Document title	**Clinical Study Report Synopsis**
Study title	**Perindopril arginine/Amlodipine *versus* Valsartan/ Amlodipine antihypertensive strategies: Efficacy and safety in mild to moderate hypertensive patients.** **A randomised, double blind 6-month study followed by an 8-month open label long-term follow-up with Perindopril arginine/Amlodipine.** **Report of long term follow-up.**
Study drug	**S 05985**
Studied indication	**Essential arterial hypertension**
Development phase	**Phase III**
Protocol code	**CL3-05985-018 (M0-M14)**
Study initiation date	**2 December 2010**
Study completion date	**11 January 2013**
Main coordinator	[redacted] **- Italy**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot, 92284 Suresnes Cedex - France** **Laboratorios Servier S.L.** **28043 Madrid - Spain** **Servier Canada Inc. ICTR Canada** **Laval, Quebec, Canada - H7V 4A7** **Servier Research and Development Limited** **Wexham Springs - SL3 6 RJ Slough - United Kingdom** **Les Laboratoires Servier Representative Office** **Paveletskaya Square 2 - Moscow 115 054 - Russia**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 10 September 2013**

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2. SYNOPSIS

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Title of study: Perindopril arginine/Amlodipine *versus* Valsartan/Amlodipine antihypertensive strategies: Efficacy and safety in mild to moderate hypertensive patients.
A randomised, double-blind 6-month study followed by an 8-month open label long-term follow-up with Perindopril arginine/Amlodipine.
Report of long-term follow-up (M0-M14)
Protocol No.:**CL3-05985-018 –** EudraCT Number: **2010-020945-28**

Coordinator [redacted] - Italy

Study centres: 225 centres were opened in 18 countries and 194 included at least one patient: 4 centres in Belgium (8 included patients), 12 centres in Brazil (148 included patients), 10 centres in Canada (38 included patients), 10 centres in Czech Republic (45 included patients), 34 centres in France (176 included patients), 24 centres in Germany (99 included patients), 13 centres in Italy (160 included patients), 7 centres in Republic of Korea (20 included patients), 6 centres in Latvia (94 included patients), 4 centres in Lithuania (58 included patients), 9 centres in Mexico (238 included patients), 3 centres in Netherlands (10 included patients), 5 centres in Portugal (22 included patients), 31 centres in Federation of Russia (433 included patients), 4 centres in Singapore (32 included patients), 8 centres in Spain (109 included patients), 4 centres in Taiwan (30 included patients), 6 centres in United Kingdom (54 included patients).

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 2 December 2010 Completion date (date of last M14 visit): 11 January 2013	III

Objectives:
The primary objective was to demonstrate the better efficacy in lowering office systolic blood pressure of the Perindopril/Amlodipine combination *versus* Valsartan/Amlodipine strategy at the end of the Perindopril/Amlodipine titration phase.
Theses analyses, along with the main safety objective of the study of assessing the safety of each dose of Perindopril/Amlodipine combination and Valsartan/Amlodipine combination at the end of the six-month double blind period, were described in a previous report (NP32419).

This report focuses on the secondary safety objective of the CL3-05985-018 study, *i.e.* to assess the long-term safety of each step of dose of the Perindopril/Amlodipine combination at the end of the open label follow-up (M14).

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Methodology:
This was a phase III, prospective, international, multicentre, comparative, double-blind, randomised in 2 parallel groups over 6 months *versus* active treatment study, followed by an open-label follow-up period of 8 months. Mild to moderate hypertensive patients were to be enrolled and received one of the treatment strategies using a fixed, 1 to 1, centralised, stratified according to the country, randomisation by Interactive Web Response System (IWRS).

The methodology of the first 6-month double-blind study period is displayed in the main study report M0-M6 (NP32419).
At M6, patients with controlled blood pressure entered in an open label follow-up period of 8 months, and received only the Perindopril/Amlodipine combination at the same step of dose as the one reached at M6 for patients previously receiving the Perindopril/Amlodipine strategy (PA/PA arm), or at an equivalent step of dose for patients previously receiving the Valsartan/Amlodipine strategy (VA/PA arm).
During the open label follow-up, patients for whom blood pressure became not controlled at two consecutive visits were to be withdrawn from the study. In case of SBP/DBP higher than 160/100 mmHg, an additional visit was to be performed within 15 days to confirm the elevated BP and withdrawn the patient. Up-titration was not allowed over this open label period.

Number of patients:
Planned at M0: 1600 (800 by treatment group).
Included at M0: 1774 (888 in the Per/Amlo group and 886 in the Val/Amlo group).

Planned in the follow-up safety set: 100 patients on each Per/Amlo dose, exposed for at least 1 year.
Included in the follow-up safety set: 1554 (887 in the PA/PA group and 667 in the VA/PA group):

- 126 patients on Per 3.5/Amlo 2.5 were exposed at least 1 year
- 136 patients on Per 7/Amlo 5 were exposed at least 1 year
- 102 patients on Per 14/Amlo 10 were exposed at least 1 year

Diagnosis and main criteria for inclusion:
Patients aged at least 18 years, with essential arterial hypertension untreated or treated at selection (no more than 2 antihypertensive drugs) who had their blood pressure controlled after the 6-month double-blind treatment period (*i.e.* SBP < 140 mmHg and DBP < 90 mmHg).

Study drug: Perindopril/Amlodipine, 1 oral capsule in the morning (Steps 1 to 3) or Perindopril/Amlodipine + Indapamide, 1 oral capsule + 1 tablet taken o.d. in the morning (Step 4), according to the following steps of doses:

- Step 1: Perindopril 3.5 mg/Amlodipine 2.5 mg.
- Step 2: Perindopril 7 mg/Amlodipine 5 mg.
- Step 3: Perindopril 14 mg/Amlodipine 10 mg.
- Step 4 (Step 3 + Indapamide): Perindopril 14 mg/Amlodipine 10 mg + Indapamide 1.5 mg Sustained Release (1.5 SR).

From M6 onwards, patients initially randomised in the Per/Amlo strategy continued the step of dose received at M6. Those initially randomised in the Val/Amlo strategy received the Per/Amlo treatment at an equivalent step of dose as follows:

- Valsartan 80 mg corresponded to Per 3.5 mg/Amlo 2.5 mg.
- Valsartan 160 mg or Val 160 mg/Amlo 5 mg corresponded to Per 7 mg/Amlo 5 mg.
- Val 160 mg/Amlo 10 mg corresponded to Per 14 mg/Amlo 10 mg.

Uptitration was not allowed during the open-label period.

Reference product: Valsartan alone or in combination with amlodipine during the M0-M6 period [see details in the main study report M0-M6 (NP32419)]. Not applicable during the M6-M14 period.

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Duration of treatment:

- Run-in period on placebo: 2 to 4 weeks.
- Double-blind titration period: 6 months. Subject of the main study report M0-M6 (NP32419).
- Open label follow-up period: 8 months. Subject of the present report.

Safety criteria for evaluation over M0-M14:

Emergent adverse events on Per/Amlo occurring during the M0-M14 period, leg oedema assessment by the investigators, clinically significant orthostatic hypotension evaluation, clinically significant biochemical and haematological abnormalities, vital signs and ECG.

Statistical methods:

Descriptive statistics in the Safety Set 2 were provided.

This set corresponded to patients who received at least one dose of study treatment during the study for patients stemming from the Perindopril/Amlodipine strategy in the double blind period and to patients who received at least one dose of study treatment during the open label follow-up (M6-M14) for patients stemming from Valsartan/Amlodipine strategy.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Overall, 2740 patients were selected for the study, of whom 1774 were included and randomly assigned to one of the two groups. The distribution of patients according to the randomised treatment allocated at inclusion was well-balanced.

A total of 887 patients were treated with the Per/Amlo strategy over the double-blind period, of whom 725 continued the study after M6, through the open label follow-up period. Among the 884 patients having received the Val/Amlo strategy over the double-blind period, 667 continued the study through the open label follow-up period and received at least one dose of the Per/Amlo treatment strategy. Consequently, 1554 patients were analysed for the long-term follow-up (Safety Set 2), as they received at least one dose of the Per/Amlo strategy.

A total of 1239 patients (79.7%) completed the M0-M14 period and 315 patients (20.3%) were prematurely withdrawn (26.4% in the PA/PA arm, and 12.1% in the VA/PA arm). Treatment withdrawals were most frequently related to other protocol withdrawal criteria (9.6%) mainly including patients with uncontrolled BP at M6 in the Per/Amlo randomisation group and though not eligible for the prolongation phase (n = 74), and patients whose BP became uncontrolled at two consecutive visits over M6-M14 period (n = 47).

No patient was lost to follow-up.

Overall disposition of patients in the Safety Set 2

		All
Included in the Safety Set 2	**N**	**1554**
Withdrawn due to	**n (%)**	**315* (20.3)**
adverse event	n (%)	109 (7.0)
non-medical reason	n (%)	50 (3.2)
other protocol withdrawal criteria	n (%)	149* (9.6)
protocol deviation	n (%)	7 (0.5)
Completed until M14	**n (%)**	**1239 (79.7)**

N Total number of patients included in the Safety Set 2
n number of patients in each category
% = (n/N) x 100
** Including 74 patients in the Per /Amlo strategy withdrawn at M6 because of uncontrolled BP*

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STUDY POPULATION AND OUTCOME (Cont'd)

In the Safety Set 2, patients had a mean age of 55.4 ± 10.5 years, with 18.7% aged 65 years or over, with a well-balanced male/female ratio. Patients had known hypertension for a mean duration of 8.1 ± 7.7 years. Hypertension was of grade I in 20.1% of patients and grade II in 79.9%. A total of 13.3% of patients reported diabetes mellitus and 3.9% leg oedema as specific medical history.

Most patients (80.1%) were previously treated for their hypertension, mainly with agents acting on the renin-angiotensin system (83.1% of the previously treated patients), diuretics (30.9%) and calcium channel blockers (29.4%).

Regarding the blood pressure parameters in the Safety Set 2, at inclusion the mean supine SBP and DBP were 163.3 ± 7.9 mmHg and 100.2 ± 3.7 mmHg, respectively, and at M6 the mean supine SBP and DBP were 131.1 ± 8.5 mmHg and 80.0 ± 6.7 mmHg, respectively.

No relevant difference between VA/PA and PA/PA arms was detected regarding demographic and other baseline characteristics as well as blood pressure parameters.

In the Safety Set 2, the mean Per/Amlo treatment duration over the M0-M14 period (period for the long-term safety analysis) was 300.5 ± 115.7 days (approximately 10 months, median 8.3 months), and global compliance over the M0-M14 period was satisfactory (mean = 97.6 ± 8.6%, median = 100%). The mean treatment duration was 109.8 days (approximately 3.7 months) on Per 3.5/Amlo 2.5, 157.5 days (approximately 5.3 months) on Per 7/Amlo 5, 193.5 days (approximately 6.5 months) on Per 14/Amlo 10 and 262.9 days (approximately 8.8 months) on Per 14/Amlo 10 + Ind.
A total of 126 patients (12.7%) on Per 3.5/Amlo 2.5, 136 patients (12.6%) on Per 7/Amlo 5 and 102 patients (14.7%) on Per 14/Amlo 10 were exposed at least 1 year. This is in accordance with the European guideline (CPMP/ICH/375/95) requirements of at least 100 patients being exposed for a minimum of one year at a considered dose, to assess the long-term safety of each Perindopril/Amlodipine dose.

SAFETY RESULTS

- **Emergent adverse events (EAEs)** (see Table below)
  In the Safety Set 2, the percentage of patients presenting with at least one emergent adverse event was similar on Per 3.5/Amlo 2.5 and Per 7/Amlo 5 considering that patients on Per 7/Amlo 5 had a higher mean duration of exposure than patients treated with Per 3.5/Amlo 2.5. The patients treated with Per 14/Amlo 10 had a slightly higher rate of adverse events than patients treated with Per 7/Amlo 5 mainy due to oedema peripheral with the 10 mg amlodipine dose and the higher extent of exposure under this dose.

Emergent adverse events (EAEs) according to Perindopril/Amlodipine intake
Main safety results over the M0-M14 period - Safety Set 2 (N = 1554)

		P3.5/A2.5 (N = 994)	P7/A5 (N = 1078)	P14/A10 (N = 695)	P14/A10 + I (N = 202)
Patients having reported					
at least one emergent adverse event	n (%)	227 (22.8)	290 (26.9)	232 (33.4)	81 (40.1)
at least one treatment-related emergent adverse event	n (%)	48 (4.8)	57 (5.3)	60 (8.6)	28 (13.9)
Patients having experienced					
at least one serious adverse event (including death)	n (%)	19 (1.9)	26 (2.4)	16 (2.3)	9 (4.5)
at least one treatment-related serious adverse event	n (%)	-	1 (0.1)	-	-
Patients who died	n (%)	-	3 (0.3)	1 (0.1)	-

Globally, the pattern of the most frequently reported EAEs on each dose is consistent with the known safety profile of the individual components, namely oedema peripheral and cough.

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SAFETY RESULTS (Cont'd)

The most frequently reported emergent adverse events were:

- On Per 3.5/Amlo 2.5: cough (2.6% of patients).
- On Per 7/Amlo 5: cough (2.8%), oedema peripheral (2.3%) and nasopharyngitis (2.2%).
- On Per 14/Amlo 10: oedema peripheral (6.6%), nasopharyngitis (2.9%) and cough (2.4%).
- On Per 14/Amlo 10 + Ind: oedema peripheral (6.4%), cough, hypokalaemia and nasopharyngitis (3.0% each), type 2 diabetes mellitus (2.5%), hyperuricaemia and pharyngitis (2.0% each).

Among these most frequent emergent adverse events, the incidence of peripheral oedema slightly increased with the use of higher dose of amlodipine (1.1% on Per 3.5/Amlo 2.5, 2.3% on Per 7/Amlo 5, 6.5% on Per 14/Amlo 10 and 6.4% on Per 7/Amlo 10 + Ind).

Orthostatic hypotension was unfrequently reported with all doses (0.2% on Per 3.5/Amlo 2.5, none on Per 7/Amlo 5, 0.1% on Per 14/Amlo 10 and none on Per 7/Amlo 10 + Ind).

Most emergent adverse events were rated as mild or moderate (96.6% on Per 3.5/Amlo 2.5, 94.1% on Per 7/Amlo 5, 95.0% on Per 14/Amlo 10 and 95.1% on Per 14/Amlo 10+Ind).

Treatment-related emergent adverse events were reported in 4.8% of patients on Per 3.5/Amlo 2.5, 5.3% of patients on Per 7/Amlo 5, 8.6% of patients on Per 14/Amlo 10 and 13.9% of patients on Per 14/Amlo 10 + Ind, and were mainly cough and oedema peripheral.

Most emergent adverse events recovered or were recovering (85.1% on Per 3.5/Amlo 2.5, 81.8% on Per 7/Amlo 5, 84.6% on Per 14/Amlo 10 and 79.2% on Per 14/Amlo 10 + Ind).

Four patients died during the study:

- 3 patients were initially randomised in the Val/Amlo group and switched to the Per 7/Amlo 5 group at M6. Death resulted from a metastatic lung cancer in one patient, a completed suicide in one patient and a myocardial infarction in one patient.
- 1 patient was initially randomised in the Per/Amlo group and continued through the open-label follow-up period on Per 14/Amlo 10. The death was due to a metastatic gastric cancer.

None of these deaths were considered as related to the study drug by the investigator.

A total of 19 patients (1.9%) on Per 3.5/Amlo 2.5, 26 patients (2.4%) on Per 7/Amlo 5, 16 patients (2.3%) on Per 14/Amlo 10 and 9 patients (4.5%) on Per 14/Amlo 10 + Ind reported emergent serious AEs according to the investigator, with no particular preferred term affected. Only one emergent SAE (drug eruption on Per 7/Amlo 5, which led to study drug withdrawal and resolved) was considered as related to the study treatment by the investigator.

The incidence of EAEs leading to premature treatment discontinuation was low whatever the dose (2.7% of patients had at least one EAE leading to treatment discontinuation on Per 3.5/Amlo 2.5, 2.7% on Per 7/Amlo 5, 5.0% on Per 14/Amlo 10 and 5.9% on Per 14/Amlo 10 + Ind), and was slightly higher with Per 14/Amlo 10 and Per 14/Amlo 10 + Ind, probably due to the expected and observed higher rate of oedema peripheral with the introduction of amlodipine 10 mg.

- **Laboratory tests**

Regarding laboratory examination, globally, no dose effect was shown with the 3 doses of perindopril/amlodipine combination.

- **Vital signs**

Concerning vital signs, no clinically relevant differences between dose groups were observed in mean BMI, waist circumference, supine heart rate and blood pressure parameters (SBP, DBP, PP and MBP).

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CONCLUSION

In patients suffering from mild to moderate hypertension, the long-term tolerance of the Perindopril/Amlodipine combination was satisfactory and in accordance with the known safety profiles of each individual product, whichever the dose.

In particular, safety of the highest dose of the combination (Per 14/Amlo 10) was consistent with the safety of the lower doses except for the expected higher rate of dose-dependent amlodipine-induced peripheral oedema that was the main contributor to increased rate of adverse events.

Date of the report: 10 September 2013