Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Safety and efficacy of fixed dose combination of Indapamide SR 1.5 mg / Amlodipine *versus* Valsartan / Amlodipine over 12-week of treatment with conditional titration based on the blood pressure control, in patients with uncontrolled essential hypertension after 1 month of Amlodipine 5 mg run-in treatment. An international, randomized, double-blind, multicentre controlled study.**
Test drug code	**S 05520 (Indapamide SR / Amlodipine)**
Indication	**Essential hypertension**
Development phase	**III**
Protocol code	**CL3-05520-006**
Study initiation date	**04 July 2013**
Study completion date	**27 February 2015**
Main coordinator	[redacted]
ABPM and HBPM coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Les Laboratoires Servier - Representative Office** **Paveletskaya Square 2, building 3** **Moscow 115 054 – Russia** **Servier UK** **Gallions - Wexham Springs** **Framewood road** **Sl3 6rj Slough** **United Kingdom**
Responsible medical officers	[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	**23 September 2015**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** S 05520 (Indapamide SR /amlodipine)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Safety and efficacy of fixed dose combination of Indapamide SR 1.5 mg / Amlodipine *versus* Valsartan / Amlodipine over 12-week of treatment with conditional titration based on the blood pressure control, in patients with uncontrolled essential hypertension after 1 month of Amlodipine 5 mg run-in treatment. An international, randomized, double-blind, multicenter controlled study. Protocol No.: CL3-05520-006. EudraCT No.: 2012-001690-84. The description of the study protocol given hereafter includes the modifications of the 2 substantial amendments to the protocol.		
Name of international coordinator: [redacted]		
Study centres: Multinational, multicentre study = 69 centres located in 13 countries included 473 patients distributed as follows: Argentina (5 centres - 51 patients), Bulgaria (7 centres - 67 patients), Hungaria (4 centres - 7 patients), Latvia (5 centres - 34 patients included), Lithuania (5 centres - 31 patients), Mexico (2 centres - 14 patients included), Poland (6 centres - 60 patients), Romania (9 centres - 41 patients), Russian Federation (6 centres - 56 patients), South Africa (5 centres - 13 patients), Thailand (3 centres - 3 patients), Ukraine (7 centres - 66 patients included), Vietnam (5 centres - 30 patients included).		
Publication (reference): Not Applicable		
Studied period: Initiation date: 04 July 2013 (date of first visit first patient) Completion date: 27 February 2015 (date of last visit last patient)	**Phase of development of the study:** III	
Objectives: The purpose of this study was to demonstrate better efficacy of indapamide/amlodipine strategy *versus* valsartan/amlodipine strategy. **Primary objectives:** **Efficacy:** - To demonstrate better efficacy of fixed-dose combination strategy Indapamide SR 1.5 mg/Amlodipine (Ind/Aml) *versus* Valsartan/Amlodipine (Val/Aml) fixed-dose in lowering office systolic blood pressure at W12. **Secondary objectives:** **Efficacy** - To assess the effect in lowering office Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and derivate parameters after the introduction of each higher dose of the Ind/Aml combination strategy and of the Val/Aml strategy at each visit and as compared to the previous doses. - To assess the response to the treatment and normalisation of blood pressure at each visit. - To assess the efficacy of both combination strategies on the Ambulatory Blood Pressure Monitoring (ABPM) parameters after 12-week (W12) of treatment. - To assess the efficacy of both combination strategies on the Home Blood Pressure Monitoring (HBPM) parameters at each week and each visit until the study end (W12). **Safety:** - To assess the safety of each dose of the Ind/Aml and Val/Aml combination, during the study, and at the end of the 12-week double-blind period.		

Methodology:
This study was an international, multicentre, randomised, double-blind, phase III, over a 12-week treatment period study, comparing single-pill fixed dose combination of indapamide SR /amlodipine *versus* single pill valsartan/amlodipine, with conditional titration based on blood pressure control, in patients with essential uncontrolled hypertension. A fixed randomisation, stratified per centre was done. All patients were proposed to participate in the ABPM and the HBPM parts of the study. The ABPM was performed within 5 days before W0 and W12 visits. The HBPM was performed over 3 days (morning and evening) preceding the study visits W0, W6 and W12, and once a week (morning and evening) from W-4 (ASSE) to W12 except the weeks preceding the study visits. Patients included in the office part of the study could refuse to participate in the ABPM/HBPM parts of the study.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned (office part of the study): 448 patients (224 in each treatment group).
Included:

- Office part of the study: 473 patients (237 patients in the Ind/Aml group and 236 patients in the Val/Aml group).
- ABPM part: 374 patients included (188 patients in the Ind/Aml group and 186 patients in the Val/Aml group).
- HBPM part: 314 patients included (154 patients in the Ind/Aml group and 160 patients in the Val/Aml goup).

Diagnosis and main criteria for inclusion:
Men or women of any ethnic origin ≥ 18 years old or legal national majority who signed Informed consent, with an essential uncontrolled combined systolic and diastolic hypertension (SDH) or isolated systolic hypertension (ISH) with the office blood pressure values: SBP ≥ 150 and < 180 mmHg and DBP < 110 mmHg. After 4 weeks of amlodipine 5 mg active run-in treatment, patients were eligible for randomisation if SBP ≥ 150 and < 180 mmHg and DBP < 110 mmHg (office BP measurement) measured with a validated automatic device in supine position after at least 10 minutes of rest (mean of the two last values of three measurements at 1 minute interval). ABPM and HBPM were proposed to all patients having accepted to be compliant with the ABPM and/or HBPM component of the study.

Test drug:
Indapamide SR 1.5 mg/amlodipine 5 mg fixe dose single-pill combination (*i.e.* dose 1) administered orally with water as one tablet daily in morning, except on visit days where the patients had to be explored after a fasting overnight.
Depending on the blood pressure titration, non-controlled patients could receive the next dose at W6: indapamide SR 1.5 mg/amlodipine 10 mg (*i.e.* dose 2).
Of note, all patients received during the run-in period amlodipine 5 mg during 4 weeks.
All patients received matching placebo during the run-in period, and the treatment period in order to receive the same number of tablets and capsules whatever the treatment period or the treatment group (a total of 2 tablets + 1 capsule per day was received by each patient).
Batch Nos. L0049043, L0054124 (Indapamide SR 1.5 mg/amlodipine 5 mg) and L0049045, L0054127 (Indapamide SR 1.5 mg/amlodipine 10 mg).

Comparator (Reference product):
Valsartan 80 mg/amlodipine 5 mg fixe dose single-pill combination (*i.e.* dose 1) administered orally with water as one capsule daily in morning, except on visit days where the patients had to be explored after a fasting overnight. Depending on the blood pressure titration, non-controlled patients could receive the next dose at W6: valsartan 160 mg/amlodipine 5 mg (*i.e.* dose 2).
Of note, all patients received during the run-in period amlodipine 5 mg during 4 weeks.
All patients received matching placebo during the run-in period, and the treatment period in order to receive the same number of tablets and capsules whatever the treatment period or the treatment group (a total of 2 tablets + 1 capsule per day was received by each patient).

Duration of treatment:
Open label run-in period (4 weeks): the run-in period was dedicated to confirm the essential uncontrolled hypertension under treatment with amlodipine 5 mg. Only eligible patients having still an uncontrolled hypertension under amlodipine 5 mg were randomised to Investigational Medicine product (IMPs).
Double-blind treatment period (12 weeks), with 2 visits at W6 and W12. At W6, all non-controlled patients (SBP ≥ 140 and < 180 mmHg and /or DBP ≥ 90 and < 110 mmHg, based on the office BP measurement) were up-titrated to the next dose of the treatment strategy, respectively fixed combination of Indapamide SR 1.5 mg/amlodipine 10 mg or fixed combination of valsartan 160 mg/amlodipine 5 mg. Patients with SBP ≥ 180 mmHg or DBP ≥ 110 mmHg (mean of the last 2 out of 3 measurements) at the W6 visit were withdrawn from the study.

Criteria for evaluation:

Efficacy measurements:

Primary efficacy criterion

- Supine SBP (Office BP Measurement): change from baseline to the last post-baseline value over the W0-W12 period with each treatment strategy.

Secondary efficacy criteria

- Office BP Measurement at each visit:
  - Supine and Standing (at 3 min) SBP, DBP.
  - Supine Mean BP (MBP), defined as MBP = 2/3 DBP + 1/3 SBP.
  - Supine Pulse Pressure (PP), defined as PP = SBP – DBP.
  - Rate of response to the treatment (defined as SBP < 140 mmHg and DBP < 90 mmHg and/or SBP decrease ≥ 20 mmHg from baseline and/or DBP decrease ≥ 10 mmHg from baseline).
  - Normalisation of blood pressure corresponding to the percentage of patients with SBP < 140 mmHg and DBP < 90 mmHg.
- ABPM: at W0 and W12 (change from baseline for: mean 24 hour ambulatory BP (mean 24h ASBP), mean ADBP over 24h (mean 24h ADBP), mean ASBP and ADBP over standard daytime period, real diurnal period, standard night-time period, real nocturnal period, the last 6 hours of measurement before study products intake, the morning period, night-to-day ratio for ASBP and ADBP, mean HR over 24-hour, diurnal period and nocturnal periods, morning ASBP and ADBP rise, hourly means for ASBP and ADBP, mean APP, mean AHR over 24-hour, daytime period and night-time periods, normalisation defined as mean ASBP over 24h lower than 130 mmHg and mean ADBP over 24h lower than 80 mmHg).
- HBPM: weekly at home and at each study visit (change from baseline over the 3 days preceding the study visit of: mean home systolic blood pressure (HSBP), mean home diastolic blood pressure (HDBP), mean morning/evening HSBP and HDBP, mean global/ morning/ evening home PP and Heart Rate (HR), change from baseline of: weekly variation of mean, global, morning and evening HSBP, HDBP and PP between visits, HBP normalisation defined as mean HSBP lower than 135 mmHg and mean HDBP lower than 85 mmHg).

Criteria for evaluation: (Cont'd)
Safety measurements:

- Emergent adverse events at all study visits.
- Orthostatic hypotension at all study visits.
- Complete laboratory examinations: performed in fasting conditions, at selection (or within 7 days after selection) and within 7 days before W12 visit: biochemistry (sodium, potassium, calcium, chloride, uric acid, urea, creatinine, creatinine clearance, fasting blood glucose levels, total protein, triglycerides, total cholesterol, High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) cholesterol (calculated using Friedwald's formula), ASpartate Amino Transferase (ASAT), ALanine Amino Transferase (ALAT), Gamma-Glutamyl Transferase (GGT), alkaline phosphatase), and haematology (haemoglobin, haematocrit, erythrocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes, leucocytes and platelets), and urine check for proteinuria (at selection). Results should be available at least for inclusion visit and for W12 visit.
- Simplified laboratory test prescribed at inclusion (W0), performed within W0-W6 period at the most appropriate time for each patient (according to the investigator's decision). Fasting condition were not mandatory. Results should be available at W6 visit: sodium, potassium, creatinine and creatinine clearance, uric acid ASAT, ALAT.
- Vital signs: physical examination at all study visits, height (at selection), weight (at selection and at the W12 visit), heart rate (at all visits).
- 12-lead electrocardiogram available for inclusion visit, and visit W12.

Statistical methods:
Analysis Set:
The Full Analysis Set (FAS) used for the efficacy analysis was: based on the intention-to-treat principle and ICH E9 guideline, all patients of the RS who received at least one dose of study treatment and who had at least one baseline analysable value at and one post-baseline analysable value for Supine Systolic Blood Pressure.

Efficacy analysis:
Primary endpoint:
The primary efficacy endpoint was the Supine SBP, expressed mainly in term of change from baseline to last post baseline value at W12 in the FAS. The main analysis corresponded to the between group comparison on the change from Baseline (W0) to last post baseline value at W12 of SBP using an analysis of covariance.
Secondary expressions were: change from baseline to last post baseline value at W6, value at baseline and at each post-baseline visit, change from baseline to value at W6/W12, change from W6 visit to W12 (for titration effect), change from baseline to last post baseline value under treatment at W12. The between-group and the within-group comparison were assessed.

Unplanned analyses:

- A non-inferiority analysis of Ind/Aml as compared to Val/Aml strategy on the change from baseline to last-post baseline value over the W0-W12 period was performed for office SBP and DBP (ISH and SDH gathered) in the FAS. The same model as the main analysis (ANCOVA) was used. The non-inferiority margins considered for this analysis, were 3 mmHg for SBP, and 2 mmHg for DBP (based on CPMP/EWP/238/95 (1998)). This unplanned analysis was conducted as the objective of superiority was not reached. However, as both strategies (Ind/Aml and Val/Aml) provided a clinically relevant antihypertensive effect, there was a scientific interest of assessing the extent of difference between treatments, exploring the non-inferiority of Ind/Aml against Val/Aml strategy.
- The analysis of the office SBP in the FAS over the W0-W12 period was performed in patients considered as uncontrolled regarding the ambulatory blood pressure measurements in order to take into account the white coat effect. The between group comparison was performed in the FAS on the change from Baseline (W0) to last post baseline value at W12 of office SBP using an analysis of covariance (ANCOVA) model.

Secondary endpoints:

- Mean supine DBP, MBP, PP, mean standing SBP and DBP at 3 minutes expressed in term of analysis as the main primary efficacy criterion.
- Response to treatment and normalisation of BP: expressed as number and percentage of patients.
- ABPM and HBPM parts of the study.

Study outcome and safety analysis: descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Status		Ind/Aml	Val/Aml	All
Included/randomised	**n (%)**	**237 (100)**	**236 (100)**	**473 (100)**
In compliance with the protocol	n (%)	195 (82.3)	187 (79.2)	382 (80.8)
With a protocol deviation before or at inclusion	n (%)	42 (17.7)	49 (20.8)	91 (19.2)
Withdrawn due to	**n (%)**	**17 (7.2)**	**13 (5.5)**	**30 (6.3)**
Protocol deviation	n (%)	7 (3.0)	7 (3.0)	14 (3.0)
Non-medical reason	n (%)	7 (3.0)	5 (2.1)	12 (2.5)
Adverse event	n (%)	3 (1.3)	-	3 (0.6)
Lack of efficacy	n (%)	-	1 (0.4)	1 (0.2)
Completed	**n (%)**	**220 (92.8)**	**223 (94.5)**	**443 (93.7)**
In compliance with the protocol	n (%)	202 (85.2)	203 (86.0)	405 (85.6)
With a protocol deviation after inclusion	n (%)	18 (7.6)	20 (8.5)	38 (8.0)
Full Analysis Set (FAS)	**n (%)**	**233 (98.3)**	**232 (98.3)**	**465 (98.3)**
Per Protocol Set (PPS) *	**n (%)**	**186 (79.8)**	**198 (85.3)**	**384 (82.6)**
Safety set	**n (%)**	**236 (99.6)**	**236 (100)**	**472 (99.8)**

*n: number of patients affected; %: expressed as percentage of the included/randomised patients; *: expressed as percentage of the FAS*

A total of 473 patients were included (and randomised), with a well-balanced distribution reached between-groups (237 patients in the Ind/Aml group and 236 patients in the Val/Aml group). Of them, 6.3% were withdrawn (7.2% *versus* 5.5%, respectively), including 3 patients in the Ind/Aml group withdrawn for adverse events, and one patient in the Val/Aml group for lack of efficacy. Finally, 443 patients, 93.7% of the included patients completed the study (220 patients, 92.8% and 223 patients, 94.5%, respectively). Overall, 19.2% reported protocol deviations before or at inclusion, with similar frequency in both treatment groups (17.7% *versus* 20.8%, respectively).They were mainly in relation with the study medication administration (4.6% and 4.2%, respectively). After inclusion, 13.1% reported protocol deviations (12.7% *versus* 13.6%, respectively), mainly those due to blood samples not taken (6.3% and 5.1%, respectively). No relevant between-group difference was detected.

A total of 374/473 patients, 79.1% (of the patients included in the office part of the study) participated in the ABPM part of the study (188 patients in the Ind/Aml group *versus* 186 patients in the Val/Aml group).

A total of 314/473 patients, 66.4% (of the patients included in the office part of the study) participated in the HBPM part of the study (154 patients in the Ind/Aml group and 160 patients in the Val/Aml group).

BASELINE CHARACTERISTICS

In the Randomised Set, patients were in average 57.3 ± 11.3 years old, with no relevant between-group difference. Most of them (75.1%) were between 18 and 64 years old, with a higher proportion in the Ind/Aml group than in the Val/Aml group: 76.8% *versus* 73.3%, respectively. About half of the patients were men (51.0%). BMI was on average 26.8 ± 2.5 kg/m², and 8 patients, 1.7% had a BMI ≥ 30 kg/m² (of whom 2 patients were considered as having protocol deviations at inclusion).

All patients presented at selection an essential hypertension in average since 67.6 ± 89.7 months. Most of the patients (70.6%) received at least one treatment for essential hypertension before entry in the study, mainly Agents acting on the renin-angiotensin system (52.7% *versus* 47.0%, respectively). Almost all of the patients (96.4%) were on monotherapy. No relevant between-group difference was observed.

Most of the patients (79.1%) reported additional medical history, mainly related to Metabolism and nutrition disorders (44.3% in the Ind/Aml group and 47.9% in the Val/Aml group), including mainly hypercholesterolaemia (24.5% *versus* 25.4%, respectively). Regarding risk factors, 14.0% had smoking habit, and 25.4% had alcohol habit consumption, with no relevant between-group difference.

In the Randomised Set, at baseline, the office supine SBP and DBP were in average: 159.82 ± 6.86 mmHg and 91.55 ± 9.83 mmHg, PP: 68.27 ± 10.91 mmHg, and MBP: 114.31 ± 7.33 mmHg, with no relevant between group-difference. Office standing SBP and DBP at 3 min were similar in both treatment groups at inclusion (157.6 ± 10.2 mmHg and 93.3 ± 10.6 mmHg, for standing SBP and DBP at 3 min, respectively).

All patients had at baseline an uncontrolled hypertension regarding office BP values (in the FAS), whereas 79.1% of the ABPM patients were uncontrolled at baseline regarding the ABPM BP values (in the FAS-ABPM), confirming their sustained hypertension at baseline.

SUMMARY – CONCLUSIONS (Cont'd)

Demographic and other baseline characteristics were in the same line in the other Sets and ISH (N = 189 patients in the Randomised Set) and SDH (N = 281 patients in the Randomised Set) subgroups, as well as in the ABPM and HBPM parts of the study.

EXTENT OF EXPOSURE

The global compliance was in average 98.8 ± 4.1%, with similar results in both treatment groups, in the FAS. All patients but one had an overall compliance between 70% and 130% (inclusive). No relevant between-group difference was observed.

In the FAS, regarding the treatment dose received:

- 42.6% of the patients received the dose 1 during the overall W0-W12 period.
- 54.2% of the patients received the dose 1 over W0-W6 and were up-titrated at W6 to the dose 2, with a lower frequency reported in the Ind/Aml group than in the Val/Aml group: 49.8% *versus* 58.6%, respectively.
- 3.2% received the dose 1 over W0-W6 and withdrew before the W6-W12 period.

EFFICACY RESULTS

Primary efficacy endpoint: office supine systolic blood pressure

Main analysis: change from baseline to last post-baseline value at W12

Over the W0-W12 period, the office supine SBP markedly decreased from baseline to the last post-baseline value in both treatment groups by -20.84 ± 14.85 mmHg in the Ind/Aml group *versus* -19.72 ± 16.13 mmHg in the Val/Aml group, in the FAS. The between-group difference was in favour of the Ind/Aml group but was not statistically significant. Sensitivity analyses showed same trends.

Office supine SBP (mmHg) - Change from baseline to last post-baseline value - Comparison between groups - Over W0-W12 period - FAS (N = 465)

Office supine SBP (mmHg)		**Ind/Aml (N = 233)**	**Val/Aml (N = 232)**
	n	233	232
Baseline	Mean ± SD	160.00 ± 6.60	159.77 ± 7.03
	95% CI	[159.15 ; 160.85]	[158.86 ; 160.68]
	Min ; Max	147.5 ; 179.0	133.5 ; 176.0
END W12	Mean ± SD	139.16 ± 13.57	140.05 ± 15.50
	95% CI	[137.41 ; 140.91]	[138.05 ; 142.06]
	Min ; Max	109.5 ; 185.5	101.0 ; 183.5
END W12 - Baseline	Mean ± SD	-20.84 ± 14.85	-19.72 ± 16.13
	95% CI	[-22.76 ; -18.92]	[-21.81 ; -17.64]
	Min ; Max	-62.5 ; 31.5	-62.5 ; 25.5
Statistical analysis			
	E (SE) (1)	-1.06 (1.33)	
	95% CI (2)	[-3.67 ; 1.56]	
	p (3)	0.428	

N: total number of patients in each treatment group; n: number of patients affected; (1) Estimate (Standard Error) of the difference in adjusted mean changes from baseline to last post-baseline value until W12 indapamide/amlodipine – valsartan/amlodipine using a General Linear Model with treatment, baseline and country as covariates; (2) 95% Confidence Interval of the estimate; (3) p value associated with General Linear Model

SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)
Unplanned analyses

- Office SBP: non-inferiority analysis

The non-inferiority of the Ind/Aml *versus* Val/Aml strategy (using a margins of 3 mmHg) was statistically significant (p = 0.001, in the FAS). The result obtained in the PPS was similar (p < 0.001).

- Office SBP in patients confirmed as uncontrolled at baseline, regarding ambulatory SBP and DBP values of the ABPM part of the study: superiority analysis.

Among the patients who performed the ABPM part of the study, 20.9% (57/273 patients) were already controlled at baseline in the FAS-ABPM. In the remaining uncontrolled ABPM patients having a sustained hypertension (216/273 patients, 79.1%), the office SBP decreased by -22.51 ± 13.95 mmHg in the Ind/Aml group *versus* -18.33 ± 17.03 mmHg in the Val/Aml group, in the FAS. The between-group difference was statistically significant and showed the superiority of the Ind/Aml group *versus* Val/Aml group (E (SE) = -4.67 (1.92) mmHg, 95% CI = [-8.44 ; -0.89], p = 0.016, in the FAS).

Secondary analyses
Over the W0-W6 period, a large decrease in the office supine SBP was also obtained in favour of the Ind/Aml group, with no statistically significant between-group difference: -17.26 ± 15.49 mmHg *versus* -16.10 ± 15.44 mmHg (E (SE) = -1.07 (1.35) mmHg, 95% CI = [-3.72 ; 1.59], p = 0.4, in the FAS). The within-group analysis showed a statistically significant decrease in the office SBP in each treatment group, over the W0-W6, W6-W12, and W0-W12 periods (p < 0.001, in the FAS).

In patients not controlled at W6, and uptitrated to the highest dose, a statistically significant decrease was observed in the office SBP, over W6-W12, with a greater decrease over time with the Ind/Aml strategy than with the Val/Aml group strategy: -11.52 ± 13.17 mmHg (p < 0.001) *versus* -7.20 ± 13.11 mmHg (p < 0.001), respectively, in the FAS.

Sensitivity analyses showed same trends.

Secondary efficacy endpoints
Secondary efficacy endpoints yielded similar trends in the FAS.

- The **office DBP** decreased from baseline to the last post-baseline value at W6 and W12. As expected, a marked decrease was observed in SDH patients. No statistically significant between-group difference was detected neither other W0-W6 nor over W0-W12:
  - Over W0-W12:
    - FAS SDH: -12.19 ± 8.84 mmHg in the Ind/Aml group *versus* -12.65 ± 9.50 mmHg in the Val/Aml group (E (SE) = 0.57 (1.04) mmHg, 95% CI = [-1.48 ; 2.61], p = 0.6).
    - FAS ISH: -2.41 ± 8.81 mmHg in the Ind/Aml group *versus* -1.54 ± 10.16 mmHg in the Val/Aml group (E (SE) = -0.38 (1.33) mmHg, 95% CI = [-2.99 ; 2.24], p = 0.8).
  - Over W0-W6:
    - FAS SDH: -10.38 ± 10.08 mmHg in the Ind/Aml group *versus* -11.03 ± 10.18 mmHg in the Val/Aml group (E (SE) = 0.82 (1.15) mmHg, 95% CI = [-1.45 ; 3.09], p = 0.5).
    - FAS ISH: -0.70 ± 10.58 mmHg in the Ind/Aml group *versus* -0.79 ± 9.38 mmHg in the Val/Aml group (E (SE) = 0.61 (1.33) mmHg, 95% CI = [-2.01 ; 3.23], p = 0.6).

The within-group analysis showed that the decrease in the office SBP was statistically significant in the:

- FAS SDH subgroup in each treatment group over W0-W6 and W0-W12 (p < 0.001).
- FAS ISH subgroup only in the Ind/Aml group over W0-W12 (p = 0.009).

In patients uptitrated to the highest dose, the mean office supine DBP decreased over W6-W12, and was statistically significant only in the FAS SDH subgroup: -5.49 ± 10.04 mmHg in the Ind/Aml group and -3.46 ± 8.76 mmHg in the Val/Aml group (p < 0.001 in each treatment group).

Unplanned analysis
The non-inferiority of the Ind/Aml *versus* Val/Aml strategy (using a margins of 2 mmHg) was statistically significant, with a mean change in the office DBP (in ISH or SDH patients) over W0-W12 of -8.16 ± 10.04 mmHg in the Ind/Aml group *versus* -8.16 ± 11.18 mmHg (E (SE) = 0.21 (0.81) mmHg, 95% CI = [-1.39 ; 1.81], p = 0.014, in the FAS). The result obtained in the PPS was similar (p = 0.004).

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

The **other main secondary efficacy criteria** showed also a decrease over W0-W12 in both treatment groups, with no statistically significant between-group difference detected in the FAS:

- ***Office standing SBP at 3 min***: -18.2 ± 16.8 mmHg in the Ind/Aml group *versus* -17.6 ± 17.7 mmHg in the Val/Aml group (p = 0.5).
- ***Office standing DBP at 3 min***, with a marked decrease observed only in SDH patients:
  - FAS SDH: -10.9 ± 10.9 mmHg in the Ind/Aml group *versus* -9.9 ± 11.3 mmHg in the Val/Aml group (p = 0.4).
  - FAS ISH: -3.0 ± 9.7 mmHg *versus* -3.1 ± 12.4 mmHg, respectively (p = 0.7).
- ***Office supine MBP***, with a greater decrease in SDH than ISH patients:
  - FAS SDH: -14.95 ± 9.85 mmHg in the Ind/Aml group *versus* -15.31 ± 10.58 mmHg in the Val/Aml group (p = 0.8).
  - FAS ISH: -8.73 ± 9.16 mmHg *versus* -7.34 ± 10.40 mmHg, respectively (p = 0.6).
- ***Office supine PP***, with a greater decrease in ISH than SDH patients:
  - FAS SDH: -8.28 ± 11.25 mmHg in the Ind/Aml group *versus* -7.96 ± 11.12 mmHg in the Val/Aml group (p = 0.5).
  - FAS ISH: -18.94 ± 13.79 mmHg *versus* -17.40 ± 15.92 mmHg, respectively (p = 0.4).
- The ***blood pressure control*** (defined by the percentage of patients with SBP < 140 mmHg and DBP < 90 mmHg) was reached by about half of the patients of the patients at W12: 49.8% in the Ind/Aml group *versus* 50.9% in the Val/Aml group. No statistically significant between-group difference was reached (p = 0.8).
- In the same way, most of the patients ***responded to treatment*** (defined by the percentage of patients with SBP < 140 mmHg and DBP < 90 mmHg, or SBP decrease ≥ 20 mmHg from baseline, or DBP decrease ≥ 10 mmHg from baseline): 70.4% *versus* 67.7%, respectively. There was no statistically significant between-group difference (p = 0.5).

Results obtained from the ABPM and the HBPM parts of the study were consistent with those obtained from the office BP measurements.

ABPM part of the study

A decrease in the mean **ASBP** and **DBP** over 24 h was observed in each treatment group, fom baseline to the last post-baseline value at W12 in the FAS-ABPM. No statistically significant between-group difference was evidenced.

- ASBP: -6.98 ± 11.38 mmHg in the Ind/Aml group *versus* -7.20 ± 12.92 mmHg in the Val/Aml group (p = 0.8).
- ADBP: -4.71 ± 8.06 mmHg *versus* -5.61 ± 9.09 mmHg (p = 0.4) in the FAS-ABPM SDH subgroup, and -4.15 ± 8.01 mmHg *versus* -1.94 ± 7.56 mmHg (p = 0.08) in the FAS-ABPM ISH subgroup.

For both ASBP and ADBP (for SDH subgroup), the within-group analysis showed that the decreases were statistically significant in each treatment group over W0-W12 (ASBP: p < 0.0001 in each treatment group; ADBP (SDH): p < 0.001 in each treatment group).

The **ABP control** (defined as the percentage of patients with mean 24h SBP < 130 mmHg and mean 24h DBP < 80 mmHg) was reached by 39.9% of the patients in the Ind/ Aml group *versus* 45.0% in the Val/Aml group, at the last post-baseline value at W12. No statistically significant between-group difference was detected (p = 0.4), in the FAS-ABPM.

Results of the other efficacy criteria were in line with those described above.

HBPM part of the study

The HBPM is a self-evaluation by the patient for which the results should be interpretated with caution.

A decrease in the **HSBP**, the **HDBP** and the **home HR** were observed from baseline to the last-post-baseline value at W12, over the 3 days preceding the visit. No statistically significant between-group difference was observed.

- **HSBP**: -8.99 ± 10.40 mmHg in the Ind/Aml group *versus* -8.35 ± 13.99 mmHg in the Val/Aml group, in the FAS-HBPM (p = 0.2).
- **HDBP**: -4.96 ± 8.81 mmHg in the Ind/Aml group *versus* -5.15 ± 9.01 mmHg in the Val/Aml group in the FAS-HBPM SDH subgroup (p = 0.7), and -5.85 ± 7.63 mmHg *versus* -6.98 ± 9.40 mmHg, respectively, in the FAS-HBPM ISH subgroup (p = 0.8).

SUMMARY - CONCLUSIONS (cont'd)

EFFICACY RESULTS (Cont'd)

- **Home HR**: -0.51 ± 7.36 bpm in the Ind/Aml group and -1.14 ± 7.11 bpm in the Val/Aml group (p = 0.4).

The **home blood pressure control** was reached at the last post-baseline value at W12 by 29.5% of the patients in the Ind/Aml group and 30.3% of the patients in the Val/Aml group in the FAS-HBPM. There was no statistically significant between-group difference (p = 0.9).
Results of the other efficacy criteria were in line with those described above.

SAFETY RESULTS

- **Emergent adverse events**

Overall summary for adverse events over the overall study in the Safety Set

		Ind/Aml (N = 236)	Val/Aml (N = 236)
Patients having reported at least one:			
Emergent adverse event	n (%)	47 (19.9)	28 (11.9)
Treatment-related emergent adverse event	n (%)	17 (7.2)	2 (0.8)
Emergent hypotension	n (%)	1 (0.4)	-
Emergent orthostatic hypotension	n (%)	1 (0.4)	-
Serious emergent adverse event	n (%)	2 (0.8)	2 (0.8)
Treatment-related serious adverse event	n (%)	1 (0.4)	-
Patients with treatment withdrawal due to			
Emergent adverse event	n (%)	3 (1.3)	-
Emergent serious adverse event	n (%)	-	-
Treatment-related emergent adverse event	n (%)	2 (0.8)	-
Treatment-related emergent serious adverse event	n (%)	-	-
Patients who died	n (%)	-	-

N: Number of patients by group
n: number of affected patients
*%: (n*100/N)*

Emergent adverse events (considering all treatment doses received during the study) were reported with a higher frequency in the Ind/Aml group than in the Val/Aml group: 19.9% *versus* 11.9%, respectively, in the Safety Set. The SOCs most frequently affected in both treatment groups, with a higher frequency reported in the Ind/Aml group than in the Val/Aml group was Metabolism and nutrition disorders (7.6% *versus* 3.0%, respectively). This difference was mainly due to hypokalaemia (5.5% *versus* 0.8%, respectively), expected with thiazidic diuretics and in accordance with the indapamide Summary of Product Characteristic (SmPC). The other EAE frequently reported in the Ind/Aml group (in more than 2%) was dizziness (2.1% *versus* none, respectively). In the Val/Aml group, hypercholesterolaemia was the only preferred term reported in more than 2 patients (4 patients, 1.7% in the Ind/Aml group *versus* 3 patients, 1.3% in the Val/Aml group).
No relevant between-group difference was observed for the other SOCs except for Nervous system disorders reported in 2.5% *versus* none, respectively, mainly dizziness.

Emergent hypotension was uncommon in this study. One emergent orthostatic hypotension was reported as AE in the Ind/Aml group, whereas the investigator specified that it was asymptomatic. The AE was not serious, not considered as treatment-related, and resolved spontaneously. Emergent calculated orthostatic hypotension (defined according to a mathematic rule) was detected in 3 patients in each treatment group over the W0-W12 period.

The EAEs reported in the Ind/Aml group over the overall study period were in line with events reported in the SmPC for indapamide and amlodipine: hypokalaemia are listed as very common (≥ 10%) with indapamide, and hypotension as uncommon (≥ 0.1% and < 1%), dizziness and oedema as common (≥ 1% and < 10%, each one) with amlodipine.

Most of the EAEs were rated mild (74.8%) and none was severe.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Treatment-related EAEs were reported with a higher frequency in the Ind/Aml group than in the Val/Aml group: 7.2% *versus* 0.8%, respectively, mainly due to hypokalaemia (4.7% *versus* 0.4%, respectively). Other treatment-related EAEs reported in more than one patient in any treatment group were hyperuricaemia (3 patients, 1.3% *versus* none, respectively), oedema peripheral (3 patients, 1.3% *versus* 1 patient, 0.4%, respectively), and dizziness (2 patients, 0.8% *versus* none, respectively).

Few EAEs, non-serious, led to patient's treatment withdrawal: 3 patients in the Ind/Aml group (dizziness, asthenia, hypokalaemia, while the patient received the dose 1). All these AEs were emergent, not serious, and 2 of them were considered as treatment-related (hypokalaemia, asthenia).

During the overall study period, most EAEs recovered or were recovering in both treatment groups: 76.3% *versus* 81.4% of the total of the EAEs, respectively.

Over the overall study period, 2 patients in each treatment group, both on dose 1, reported in total 4 serious EAEs (including the Sponsor's upgrade): renal cancer and hypokalaemia in the Ind/Aml group, and colon adenoma and myocardial ischaemia in the Val/Aml group. One event (hypokalaemia, for which the seriousness was upgraded by the sponsor, and recovered) was considered as treatment-related, and none of the serious EAEs led to study drug withdrawal.
None of the patients died during the study.

Regarding the analysis of the EAEs in patients that received dose 1 and those that received dose 2, similar safety profiles were obtained.

Laboratory tests

Neither clinically relevant change over time nor relevant between-group difference was observed for biochemistry and haematological parameters, in the Safety Set. Emergent potentially clinically significant abnormal (PCSAs) values for biochemical values were reported in less than 5% of the patients in any treatment group and for each parameter, except for triglycerides (high values) reported with a lower frequency in the Ind/Aml group than in the Val/Aml group: 3.7% *versus* 7.4%, respectively.
For haematology, PCSAs values affected less than 2% of the patients in any treatment group. Most frequent PCSAs were observed for hematocrit (low value) in 0.9% *versus* 1.8%, respectively.

Vital signs

Neither relevant change over time neither between-group difference was observed was observed for the heart rate, and the weight.

ECG

Among patients that performed an ECG, significant ECG abnormality was detected at W12 in one patient, 0.5% in the Ind/Aml group *versus* 2 patients, 0.9% in the Val/Aml group.

CONCLUSION

This international double-blind Phase III study, conducted in 473 patients, aimed to demonstrate a better efficacy of indapamide/amlodipine strategy *versus* valsartan/amlodipine strategy in lowering the office systolic blood pressure, in patients with essential hypertension (combined systolic and diastolic hypertension or isolated systolic hypertension) not controlled on amlodipine monotherapy.

Over 12-week of treatment, a large decrease in the office supine SBP was observed with both treatment strategies (-20.84 ± 14.85 mmHg *versus* -19.72 ± 16.13 mmHg), with no statistically significant between-group difference evidenced.
However, an unplanned analysis showed the statistically significant non-inferiority of the indapamide/amlodipine strategy *versus* valsartan/amlodipine strategy in lowering the office systolic blood pressure (using a margins of 3 mmHg) over 12-week of treatment.
In patients confirmed with an uncontrolled hypertension at both office and ambulatory blood pressure monitoring (sustained hypertension), the statistically significant superiority of the indapamide/amlodipine strategy was demonstrated over 12-week of treatment (unplanned analysis).

An important decrease in the office supine SBP was already obtained after 6 weeks of treatment, similar with each treatment strategy.

At the end of the study, half of the patients in both treatment groups had an office supine BP controlled (49.8% *versus* 50.9%, respectively), and most of the patients had a positive response to treatment for antihypertensive therapy (70.4% *versus* 67.7%, respectively). No statistically significant between-group difference was observed. The titration, performed in patients not controlled at W6, allowed an expected decrease on the office supine SBP and DBP.
Secondary efficacy criteria including the ABPM and HBPM parts of the study yeldied similar trends.

No safety concern was raised and the safety profile was in accordance with the known Summary of the Product Characteristic of each treatment.

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