## 2.  SYNOPSIS

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| **Name of Sponsor:**<br>**Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**22, route 128 – 91190 Gif-sur-Yvette – France** | *(For National Authority Use only)* |

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|---|
| **Name of Finished Product:** Not applicable<br>**Names of Active Ingredients:**<br>Perindopril/indapamide/amlodipine/bisoprolol (S05179) |

**Title of study:** Evaluation of the clinical efficacy and safety of perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 or 10 mg/bisoprolol 5 mg in single-pill combination after 8 weeks of treatment *versus* the free combination of perindopril 10 mg, indapamide 2.5 mg and amlodipine 5 or 10 mg in patients with uncontrolled essential hypertension. An international, multicentre, randomised, double-blind, 16-week study.

Protocol No.: CL3-05179-002
EudraCT No.: 2020-004891-16

**International coordinator:**
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**Number of countries and patients:**
In all, 13 countries included a total of 183 patients:
56 patients in Armenia, 30 patients in Russian Federation, 27 patients in Argentina, 14 patients in Poland, 10 patients in Latvia, 8 patients in Brazil, 8 patients in Czech Republic, 8 patients in Italy, 7 patients in Kazakhstan, 5 patients in Bulgaria, 5 patients in Hungary, 4 patients in Lithuania, 1 patient in Slovakia.

No patients were included in the following countries where investigator sites were opened: Croatia, Portugal, Romania and Ukraine. In Portugal and Romania, patients were selected but not included.

**Study period:**
Initiation date: 12 February 2022
Completion date: 14 December 2023

**Phase of development of the study:**
Phase III

**Publication (reference):**
Not applicable.

**Background and rationale for the study:**
The Global Burden of Disease Study organised by the World Health Organization has since 2003 considered hypertension (HT) as the most important global risk factor for morbidity and mortality. Individuals having a blood pressure (BP) above the recommended target of Systolic Blood Pressure (SBP) ≥ 140 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 90 mm Hg are at high risk of HT-Mediated Organ Damage (HMOD), Chronic Kidney Disease (CKD), premature cardiovascular events and cardiovascular diseases. Approximately 10% of treated hypertensive patients have what may be described as Resistant Hypertension (RH).
RH is defined (by European Society of Cardiology/European Society of Hypertension [ESC/ESH] guidelines), as BP that remains uncontrolled despite adherence to 3 or more different antihypertensive drug classes at maximally tolerated doses, with one being a diuretic. To improve adherence and BP control, a major emphasis of the guidelines is also to simplify the treatment regimen by prescribing single-pill therapy.

S05179 is a Single-Pill Combination (SPC) of 4 active substances which are well established antihypertensive agents belonging to 4 different and complementary pharmacological classes, respectively:
- An angiotensin-converting enzyme (ACE) inhibitor.
- A thiazide-like diuretic.
- A long-acting calcium antagonist of the dihydropyridine family (CCB).
- A cardio-selective beta-blocking agent.

The hypothesis was that S05179 SPC would provide superior BP control than a tritherapy free combination of Per, Ind and Aml in patients with sustained uncontrolled essential HT.

**Objectives, endpoints and estimands:**

| | Objectives | Endpoints* |
|---|---|---|
| **Primary objective** | To demonstrate the superiority of S05179 over Free [Per + Ind + Aml] (a tritherapy) on the lowering of office sitting SBP after 8 weeks of treatment (following a tritherapy run-in period). | Office sitting SBP *(expressed as the change from W000 to W008).* Evaluation of treatment effect independently of unauthorised concomitant treatments or treatment discontinuation for non-medical reasons since those patients would have theoretically continued to be treated as planned in clinical practice. |

**The attributes of the primary estimand** were defined as follows:
Treatment condition: S05179 or Free [Per + Ind + Aml].
Population: RS - Patients with HT who remain non-controlled despite 8 weeks run-in on Free [Per + Ind + Aml].
Variable: Change from baseline (W000) to W008 in office sitting SBP.
Summary measure: Difference in means between treatment groups.
Intercurrent events (ICE) strategy:
- ICE1 (discontinuation): Data post ICE1 were imputed using a return-to-baseline model.
- ICE2 (unauthorised treatments): Data post ICE2 were imputed using a multiple imputation model, under Missing At Random (MAR) assumption.

| | Objectives | Endpoints* |
|---|---|---|
| **Main secondary objective** | To demonstrate the superiority of S05179 over the tritherapy free combination [Per + Ind + Aml] on the lowering of ambulatory SBP over entire 24h-period after 8 weeks of treatment. | Mean ambulatory SBP over 24h (from 24h-ABPM) *(expressed as the change from W000 to W008)* Evaluation of treatment effect independently of unauthorised concomitant treatments or treatment discontinuations for non-medical reasons because those patients would have theoretically continued to be treated as planned in clinical practice. |

The attributes were the same as for the primary estimand, except for the endpoint (*i.e.* variable attribute).

| | Objectives | Endpoints* |
|---|---|---|
| **Supportive secondary objectives** | To demonstrate the superiority of S05179 over the tritherapy free combination [Per + Ind + Aml] on sitting office BP parameters: DBP, Mean Arterial Pressure (MAP), Pulse Pressure (PP) as well as on BP control, BP target and response to the antihypertensive therapy after 8 weeks of treatment. | Office sitting DBP *(expressed as the change from W000 to W008)* BP control[a], and Response to the antihypertensive therapy[b] *(expressed as proportion of patients at W008)* Note: the analysis of MAP, PP and BP target were omitted from the final statistical analysis plan (SAP) |

The attributes are the same as for the primary estimand except for the endpoint (*i.e.* variable attribute).

| | Objectives | Endpoints* |
|---|---|---|
| **Other secondary objectives** | To evaluate the efficacy of S05179 *versus* Free [Per + Ind + Aml] on 24h-ABPM parameters after 8 weeks of treatment (following a tritherapy run-in period). | Ambulatory SBP and DBP measurements, including: - Mean measurements over the following periods: 24h-period, real and standard daytime periods, real and standard night-time periods, over the last 6 hours before IMP intake. - Morning BP rise - Hourly means. Mean HR (24h-, daytime and night-time periods). Normalisation. *(described at W000 and W008)* |
| | To evaluate the efficacy of S05179 *versus* Free [Per + Ind + Aml] on HBPM parameters after 8 weeks of treatment (following a tritherapy run-in period). | Mean HSBP and HDBP (overall, morning and evening). Normalisation. *(described at W000, W004 and W008)* |
| **Safety objective** | Assessment of the safety of the S05179 SPC after 8 weeks of treatment | Clinical examination including vital signs, laboratory examinations, AEs, orthostatic hypotension test and 12-lead ECG |

*24h-ABPM 24-hour Ambulatory Blood Pressure Monitoring; BP Blood Pressure; DBP Diastolic Blood Pressure; HBPM Home Blood Pressure Monitoring; ECG electrocardiogram; HDBP Home Diastolic Blood Pressure; HSBP Home Systolic Blood Pressure; HR Heart Rate; ICE Intercurrent Event; IMP Investigational Medicinal Product; SBP Systolic Blood Pressure*
*(a) BP control office sitting SBP < 140 mm Hg and DBP < 90 mm Hg (mean of at least 2 measurements).*
*(b) Response to the antihypertensive therapy control of BP and/or SBP decrease from baseline ≥ 20 mm Hg and/or DBP decrease from baseline ≥ 10 mm Hg.*

*\* Note Since the recruitment to the study was stopped prematurely, some statistical analyses planned in the study protocol were not performed.*

**Study design:**

The present study was an international, phase III, randomised, double-blind study of S05179 SPC (quadritherapy, Per/Ind/Aml/Biso [10/2.5/5/5 or 10/2.5/10/5 mg]) *versus* a free combination of Per, Ind and Aml (10/2.5/5 or 10/2.5/10 mg, designated: Free [Per + Ind + Aml]) in patients with sustained uncontrolled BP despite treatment over an 8-week run-in on the same 3 components Per, Ind and Aml (10/2.5/5 or 10/2.5/10 mg).

The primary BP endpoint was assessed after 8 weeks of randomised double-blind treatment period. The treatment allocation was done by centralised randomisation using interactive web response system (IWRS) and stratified on the country and the Aml dose.
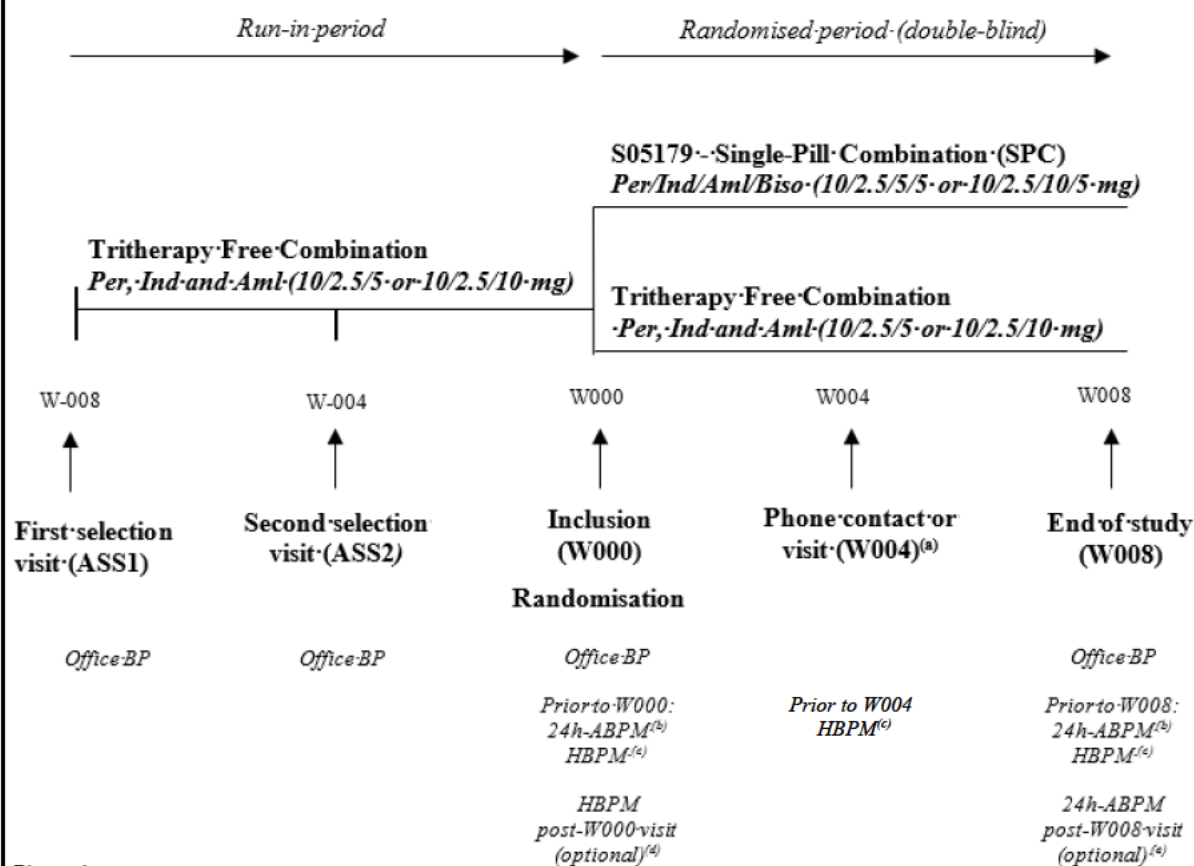


*Planned*
*N = 484 patients for S05179 group*
*N = 484 patients for Free [Per + Ind + Aml] group*

*24h-ABPM  24-hour Ambulatory Blood Pressure Monitoring; BP  Blood Pressure; HBPM  Home Blood Pressure Monitoring; HSBP  Home Systolic Blood Pressure; Wx  study visit (x [-008; 008] represents week number).*
*(a) A phone contact was scheduled to check HBPM results at W004. An additional W004 visit was scheduled if mean HSBP ≥ 160 mm Hg and/or HDBP ≥ 100 mm Hg and/or if the investigator considers this additional visit necessary for the safety of the patient.*
*(b) 24h-ABPM assessments were performed within the week prior to W000 and W008 (results to be available at W000 and W008 visits).*
*(c) HBPM assessments were performed within the week prior to W000, W004 and W008 visits (results to be available at W000, W004, W008 visits or phone contact).*
*(d) For an exploratory purpose, an additional HBPM assessment was started on the day after W000 visit (HBPM post-W000 visit).*
*(e) For an exploratory purpose, an additional 24h-ABPM assessment was started at W008 visit after clinic BP assessment and with 1-day intentional omission of any antihypertensive treatment on that day (24h-ABPM post-W008 visit).*

In July 2023, the sponsor decided to close patient selections before reaching the planned number of included patients (968 included patients, 484 in each arm). This decision was taken due to recruitment difficulties, but not for safety reasons.
This study was performed in strict accordance with Good Clinical Practice (GCP).

**Number of participants (Planned and Analysed):**
Planned: 968 included patients (484 in each group)
Included and analysed: 183 patients; 89 randomised to S05179 and 94 randomised to Free [Per + Ind + Aml].

**Diagnosis and main criteria for inclusion/exclusion:**
The participants were men and women of any ethnic origin, aged at least 18 years old, having a body mass index (BMI) not exceeding 35 kg/m² and having on the day of the selection visit (ASS1) an uncontrolled BP (office sitting SBP ≥ 140 mm Hg while being treated for essential HT with 3 antihypertensive drugs, including a diuretic, taken at the optimal tolerated doses for at least 1 month prior to the visit). Patients with very high cardiovascular risk were not accepted. To be included, after 8 weeks of run-in therapy, patients were again required to have office sitting SBP ≥ 140 and < 180 mm Hg and DBP < 110 mm Hg and mean 24h-period ambulatory SBP ≥ 130 mm Hg.

**Investigational Medicinal Product:**
Run-in:
During run-in, patients were to take orally each morning before breakfast 3 tablets:
- 1 tablet of perindopril 10 mg.
- 1 tablet of indapamide 2.5 mg.
- 1 tablet of amlodipine 5 or 10 mg (amlodipine dose defined at ASS1 visit).

Test drug (S05179):
Patients randomised on test drug arm were to take orally each morning before breakfast (except on the days of visits or on the days when the Ambulatory Blood Pressure Monitoring (ABPM) device was fitted): 2 capsules and 1 tablet, including:
- 1 capsule of S05179 SPC at one of the following strengths: Per/Ind/Aml/Biso 10/2.5/5/5 mg or 10/2.5/10/5 mg (amlodipine dose defined at ASS1 visit).
- 1 capsule of placebo (to maintain the blind with the tritherapy free combination group).
- 1 tablet of placebo (to maintain the blind with the tritherapy free combination group).

**Comparator:**
Patients randomised on comparator drug arm were to take orally each morning before breakfast 2 capsules and 1 tablet, including:
- 1 capsule of perindopril 10 mg.
- 1 tablet of indapamide 2.5 mg.
- 1 capsule of amlodipine 5 or 10 mg (amlodipine dose defined at ASS1 visit).

**Duration of treatment:**
Run-in period: 8 weeks
Randomised treatment period: 8 weeks

**Criteria for evaluation:**
Efficacy measurements
*Primary efficacy endpoint*:
Office BP was measured at all visits (except at visit W004 when performed by phone call). All office BP measurements were performed at 'trough' (*i.e.* 24 hours ± 3 hours after the last intake of the study medication) in the morning, between 6 a.m. and 11.00 a.m.
Office BP was measured by the investigator using a validated automatic device. The measurements were made in the sitting position. For each office sitting assessment, a set of 3 BP measurements was performed, respecting a 1-3 min interval between each measurement.

*Secondary efficacy endpoint*:
A 24h-ABPM assessment was performed within the week prior to W000 and W008 visits for all patients. An optional, exploratory, 24h-ABPM post-W008 visit was also performed in patients who agreed to participate.
Validated ABPM devices were used. Patients were provided with a paper diary and were requested to record information on time for getting up, taking study treatment, going to bed. For the statistical analyses, real daytime and night-time periods are based on the information reported by the patient in the diary.

*Other efficacy measurements:*
HBPM measurements were performed on 4 consecutive days within the week prior to W000, W004 and W008 visits for all patients.
Patients were provided with a validated electronic BP measuring device for self-measurement of BP and a paper diary. They were trained by the investigator to use the device and fill-in the diary.

Safety Measurements
Safety measurements included clinical examination, adverse events (AE), orthostatic hypotension, heart rate (HR), laboratory examinations (haematology, blood biochemistry, blood and urine pregnancy tests), and 12-lead electrocardiogram (ECG).

**Statistical methodology:**
*Analysis Sets:*
**Randomised Set (RS):**
All included patients to whom a therapeutic unit was randomly assigned using the IWRS.

**Full Analysis Set (FAS):**
All patients of the RS having taken at least one dose of Investigational Medicinal Product (IMP) and having a value at baseline and at least one analysable post-baseline value for the sitting SBP.

**Safety Set (SS):**
All patients having taken at least one dose of IMP (treatment actually received).

**Safety Set Run-In (SSR):**
All patients having taken at least one dose of run-in IMP.

*Optional set:*
**24h-ABPM voluntary set (24h-ABPM VS):** All patients of the RS who took at least one dose of IMP and who had a valid 24h-ABPM (Ambulatory SBP and DBP respectively) measurement starting at W008 visit with 1-day intentional omission of any antihypertensive treatment on that day.

No subgroup analysis was planned for this study.

*Efficacy analysis:*
Refer to objectives and endpoints table above for details.

**Study participants:** disposition, baseline characteristics and treatments analysis: Descriptive statistics were provided.

*Safety analysis:*
Descriptive statistics of AEs, clinical laboratory evaluation, vital signs and clinical examination were provided.

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**Summary of Results and Conclusions:**
Disposition of patients and analysis sets:

A total of 798 patients were screened for the study, 469 were selected and 183 were randomised.

The disposition of patients is indicated in Table 1.

**Table 1 - Disposition of patients and composition of analysis sets**

|  |  | S05179 | Free [Per + Ind + Aml] | All |
|---|---|---|---|---|
| **Included (Randomised)** | **N** | **89** | **94** | **183** |
| **Withdrawn due to** | **n (%)** |  |  |  |
| Protocol violation | n (%) | - | 1 (1.1) | 1 (0.5) |
| **Completed** | n (%) | 89 (100) | 93 (98.9) | 182 (99.5) |
| **Full Analysis Set** | **n** | 89 (100) | 92 (97.9) | 181 (98.9) |
| **Safety Set*** | **n** | **88** | **95** | **183** |

*N Total patients of included (randomised); %  n/N x 100*
*\* One patient who was randomised to S05179 was erroneously dispensed the Free [Per + Ind + Aml] treatment*

Baseline characteristics:
The demographic and other baseline characteristics of the randomised patients were in line with the selection/inclusion criteria of the study protocol. The global mean office sitting SBP and DBP values were 150.35 ± 8.49 mm Hg and 90.09 ± 8.23 mm Hg, respectively, with no relevant difference between treatment groups. The global mean ambulatory SBP and DBP values over 24 hours were 139.87 ± 8.69 mm Hg and 86.15 ± 8.07 mm Hg, respectively, with no relevant difference between groups.

Extent of exposure:
The treatment duration over the W000-W008 period was on average 58.16 days (median: 57 days). No relevant difference between groups in the RS was observed.
The global compliance, estimated by tablet count, was on average 99.21 ± 3.38%. All participants (100%) had a compliance between 70% and 130%. The compliance was similar in both groups. Similar data were observed in the SS.

**Efficacy results:**

Primary efficacy endpoint: office sitting SBP

In the RS, 163 patients were considered as being non-controlled at baseline despite 8 weeks on the tritherapy run-in IMP (80 in the S05179 group *versus* 83 in the Free [Per + Ind + Aml] group). The primary efficacy analysis was performed in these patients.

A significantly superior decrease in mean office sitting SBP was observed in the S05179 group as compared to the triple therapy Free [Per + Ind + Aml] group after 8 weeks. The mean changes ± SD were -20.67 ± 15.37 mm Hg *versus* -11.32 ± 14.77 mm Hg, respectively. The adjusted estimate of the between-group difference in the change from baseline to W008 was -8.04 mm Hg, 95% CI = [-11.99; -4.09]; demonstrating statistically significant superiority in favour of the S05179 group.

**Table 2 - Office sitting SBP - Primary analysis - Patients with essential hypertension in the RS who remained non controlled at baseline (n = 163)**

|  |  | S05179 | Free [Per + Ind + Aml] |
|---|---|---|---|
|  | n | 80 | 83* |
| **Baseline** | Mean ± SD | 151.00 ± 8.59 | 150.24 ± 8.27 |
| **W008** | Mean ± SD | 130.33 ± 14.20 | 138.91 ± 13.03 |
| **Change (W008 – Baseline)** | Mean ± SD | -20.67 ± 15.37 | -11.32 ± 14.77 |
|  | E (SE) (1) | -8.04 (2.02) |  |
|  | 95% CI (2) | [-11.99; -4.09] |  |

*N  Number of patients in each group*
*\* At W008, there were 82 patients in the Free [Per + Ind + Aml] group due to an intercurrent event.*
*(1) Estimate (Standard Error) of the adjusted difference from baseline to W008 between treatment groups means  S05179 minus [Per + Ind +Aml] using a GLM with covariates of baseline, amlodipine dose and country.*
*(2) Two-sided 95% Confidence Interval of the estimate*

Secondary efficacy endpoints:

*Mean ambulatory SBP over the 24-h period (main secondary endpoint):* The decrease in mean ambulatory SBP over 24 hours, from baseline to W008, was greater in the S05179 group than in the Free [Per + Ind + Aml] group: -14.09 ± 12.64 mm Hg *versus* -6.97 ± 12.29 mm Hg, respectively.

The adjusted estimate of the between-group difference in the change was -7.53 mm Hg, 95% CI = [-10.95; -4.11]; demonstrating the statistically significant superiority of S05179 over Free [Per + Ind + Aml] group on ambulatory SBP reduction.

**Table 3 - Mean ambulatory SBP over the 24h-period - Main secondary efficacy endpoint - Patients with essential hypertension in the RS who remained non controlled at baseline (n = 163)**

|  |  | S05179 | Free [Per + Ind + Aml] |
|---|---|---|---|
|  | n | 80 | 83* |
| **Baseline** | Mean ± SD | 140.88 ± 8.56 | 141.18 ± 7.92 |
| **W008** | Mean ± SD | 126.55 ± 11.37 | 134.41 ± 10.17 |
| **Change (W008 – Baseline)** | Mean ± SD | -14.09 ± 12.64 | -6.97 ± 12.29 |
|  | E (SE) (1) | -7.53 (1.74) |  |
|  | 95% CI (2) | [-10.95; -4.11] |  |

*N  Number of patients in each group*
*\* At W008, there were 82 patients in the Free [Per + Ind + Aml] group due to an intercurrent event.*
*(1) Estimate (Standard Error) of the adjusted difference from baseline to W008 between treatment groups means  S05179 minus [Per + Ind +Aml] using a GLM with covariates of baseline, amlodipine dose and country.*
*(2) Two-sided 95% Confidence Interval of the estimate*

*Office sitting diastolic blood pressure:* A decrease in the office sitting DBP was observed in the S05179 group compared to the Free [Per + Ind + Aml] group with mean changes ± SD of -10.50 ± 10.17 mm Hg *versus* -5.31 ± 10.31 mm Hg, respectively. The estimated of the adjusted between-group difference in the change (from baseline to W008) was -6.14 mm Hg, 95% CI = [-9.00; -3.27]; demonstrating the statistically significant superiority of S05179 over [Per + Ind + Aml] tritheraphy.

*Office sitting blood pressure control:* The proportion of patients with BP controlled at W008 was significantly greater in the S05179 group (66.3%) than in the Free [Per + Ind + Aml] group (42.7%) with an estimated odds ratio of 3.12; 95% CI = [1.51; 6.44]. The odds of achieving BP control were therefore 3 times higher in the S05179 group than in the Free [Per + Ind + Aml] group.

*Office sitting blood pressure response to the antihypertensive therapy:* The proportion of BP responders at W008 was significantly greater in the S05179 group (73.8%) than in the Free [Per + Ind + Aml] group (53.7%) with an estimate of the odds ratio of 2.78 (95% CI = [1.34; 5.74]).

*Office sitting DBP in the subset of patients with systolic-diastolic hypertension:* In the RS, there were 92 patients who were non-controlled at baseline and had systolic-diastolic hypertension (47 in the S05179 group *versus* 45 in the Free [Per + Ind + Aml] group). The decrease in office sitting DBP from baseline to W008 was greater in the S05179 group than in the Free [Per + Ind + Aml] group with a mean change ± SD of -14.14 ± 10.17 mm Hg *versus* -6.80 ± 10.87 mm Hg, respectively. The estimated between-group difference in the change was -8.95 mm Hg, 95% CI = [-12.62; -5.27], demonstrating statistical superiority of S05179.

*Office sitting BP control in the subset of patients with systolic-diastolic hypertension:* The results of this analysis of BP control at W008 evidenced an estimated odds ratio of 3.77 (95% CI = [1.34; 10.60]) demonstrating a statistical superiority of S05179.

*Office sitting BP response to the antihypertensive therapy in the subset of patients with systolic-diastolic hypertension:* The results of this analysis of BP response at W008 evidenced an estimated odds ratio of 3.78 (95% CI = [1.37; 10.48]) demonstrating a statistical superiority of S05179.

*ABPM - Mean SBP and DBP over 24 hours:* At baseline, the mean ambulatory SBP values were similar in both treatment groups (just under 140 mm Hg). At W008, the mean ambulatory SBP showed a marked decrease in the S05179 group (reaching a mean of 126.27 mm Hg) compared to the Free [Per+Ind+Aml] group (mean: 134.08 mm Hg). At baseline, the mean ambulatory DBP values were similar in both treatment groups (~86 mm Hg). At W008, the mean ambulatory DBP showed a marked decrease in the S05179 group (reaching a mean of 77.91 mm Hg) compared to the Free [Per+Ind+Aml] group (mean: 82.48 mm Hg).

*ABPM - Mean SBP and DBP over real daytime period:* At baseline, the mean ambulatory SBP values were similar in both treatment groups (~144 mm Hg). At W008, the mean ambulatory SBP showed a marked decrease in the S05179 group (reaching a mean of 128.38 mm Hg) compared to the Free [Per+Ind+Aml] group (mean: 137.75 mm Hg). At baseline, the mean ambulatory DBP values were similar in both treatment groups. The mean ambulatory DBP, at W008, was 80.22 mm Hg in the S05179 group *versus* 85.16 mm Hg in the Free [Per+Ind+Aml] group.

*ABPM - Mean SBP and DBP over real night-time period:* At baseline, the mean ambulatory SBP values were similar in both treatment groups (~130 mm Hg). At W008, the mean ambulatory SBP showed a marked decrease in the S05179 group (reaching a mean of 120.80 mm Hg) compared to the Free [Per+Ind+Aml] group (mean: 125.28 mm Hg). The mean ambulatory DBP, at W008, was 72.74 mm Hg in the S05179 group *versus* 75.39 mm Hg in the Free [Per+Ind+Aml] group.

*ABPM – Mean SBP and DBP over the last 6 hours before study drug intake:* At baseline, the mean ambulatory SBP values were similar in both treatment groups. At W008, the mean ambulatory SBP was lower in the S05179 group (125.62 mm Hg) compared to the Free [Per+Ind+Aml] group (131.12 mm Hg). The mean ambulatory DBP values, at W008, were 76.81 mm Hg in the S05179 group compared to 80.43 mm Hg in the Free [Per+Ind+Aml] group.

*ABPM - Mean SBP and DBP morning rise (morning BP – lowest BP):* The mean ambulatory SBP and DBP morning rise values at baseline were similar in both treatment groups. At W008, the mean ambulatory SBP morning rise was lower in the S05179 group (21.83 mm Hg) compared to the Free [Per+Ind+Aml] group (24.74 mm Hg). At W008, the mean ambulatory DBP morning rise was lower in the S05179 group (18.90 mm Hg) compared to the Free [Per+Ind+Aml] group (21.74 mm Hg).

*ABPM - SBP and DBP hourly means:* At baseline, SBP/DBP fluctuations over time had a similar pattern and levels in the S05179 group and in the Free [Per+Ind+Aml] group. At W008, SBP/DBP had a somewhat flattened diurnal pattern, in the S05179 group, with fluctuations that were lower than in the Free [Per+Ind+Aml] group.

*ABPM – Normalisation of BP:* At W008, the proportion of patients with controlled ambulatory BP was greater in the S05179 group (51.2%) compared to the Free [Per+Ind+Aml] group (20.7%). The odds ratio (post-hoc analysis) was: 4.12 (95% CI = [2.05; 8.27]).

*ABPM - Mean Heart Rate over 24 hours, daytime, and night-time periods:* The mean ambulatory HR values at baseline were similar in both treatment groups. The mean ambulatory HR at W008 was lower in the S05179 group (66.79 bpm) compared to the Free [Per+Ind+Aml] group (76.23 bpm), which was expected due to the HR lowering effect of bisoprolol. Expected similar results were observed during the daytime and night-time periods.

*HBPM – Mean SBP and DBP:* A total of 113 patients (55 *versus* 58) had validated home BP measurements at baseline. At baseline, the mean overall home SBP values were comparable in the 2 treatment groups (means: 141 vs 144 mm Hg). At W004, the mean ambulatory SBP showed a marked decrease in the S05179 group as compared to the Free [Per+Ind+Aml] group (reaching ~131 vs ~139 mm Hg). At W008 there was a further decrease in each group (reaching ~129 *versus* ~137 mm Hg). Similar results were observed for the mean overall home DBP values.

*HBPM – BP normalization:* At baseline, the proportion of patients with controlled home BP was similar in both treatment groups (14.5% in the S05179 group *versus* 12.1% in the Free [Per+Ind+Aml] group). At W008, the proportion of patients with controlled home BP was greater in the S05179 group (60.7%) compared to the Free [Per+Ind+Aml] group (25.4%). The odds ratio (post-hoc analysis) was: 4.99 (95% CI = [2.24; 11.13]).

**Safety results:**
The main safety analyses were carried out in the SS on data collected during W000-W008 period by treatment group. An analysis of the AEs occurring during the run-in period was performed in the SS Run-in.

Adverse events during the run-in period
During the run-in period in the SS Run-in, 63/466 patients (13.5%) reported at least one AE. Among them, 2 patients (0.4%) reported 2 serious adverse events (SAE): gastroenteritis and hand fracture. Both events were considered as not related to run-in IMP and resolved.

Treatment-emergent adverse events
The main results for TEAEs in the SS are described in the Table below.

**Table 4 – Summary of treatment-emergent adverse events – Safety Set (N = 183) – During the W000-W008 period**

| Type of Adverse Events | S05179 (N = 88) | | | Free [Per+Ind+Aml] (N = 95) | | |
|---|---|---|---|---|---|---|
| | NEAE | n | % | NEAE | n | % |
| TEAE | 12 | 10 | 11.4 | 10 | 8 | 8.4 |
| Treatment-related TEAE | 1 | 1 | 1.1 | 1 | 1 | 1.1 |
| TEAE leading to IMP withdrawal | - | - | - | 1 | 1 | 1.1 |

*NEAE Number of events; TEAE treatment-emergent adverse event*
*Percentages are based on N*

In both treatment groups, the most frequently reported SOCs were the following:
- Vascular disorders: 3 patients (3.4%) in the S05179 group and 1 patient (1.1%) in the Free [Per+Ind+Aml] group.
- Metabolism and nutrition disorders: 2 patients (2.3%) in the S05179 group and 2 patients (2.1%) in the Free [Per+Ind+Aml] group, respectively.
- Musculoskeletal and connective tissue disorders: 2 patients (2.3%) in the S05179 group.
- Investigations: 1 patient (1.1%) in the S05179 group and 2 patients (2.1%) the Free [Per+Ind+Aml] group, respectively.
- Infections and infestations: 2 patients (2.1%) in the Free [Per+Ind+Aml] group.

The percentage of patients with at least 1 treatment-emergent adverse event (TEAE) by preferred term (PT) was similar in both treatment groups: 10 patients (11.4%) in the S05179 group *versus* 8 patients (8.4%) in the Free [Per+Ind+Aml] group. The most frequent TEAEs in the S05179 group were orthostatic hypotension reported by 3 patients (3.4%) and hypercholesterolaemia reported by 2 patients (2.3%). All other events were reported by 1 patient (1.1%), each. The most frequent TEAEs in the Free [Per+Ind+Aml] group were upper respiratory tract infection reported by 2 patients (2.1%). All other events were reported by 1 patient (1.1%), each.

All but one TEAEs were rated mild in both treatment groups: 11 TEAEs (91.7%) in the S05179 group *versus* 10 TEAEs (100%) in Free [Per+Ind+Aml] group, respectively. One TEAE reported in the S05179 group was of moderate intensity; no TEAEs with severe intensity were reported.

Treatment-related TEAE were reported by 1 patient (1.1%) in each treatment groups: bradycardia in the S05179 group and palpitations in the Free [Per+Ind+Aml] group. None of these events were serious or severe.

The percentage of patients with TEAE requiring new treatment or modification of ongoing concomitant treatment during the W000-W008 treatment period was low and similar in both treatment groups; 2 patients (2.3%) in the S05179 group *versus* 4 patients (4.2%) in the Free [Per+Ind+Aml] group.

In the S05179 group, most of the TEAEs were reported as recovered (75%) or recovering (8.3%), while 2 TEAEs (16.7%) were reported as not recovered. Similarly, in the Free [Per+Ind+Aml] group, all TEAEs were reported as recovered (60%) or recovering (40%).

No deaths were reported during the study.

No serious TEAEs were reported during the W000-W008 treatment period.

One patient (1.1%) in the Free [Per+Ind+Aml] group experienced a TEAE leading to IMP withdrawal: acute sinusitis. This event was considered not related to IMP and resolved by the end of the study. No patient in the S05179 group experienced a TEAE leading to IMP withdrawal.

Laboratory tests
*Haematology*
No clinically meaningful trend was observed in any of the haematological results over time in either of the treatment groups.

*Biochemistry*
No clinically meaningful trends were observed in any biochemical parameter results over time in either of the treatment groups.

Other safety evaluations
*Vital signs and clinical evaluation*
Neither clinically relevant changes nor differences between groups in mean change to last post-baseline values were detected during the W000-W008 period, except for sitting HR. Office sitting HR decreased from baseline to W008 in the S05179 group (-9.45 ± 10.45 bpm), which was expected due to the heart rate lowering effect of bisoprolol and remained stable in the Free [Per+Ind+Aml] group (0.79 ± 9.10 bpm).

*Orthostatic hypotension*
Emergent orthostatic hypotension (calculated on office BP sitting and standing values) over the W000-W008 period was detected in 4 patients in the S05179 group and in 4 patients in the Free [Per+Ind+Aml] group.

**Conclusion:**
**This international, multicentre, randomised, double-blind phase III study showed that in patients with essential hypertension who remain non-controlled after 8 weeks of tritherapy, an 8-week treatment with S05179 (quadritherapy Single-Pill Combination of Perindopril/Indapamide/Amlodipine/Bisoprolol [Per/Ind/Aml/Biso]) resulted in a robust and significant decrease in BP as compared to continuing with the tritherapy (Free [Per+Ind+Aml]). The mean decrease (± SD) in the office sitting SBP (primary endpoint) was -20.67 ± 15.37 mm Hg in the S05179 group (n = 80) *versus* -11.32 ± 14.77 mm Hg in the Free [Per + Ind + Aml] group (n = 83). The adjusted estimate of the between-group difference was -8.04 mm Hg (95% Confidence Interval (CI): [-11.99; -4.09]); demonstrating the statistically significant superiority of S05179.**

**This result was confirmed by the analyses of ABPM, which showed statistically significant superior decreases in mean SBP over 24 hours at W008 of -14.09 ± 12.64 mm Hg in the S05179 group *versus* -6.97 ± 12.29 mm Hg in the Free [Per + Ind + Aml] group (main secondary endpoint). The estimate of the between-group difference was -7.53 mm Hg (95% CI = [-10.95; -4.11]).**

**Further analyses on office, ambulatory and home BP measurements (including DBP and BP normalisation) also confirmed the main efficacy results.**

**No safety concerns were raised during the study. The safety profile of S01579 was similar to that of the Free [Per + Ind + Aml] combination.**

**Date of the report: 10 October 2024**