (63.4%) in Per group...

In FAS and PPS, demographic data and primary baseline characteristics were consistent with RS.

The primary demographics and other baseline characteristics of patients participating in

Sponsor: Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)	Separate study form serves as one part of this document	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: Perindopril/Amlodipine (S05985)	**Page(s):**	

ABPM assessment were similar to those for the overall population; no relevant between-group difference was noted.

Efficacy results

Primary efficacy endpoint: sitting SBP

Primary analysis : sitting SBP change from baseline to W8

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

Sitting SBP over W000-W008 period (FAS, N = 346)

Sitting SBP (mmHg)		Per/Amlo (N = 173)	Per (N = 173)
Statistical description			
Baseline value (W000)	Mean ± SD	150.6 ± 6.8	150.0 ± 6.9
Last post-baseline value (W008)	Mean ± SD	134.8 ± 13.1	142.2 ± 14.0
Change from baseline to last post-baseline value (W008)	Mean ± SD	-15.8 ± 12.1	-7.8 ± 13.7
Statistical analysis:			
Between-group difference in change from baseline to last post-baseline value (W008)			
	E (SE) (1)	-7.6 (1.4)	
	95% CI(2)	[-10.3 ; -5.0]	
	P value(3)	<.0001	

Superiority test of perindopril/amlodipine combination (Per/Amlo) as compared to perindopril monotherapy (Per). Two-sided type I error rate: 0.05.
(1) Estimate (standard error) of the difference between baseline and study centre adjusted treatment group means: Per/Amlo group minus Per group.
(2) 95% confidence interval of the estimate
(3) General linear model, with baseline and study centre (fixed factors) as the covariates.

In FAS, with respect to the change from baseline in last post baseline sitting SBP over 8 weeks treatment, the decrease was greater in the Per/Amlo group than in the Per group (-15.8 ± 12.1 mmHg and -7.8 ± 13.7 mmHg, respectively); the estimated difference between the groups (general linear model) was -7.6 mmHg (95% CI: [-10.3; -5.0]), superiority test $p < 0.0001$. The difference was statistically significant, thereby demonstrating that the Per 5/Amlo 5 combination had superior efficacy in comparison to Per 4 monotherapy in patients insufficiently controlled by a first month treatment with perindopril 4mg.

Secondary analysis :
In FAS, relative to baseline, after 12 weeks of treatment in the 4 treatment strategies, sitting SBP was reduced: P5/A5, -21.4 ± 10.4 mmHg; P5/A5-P10/A5, -12.6 ± 10.9 mmHg; P4, -16.6 ± 13.7 mmHg; and P4-P5/A5, -14.3 ± 10.5 mmHg.

In **FAS**, patients whose blood pressure was poorly controlled at W008, and with an uptitrated

Sponsor: Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)	Separate study form serves as one part of this document	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: Perindopril/Amlodipine (S05985)	**Page(s):**	

drug dose (P5/A5-P10/A5, P4-P5/A5), had further decreases in sitting SBP between W008 and W012: -4.8 mmHg (95% CI: [-7.3; -2.2]) in P5/A5-P10/A5 and -12.2 mmHg (95% CI: [-14.4; -10.0]) in P4-P5/A5. Patients whose blood pressure was controlled at W008, and continued with the original drug dose (P5/A5, P4), remained stable in terms of mean SBP between W008 and W012.
With respect to sitting SBP after 8 weeks and 12 weeks of treatment, PPS_W8 and PPS_W12, analysis results were consistent with those of FAS.

Secondary efficacy endpoints

- **Sitting DBP**

In FAS, there was greater change in last post baseline sitting DBP relative to baseline after 8 weeks of treatment in the Per/Amlo group than the Per group (-10.6 ± 8.1 mmHg and -6.2 ± 8.6 mmHg, respectively); estimated difference between groups was -4.3 mmHg (95% CI: [-6.0; -2.6]); superiority test $p < 0.0001$. The difference was statistically significant.
After 12 weeks of treatment, sitting DBP was reduced in the 4 treatment strategies.
In FAS, in patients whose blood pressure was not controlled at W008, and who received uptitrated drug dose for continued 4 weeks of treatment, titration to a higher dose provided an additional decrease in sitting DBP between W008 and W012 in both titrated strategies -2.4 mmHg (95% CI: [-3.9; -1.0]) in P5/A5-P10/A5 and -5.7 mmHg (95% CI: [-7.0; -4.5]) in P4-P5/A5). Patients who continued with the original drug dose (P5/A5 and P4) for 12 weeks remained stable in terms of mean DBP between W008 and W012.

- **Blood pressure normalisation rate**

In FAS, the percentage of patients with normalised blood pressure was higher in the Per/Amlo group (54.3%) compared to the Per group (31.8%) after 8 weeks of treatment. The estimated value of the difference between groups was 22.5% (95% CI: [12.4; 32.7]);
The results were favourable to the Per/Amlo group. Among the patients whose BP was not controlled after 8 weeks of treatment and who were uptitrated, after the continued 4 weeks of treatment, the percentage of patients with blood pressure controlled to normal increased from zero at W008 to: 26.3% in P5/A5-P10/A5 and 34.2% in P4- P5/A5 at W012 respectively.

- **Response to treatment**

In FAS, the percentage of responders to treatment was greater in the Per/Amlo group (68.8%) compared to the Per group (40.5%) after 8 weeks of treatment. The estimated value of the difference between the groups was 28.3% (95% confidence interval: [18.3; 38.4], the results were favourable to the Per/Amlo group.
Among the patients who were not controlled after 8 weeks of treatment and who were uptitrated, more patients responded to treatment.

- **Pulse pressure (PP)**

In FAS, the decrease in PP was greater in the Per/Amlo group compared to the Per group (-5.2 ± 9.7 mmHg and -1.6 ± 9.6 mmHg, respectively) after 8 weeks of treatment. The

Sponsor: Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)	Separate study form serves as one part of this document	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: Perindopril/Amlodipine (S05985)	**Page(s):**	

estimated value of between-group difference was -3.3 mmHg (95% CI: [-5.2; -1.4]). The results were favourable to the Per/Amlo group.

- **Mean blood pressure (MBP)**

In FAS, the decrease was greater in the Per/Amlo group compared to the Per group (-12.3 ± 8.5 mmHg and -6.8 ± 9.6 mmHg, respectively) after 8 weeks of treatment. The estimated difference between the groups was -5.4 mmHg (95% CI: [-7.3; -3.6]). The results were favourable to the Per/Amlo group.

- **24-hour ABPM parameters**

ABPM was performed in a subset (FAS-ABPM = 34) of the study population (**FAS, N = 346**) and, as planned by study design, ABPM was performed in 4 different treatment strategies leading to a very low number of patients and imbalanced distribution among each strategy (P5/A5 = 8 patients, P5/A5-P10/A5 = 11 patients, P4 = 5 patients, P4-P5/A5 = 10 patients). Therefore, the interpretation from ABPM data should be carried out with caution.

Results from ABPM showed that after 12 weeks of treatment, for different time stages in the 4 treatment strategies (**24-hour, standard daytime, standard nighttime, daytime, nighttime, real diurnal, real nocturnal, last 6 hours before taking the study drug, and morning**), **the mean SBP and mean DBP** were reduced by varying degrees.

ABPM-24 Hour Mean SBP and DBP (mmHg, FAS-ABPM)

Statistical description		P5/A5 (N = 8)	P5/A5-P10/A5 (N = 11)	P4 (N = 5)	P4-P5/A5 (N = 10)
24 hour mean SBP					
Baseline	Mean ± SD	146.52 ± 7.66	150.07 ± 12.79	144.05 ± 4.25	143.71 ± 5.82
W012	Mean ± SD	135.47 ± 12.27	135.81 ± 10.42	135.93 ± 7.73	124.84 ± 7.69
W012 – baseline	Mean ± SD	-11.04 ± 13.73	-14.26 ± 8.62	-8.13 ± 9.45	-18.87 ± 8.74
24 hour mean DBP					
Baseline	Mean ± SD	91.56 ± 9.73	96.48 ± 5.33	92.63 ± 4.67	93.27 ± 6.80
W012	Mean ± SD	85.11 ± 5.26	88.09 ± 5.88	87.06 ± 7.05	81.83 ± 6.40
W012 – baseline	Mean ± SD	-6.45 ± 9.81	-8.39 ± 5.83	-5.56 ± 8.16	-11.44 ± 4.91

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

Safety results

The safety set (SS) included 353 patients (Per/Amlo = 178 patients, Per group = 175 patients). The treatment duration and exposure for the two groups were similar. Based on the study drug dose adjustment at the W008 visit, patients were separated into 4 treatment strategies and distribution in SS was: P5/A5 strategy = 102 patients, P5/A5-P10/A5 strategy = 76 patients, P4 strategy = 64 patients, P4-P5/A5 strategy = 111 patients.

Sponsor: **Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)**	**Separate study form serves as one part of this document**	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: **Perindopril/Amlodipine (S05985)**	**Page(s):**	

Emergent Adverse Event Brief Summary (W000-W012, SS)

		P5/A5 (N = 102)	P5/A5-P10/A5 (N = 76)	P4 (N = 64)	P4-P5/A5 (N = 111)	Total (N = 353)
Patients reporting at least 1 EAE	n (%)	31(30.4%)	20(26.3%)	16(25.0%)	26(23.4%)	93(26.3%)
severe EAE	n (%)	-	-	-	2(6.9%)	2(1.8%)
EAE related to study drug	n (%)	10(9.8%)	5(6.6%)	4(6.3%)	6(5.4%)	25(7.1%)
Withdrawal because of EAE	n (%)	2(2.0%)	-	2(3.1%)	1(0.9%)	5(4.3%)
Patients reporting at least 1 serious EAE	n (%)	1(1.0%)	-	-	-	1(0.3%)
Serious EAE related to study drug	n (%)	-	-	-	-	-
Death	n (%)	-	-	-	-	-
Withdrawal because of serious EAE	n (%)	-	-	-	-	-

Adverse events

During the run-in period with perindopril tert-butylamine 4 mg monotherapy, the most commonly reported adverse events were hyperlipidaemia (8.2%), cough (5.7%), upper respiratory tract infection (4.8%), and impaired fasting glucose (4.2%).

In SS, during W000-W008 period, onset rates reported for **emergent adverse events (EAE)** in the two groups were within the expected range in both groups, respectively 19.1% (34 patients) in the Per/Amlo group and 13.1% (23 patients) in the Per group. During W000-W012 period, EAEs reported in the 4 treatment strategies were, respectively: P5/A5, 31 patients (30.4%); P5/A5-P10/A5, 20 patients (26.3%); P4, 16 patients (25.0%); P4-P5/A5, 26 patients (23.4%).

In SS, during the W000-W012 period, the most common affected System Organ Class (SOC) by EAEs in the 4 treatment strategies (P5/A5, P5/A5-P10/A5, P4, P4-P5/A5) were as follow: respiratory, thoracic, and mediastinal disorders (12.7%, 6.6%, 7.8%, 6.3%, respectively), infections and infestations (7.8%, 10.5%, 6.3%, 8.1%, respectively), metabolism and nutrition disorders (8.8%, 6.6%, 9.4%, 1.8%, respectively). The most commonly reported EAEs (total onset rate exceeding 3.0%) were cough (12.7%, 6.6%, 6.3%, 5.4%, respectively) and upper respiratory tract infection (6.9%, 7.9%, 4.7%, 5.4%, respectively).
The intensity of most EAE was mild (82.5%) or moderate (15.8%), only very small minority (1.8%) were severe EAEs.
The outcome of most EAE was “recovery” (76.3%) or “improving” (5.3%).
A total of 5 patients withdrew from the study because of **emergent adverse events**, the 5 events were all non-serious adverse events, the outcomes were “recovered” respectively: P5/A5 group 2 patients “cough” (both unrelated to study drug), P4 group 1 patient “cough” (related to study drug) and 1 patient “rash” (not related to study drug), P4-P5/A5 group 1 patient “facial flush” (related to study drug) .

In SS, during the W000-W012 period, 25 patients had 26 **emergent adverse events related to study drug**: P5/A5, 10 patients (9.8%); P5/A5-P10/A5, 5 patients (6.6%); P4, 4 patients (6.3%); P4-P5/A5, 6 patients (5.4%). The most common affected SOCs in the 4 treatment

Sponsor: Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)	Separate study form serves as one part of this document	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: Perindopril/Amlodipine (S05985)	**Page(s):**	

strategies (P5/A5, P5/A5-P10/A5, P4, P4-P5/A5) were respiratory, thoracic and mediastinal disorders (8.8%, 5.3%, 6.3%, 4.5%, respectively), "cough" was the most frequently reported (8.8%, 5.3%, 6.3%, 4.5%, respectively).
In SS, during the whole study period**,** only 1 patient (P5/A5) experienced a serious adverse event **(SAE)**. The patient was male, in P5/A5 stratedy, 58 years old, and on Day 9 after first intake of the study drug during W000-W008, he experienced "eventration of diaphragm". He recovered after undergoing "thoracic diaphragm enfolding surgery". By the judgment of investigator, the event was unrelated to the study drug. The patient did not stop taking study drug and completed the study.

There were no deaths during the study.

Blood biochemistry and haematology parameters
In SS, during 12-week treatment period, very few potentially clinical significant emergent blood biochemical and haematological abnormalities were observed. There were no relevant differences between the various treatment strategies.

Vital signs and orthostatic hypotension
In SS, during 12 weeks of treatment, heart rate declined slightly for patients in all various treatment strategies, bodyweight remained stable. No relevant between-group difference was seen.
In SS, 3 patients had onset of orthostatic hypotension after treatment (Per/Amlo group 2 cases, Per group 1 case) during the 8-week treatment period. During continuing 4 weeks of treatment there was no orthostatic hypotension reported (regardless of dose uptitration).

Electrocardiogram testing
In SS, based on investigator's judgement, 6 patients at baseline and 2 patients at the end of study experienced abnormal electrocardiograms with clinical significance.

Sponsor: **Institut de Recherches Internationales Servier (I.R.I.S., Servier International Research Centre)**	**Separate study form serves as one part of this document**	*(for National Authority Use only)*
Commercial name of study drug:	**Volume:**	
Name of active ingredients: **Perindopril/Amlodipine (S05985)**	**Page(s):**	

Conclusion

The study is a randomised, double blind, 12-week study with up-titration after 8 weeks in non-controlled patients. The efficacy and safety of the fixed oral perindopril arginine 5mg/amlodipine 5mg combination were compared with perindopril 4 mg alone in patients not adequately controlled with perindopril 4mg monotherapy.
The study demonstrated that the perindopril 5mg/amlodipine 5mg combination was superior, with statistical significance, to the continuation of perindopril 4 mg monotherapy in the treatment of hypertensive patients not adequately controlled with perindopril 4 mg monotherapy (change in sitting SBP and sitting DBP from baseline after 8 weeks treatment). Also, the perindopril 5mg/amlodipine 5mg combination was superior to the continuation of perindopril 4 mg monotherapy in reducing Pulse Pressure and Mean Blood Pressure and in increasing the proportion of patients with BP normalisation and response to treatment over 8 weeks of treatment in patients not adequately controlled with perindopril 4 mg monotherapy.

For patients uncontrolled after 8 weeks of treatment, uptitration to the perindopril arginine 10mg/amlodipine 5mg 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 concern was identified for perindopril arginine 5mg/amlodipine 5mg or perindopril arginine 10mg/amlodipine 5mg.

Report date: February 06, 2012