## 2. SYNOPSIS

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|---|---|---|
| **Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France** | | *(For National Authority Use only)* |
| **Test drug**<br>**Name of Finished Product:**<br><br>**Name of Active Ingredient:**<br>Atorvastatin/perindopril arginine (S 05167) | | |
| **Individual Study Table Referring to Part of the Dossier** | **Volume:** | **Page:** |

**Title of study:** Efficacy and safety of Atorvastatin/Perindopril Fixed-Dose Combination S05167 in adult patients with arterial hypertension and dyslipidaemia, 8 weeks, phase 3, randomised, double-blind, active-control, multinational, multi-centre, parallel study.
Protocol No.: CL3-05167-005
EudraCT No.: 2019-003294-25, ClinicalTrials.gov Identifier: NCT04591808

**International coordinator:**
None assigned

**Study centres:**
35 centres located in 3 countries screened 334 patients and randomised 147 patients: 14 centres in Russia, 13 centres in Ukraine, and 8 centres in Georgia.
35 centres screened at least one patient.

**Publication (reference):**
Not applicable

| **Studied period:** | **Phase of development of the study:** |
|---|---|
| Initiation date: 10 September 2021 (date of first visit first patient)<br>Completion date: 08 April 2022 (date of early study termination) | phase III |

**Objectives:**
The primary objectives were:

- to demonstrate the superiority of atorvastatin/perindopril fixed-dose combination (FDC) S05167 as compared to atorvastatin reference drug alone on systolic blood pressure (SBP) decrease in patients presenting with hypertension and dyslipidaemia after 8 weeks of treatment; and
- to demonstrate the superiority of atorvastatin/perindopril FDC S05167 as compared to perindopril reference drug alone on low-density lipoprotein cholesterol (LDL-c) decrease, in patients presenting with hypertension and dyslipidaemia after 8 weeks of treatment.

The secondary objectives were:

- to evaluate the effect of atorvastatin/perindopril FDC S05167 on the other efficacy endpoints, clinical and biological in patients with hypertension and dyslipidaemia after 8 weeks of treatment.

**Methodology:**

This was a phase 3, randomised, double-blind, active-control, multinational, multi-centre, parallel study. Adult patients presenting with hypertension and dyslipidaemia were the target population for this study.
The expected duration of the study was 12 weeks, including a selection visit (ASSE) followed by 4 weeks placebo run-in period starting at selection, and an 8-week double-blind treatment period. The study started with a 4-weeks run-in period without antihypertensive and lipid-lowering drugs which was considered compatible with the level of risk of patients in terms of hypertension and dyslipidaemia. During this period, the patients were reminded or instructed to follow their healthy diet/lifestyle modifications as recommended by 2013 AHA-ACC Guideline on lifestyle management to reduce cardiovascular risk.
After the run-in period, at inclusion visit (W000) patients were randomised using a 2:2:1 ratio to either the fixed-dose atorvastatin/perindopril (40 mg/10 mg) or atorvastatin 40 mg alone or perindopril 10 mg alone once daily, each day before breakfast, for 8 weeks.
Also, two weeks after randomisation, there was a telephone call (W002) focused on patient's well-being and potential AE/SAE(s) assessment, treatment adherence, and concomitant medications. Patient was asked to come to the clinic for further investigation if the investigator considered necessary for patient's safety.
An additional visit at W004 (± 3 days) was planned for additional assessments, safety control and study drug dispensing. At W008 (± 3 days) visit, patients returned for a final assessment.

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

The study was early terminated by the sponsor. An abbreviated study report was written due to premature stopping the S05167 product development for the business reasons.

**Number of patients:**
Planned:
Total: screened – 910, randomised – 545.
By group: S05167 group: screened – 364 , randomised – 218; Lipitor® group: screened – 364, randomised – 218; Coversyl® group: screened – 182, randomised – 109.
Actual:
Total: screened – 334, randomised – 147.
By group: S05167 group: randomised – 59; Lipitor® group: randomised – 59; Coversyl® group: randomised – 29.
The number of patients actually included was much lower than planned due to the early termination of the study by the sponsor due to stopping the S05167 product development for business reasons.

**Diagnosis and main criteria for inclusion:**
Required diagnosis: hypertension and dyslipidaemia.

*Inclusion criteria:*

1. Blood pressure[1] 150 mmHg ≤ SBP <160 mmHg and 90 mmHg ≤ diastolic blood pressure (DBP) < 100 mmHg.
2. Confirmed dyslipidaemia on lipid profile dosage at Selection visit (ASSE): 110 mg /dL (or 2.84 mmol/L) LDL-c 190 mg/dL (or 4.91 mmol/L).
3. Treatment compliance ≥70% and ≤130% during the run-in period with placebo hard-gelatine capsule.
4. Respect of all selection and non-selection criteria.

**Test drug:**

S05167 (atorvastatin/perindopril arginine), capsules 40/10 mg

Manufacturer : Les Laboratoires Servier Industrie, Gidy, France
During treatment period patients were administered 1 over-encapsulated S05167 capsule once daily each day before breakfast.
Batch no.: L0071439 (hard capsules), L0072104 (over-encapsulated capsules)

**Comparator (Reference products, placebo):**

Placebo, capsules

Manufacturer : Les Laboratoires Servier Industrie, Gidy, France
During run-in period patients were administered 1 over-encapsulated placebo once daily each day before breakfast.
Batch no.: L0072043 (over-encapsulated capsules)

Lipitor® (atorvastatin), tablets 40 mg

Manufacturer: Pfizer Manufacturing Deutschland GmbH
During treatment period patients were administered 1 over-encapsulated atorvastatin tablet once daily each day before breakfast.
Batch no.: L0072157 (over-encapsulated tablets**)**, L0072158 (over-encapsulated tablets**)**

Coversyl® (perindopril arginine), tablets 10 mg

Manufacturer: Servier Ireland Industrie ltd, Arklow, Ireland
During treatment period patients were administered 1 over-encapsulated perindopril tablet once daily each day before breakfast.
Batch no.: L0072284 (over-encapsulated tablets)

**Duration of treatment:**
**Run-in period:** 4 weeks
**Treatment period:** 8 weeks

[1] Measured as per protocol standardised specific blood pressure measurement instructions.

**Endpoints:**

Primary efficacy endpoints:

- Mean change from baseline in sitting SBP in the S05167 group as compared with the Lipitor® group (in terms of superiority) [Time frame: W0; W008].
- Percent change from baseline in LDL-c in the S05167 group as compared with the Coversyl® group (in terms of superiority) [Time frame: W0; W008].

Secondary efficacy endpoints:

- Mean change from baseline in sitting SBP in the S05167 group as compared with Coversyl® group [Time frame: W0; W008].
- Percent change from in LDL-c level in the S05167 group as compared with the Lipitor® group; [Time frame: W0; W008].
- Mean change from baseline in diastolic blood pressure (DBP) and pulse pressure in each group.
- Percent change from baseline in other lipid parameters (total cholesterol, High-Density Lipoprotein cholesterol (HDL-c) level, triglycerides level and apolipoprotein B level) in each group.
- Percent of responders (in terms of blood pressure response defined by patients with BP< 140/90 mm Hg or SBP decrease ≥ 20 mm Hg or DBP decrease ≥10 mm Hg).
- Percent of blood pressure control: BP< 140/90 mm Hg AND percent of blood pressure control: BP < 130/80 mm Hg.
- Percent of responders (in terms of lipids control: an absolute reduction to LDL-c level< 2.6 mmol/L [100 mg/dL] or a reduction at least 50% (as defined in ESC/EAS 2019).

Safety endpoints:

- Treatment Emergent Adverse events (TEAEs) and Serious adverse events (SAEs) including clinically significant abnormalities observed from ECG recordings and from laboratory parameters (all visits).
- Vital signs by measuring blood pressure (BP), pulse rate (PR) and respiratory rate (RR) (all visits).
- ECG (all visits).
- Clinical laboratory tests, including haematology and serum biochemistry (all visits).

***Efficacy measurements:***

- Standardized assessment of blood pressure; determining a reference arm.
- Central assessment of laboratory parameters.

***Safety measurements:***

- Treatment Emergent adverse events (TEAE) and Serious adverse events (SAE).
- Vital signs: blood pressure (BP), pulse rate (PR) and respiratory rate (RR).
- 12-lead ECG;
- Clinical laboratory tests, including haematology and serum biochemistry

**Statistical methods:**

***Analysis Sets:***

*Randomised Set (RS)*

All patients to whom therapeutic unit was randomly assigned.

*Full Analysis Set (FAS)*

In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all patients of the RS who took at least one dose of IMP and had a value at baseline and at least one post-baseline value for the primary efficacy endpoint.

*Per Protocol Set (PPS)*

All patients of the FAS without relevant deviations, which could affect the evaluation of the IMP effect on the primary efficacy endpoint.

*Safety Set (SS)*

All patients who took at least one dose of IMP.

***Efficacy analysis:***

*Primary efficacy endpoint:*

Primary efficacy analysis was performed on the FAS and PPS populations. The primary analysis population was FAS, PPS – supportive sensitivity analysis.

In order to meet the primary objectives of the study, the superiority of atorvastatin/perindopril FDC S05167 as compared to:

- atorvastatin after 8-week treatment period was assessed in the FAS, on systolic blood pressure decrease expressed in term of mean change from baseline to W008.
- perindopril after 8-weeks treatment period was assessed in the FAS, on LDL cholesterol decrease expressed in term of relative change from baseline to W008.

*Secondary endpoints*:

For SBP, mean change from baseline to W008 was assessed compared to Coversyl® group.

For LDL-c-, relative change from baseline to W008 was assessed compared to Lipitor® group.

***Safety analysis:***

The safety endpoints were carried-out on patients of the safety population (Safety set).

Safety measurements were studied using descriptive statistics.

Descriptive statistics was provided for AEs, vital signs and clinical examination, as well as overall acceptability.

Safety population: the patients who had received at least 1 dose IMP were included in the Safety population. Patients were analysed as treated (in case of incorrect randomization).

An AE overview summary table was prepared including the number of patients reporting AE, the percentage of patients (%) with an AE, and the number of events reported.

Adverse events were tabulated and summarized by severity, as well as System Organ Class and Preferred Term using the Medical Dictionary for Regulatory activities (MedDRA version 25.1).

**SUMMARY - CONCLUSIONS**

DISPOSITION OF PATIENTS AND ANALYSIS SETS

The study was conducted in three countries at 35 sites: 334 patients were screened, 147 patients were randomised, 38 patients early discontinued the study, and 109 patients completed study per protocol.

| **Status** | **S05167** | **Lipitor®** | **Coversyl®** | **All** |
|---|---|---|---|---|
| **Screened** | | | | 334 |
| **Selection failure** | | | | 72 |
| **Inclusion failure** | | | | 115 |
| **Randomised Set (RS)** | 59 (100.0%) | 59 (100.0%) | 29 (100.0%) | 147 (100%)) |
| **Early discontinued due to:** | 15 (25.4%) | 18 (30.5%) | 5 (17.2%) | 38 (25.9%) |
| adverse event | 0 (0.0%) | 1 (1.7%) | 0 (0.0%) | 1 (0.7%) |
| withdrawal by patient | 0 (0.0%) | 4 (6.8%) | 0 (0.0%) | 4 (2.7%) |
| protocol deviation | 1 (1.7%) | 1 (1.7%) | 0 (0.0%) | 2 (1.4%) |
| study termination by sponsor | 13 (22.0%) | 12 (20.3%) | 4 (13.8%) | 29 (19.7%) |
| other | 1 (1.7%) | 0 (0.0%) | 1 (3.4%) | 2 (1.4%) |
| **Completed study per protocol** | 44 (74.6%) | 41 (69.5%) | 24 (82.8%) | 109 (74.1%) |
| **Safety Set (SS)** | 59 (100.0%) | 59 (100.0%) | 29 (100.0%) | 147 (100%) |
| **Full Analysis Set (FAS)** | 54 (91.5%) | 55 (93.2%) | 27 (93.1%) | 136 (92.5%) |
| **Per Protocol Set (PPS)** | 40 (67.8%) | 38 (64.4%) | 21 (72.4%) | 99 (67.3%) |

A total of 157 protocol deviations were registered in 107 patients. Out of 157 protocol deviations, 25 were major (in 22 patients), 74 were minor.

BASELINE CHARACTERISTICS

The mean (SD) age in RS population was 53.6 (10.56) years. The mean (SD) age was 52.7 (11.11) years in S05167 group, 53.5 (10.49) years in Lipitor® group and 55.6 (9.63) years in Coversyl® group.

There were 85/147 (57.8%) women and 62/147 (42.2%) men in RS population. S05167 group included 32/59 (54.2%) women and 27/59 (45.8%) men, Lipitor® group – 36/59 (61.0%) women and 23/59 (39.0%) men and Coversyl® group – 17/29 (58.6%) women and 12/29 (41.4%) men.

All 147/147 (100%) patients in RS population were white.

The mean (SD) BMI in RS population was 28.17 (2.836) kg/m$^2$, in S05167 group – 27.86 (2.939) kg/m$^2$, in Lipitor® group – 28.16 (2.875) kg/m$^2$and in Coversyl® group – 28.80 (2.509) kg/m$^2$.

EXTENT OF EXPOSURE

In the RS population, treatment duration (exposure to drug) ranged between 1 and 64 days with a mean (SD) of 50.9 (14.54) days in S05167 group, between 6 and 69 days with mean (SD) of 50.0 (13.57) days in the Lipitor® group, and between 4 and 65 days with a mean of 53.3 (12.48) days in Coversyl® group.

Treatment compliance

In the RS population, the treatment compliance during the whole study ranged between 83.0 and 100.0% with a mean (SD) compliance of 98.75 (3.20) % in S05167 group, between 76.5 and 102.0% with mean (SD) compliance of 97.75 (4.98) % in the Lipitor® group, and between 88.5 and 105.5% with a mean of 99.35 (2.64) % in Coversyl® group.

EFFICACY RESULTS

- Primary analysis

Primary efficacy endpoint no.1: Mean change from baseline in sitting SBP at W008 (S05167 group vs Lipitor group)

FAS was the primary population, PPS – was supportive population.

**Mean change from baseline in sitting SBP at W008 (S05167 group vs Lipitor® group). Primary efficacy analysis– FAS population**

| **Change from baseline at W008 [mmHg]** | **S05167 (N = 54)** | **Lipitor (N = 55)** |
|---|---|---|
| n | 49 | 52 |
| Mean (SD/SE) | -22.7 (12.85/1.84) | -11.6 (9.38/1.30) |
| Q1; Q3 | -32.0; -15.0 | -16.0; -4.5 |
| LS mean (SE) with two-sided 95% CI | -22.6 (1.55) [-25.70; -19.54] | -12.4 (1.52) [-15.38; -9.34] |
| **t-test (superiority)** | | 0.004 |
| μR-μT (SE) with one-sided 95% CI | | 11.1 (2.25) [7.36; ∞] |
| p-value ($H_0$: μR-μT ≤ 5; $H_1$: μR-μT > 5) | | 0.004 |
| **Model (superiority)** | | |
| μR-μT (SE) with one-sided 95% CI | | 10.3 (2.18) [6.65; ∞] |
| p-value ($H_0$: μR-μT ≤ 5; $H_1$: μR-μT > 5) | | 0.009 |

*N: Number of patients in each treatment group.*
*n: Number of observed values.*
LS mean: Least Square mean.
*SE: Standard error.*
*95% CI: 95% confidence interval of the estimated difference.*
*μT – LS mean in SBP for the S05167 group.*
*μR – LS mean in SBP for the Lipitor® group*

The difference in LS means ($\mu_R$-$\mu_T$) with one-sided 95% CI was 10.3±2.18 [6.65; ∞] mmHg, so the null hypothesis ($H_0$: $\mu_R$-$\mu_T \leq 5$ mmHg) *could be rejected*. P-value was 0.009, so this difference was *statistically significant.* Therefore, S05167 was more effective (superior) in decreasing SBP as compared to Lipitor® after 8-week treatment period.

**Mean change from baseline in sitting SBP at W008 (S05167 group vs Lipitor® group). Primary analysis– PPS population**

| **Change from baseline at W008 [mmHg]** | **S05167 (N = 40)** | **Lipitor® (N = 38)** |
|---|---|---|
| n | 40 | 38 |
| Mean (SD/SE) | -23.0 (12.89/2.04) | -12.1 (9.58/1.55) |
| Q1; Q3 | -32.0; -14.5 | -19.0; -5.0 |
| LS mean (SE) with two-sided 95% CI | -23.0 (1.74) [-26.50; -19.58] | -12.1 (1.78) [-15.62; -8.51] |
| **t-test (superiority)** | | |
| μR-μT (SE) with one-sided 95% CI | | 10.9 (2.56) [6.676; ∞] |
| p-value ($H_0$: μR-μT ≤ 5; $H_1$: μR-μT > 5) | | 0.012 |
| **Model (superiority)** | | |
| μR-μT (SE) with one-sided 95% CI | | 11.0 (2.49) [6.83; ∞] |
| p-value ($H_0$: μR-μT ≤ 5; $H_1$: μR-μT > 5) | | 0.009 |

*N: Number of patients in each treatment group; n: Number of observed values.*
LS mean: Least Square mean; *SE: Standard error.*
*95% CI: 95% confidence interval of the estimated difference.*
*μT – LS mean in SBP for the S05167 group.*
*μR – LS mean in SBP for the Lipitor® group*

The difference in LS means ($\mu_R$[2]-$\mu_T$[3]) with one-sided 95% CI was 11.0±2.49 [6.83; ∞] mmHg, so the null hypothesis ($H_0$: $\mu_R$-$\mu_T \leq 5$ mmHg) *could be rejected*. P-value was 0.009, so this difference was *statistically significant.* Therefore, S05167 was more effective (superior) in decreasing SBP as compared to Lipitor® after 8-week treatment period.
In both FAS and PPS populations results for this primary endpoint no. 1 were similar.
Primary efficacy endpoint no.2: Percent relative change from baseline in LDL-c level at W008 (S05167 group vs Coversyl® group)

**Percent change from baseline in LDL-c at W008 (S05167 group vs Coversyl® group). Primary efficacy analysis– FAS population**

| **Change from baseline at W008 [%]** | **S05167 (N = 54)** | **Coversyl® (N = 27)** |
|---|---|---|
| n | 43 | 23 |
| Mean (SD/SE) | -0.377 (0.2227/0.0340) | 0.057 (0.3093/0.0645) |
| Q1; Q3 | -0.534; -0.276 | -0.134; 0.190 |
| LS mean (SE) with two-sided 95% CI | -0.362 (0.0410)<br>[-0.4436; -0.2811] | 0.037 (0.0565)<br>[-0.0752; 0.1492] |
| **t-test (superiority)** | | |
| μR-μT (SE) with one-sided 95% CI | | 0.434 (0.0729) [0.3104; ∞] |
| p-value ($H_0$: μR-μT ≤ 0.3; $H_1$: μR-μT > 0.3) | | 0.038 |
| **Model (superiority)** | | |
| μR-μT (SE) with one-sided 95% CI | | 0.399 (0.0698) [0.2835; ∞] |
| p-value ($H_0$: μR-μT ≤ 0.3; $H_1$: μR-μT > 0.3) | | 0.079 |

*N: Number of patients in each treatment group.*
*n: Number of observed values.*
LS mean: Least Square mean.
*SE: Standard error.*
*95% CI: 95% confidence interval of the estimated difference.*
*μT – LS mean in LDL-c for the S05167 group.*
*μR – LS mean in LDL-c for the Coversyl® group*

The difference in LS means ($\mu_R$-$\mu_T$) with one-sided 95% CI was 0.399±0.0698 [0.2835; ∞] %, so the null hypothesis ($H_0$: $\mu_R$-$\mu_T \leq 0.3$) *could not be rejected*. P-value was 0.079, the difference between these two groups for FAS population was not statistically significant.

**Percent relative change from baseline in LDL-c at W008 (S05167 group vs Coversyl® group). Primary efficacy analysis– PPS population**

| **Change from baseline at W008 [%]** | **S05167 (N = 40)** | **Coversyl® (N = 21)** |
|---|---|---|
| n | 40 | 21 |
| Mean (SD/SE) | -0.406 (0.1762/0.0279) | 0.064 (0.3235/0.0706) |
| Q1; Q3 | -0.537; -0.318 | -0.134; 0.190 |
| LS mean (SE) with two-sided 95% CI | -0.393 (0.0401)<br>[-0.4730; -0.3138] | 0.052 (0.0553)<br>[-0.0581; 0.1613] |
| **t-test (superiority)** | | |
| μR-μT (SE) with one-sided 95% CI | | 0.469 (0.0759) [0.3401; ∞] |
| p-value ($H_0$: μR-μT ≤ 0.3; $H_1$: μR-μT > 0.3) | | 0.017 |
| **Model (superiority)** | | |
| μR-μT (SE) with one-sided 95% CI | | 0.445 (0.0683) [0.3315; ∞] |
| p-value ($H_0$: μR-μT ≤ 0.3; $H_1$: μR-μT > 0.3) | | 0.018 |

*N: Number of patients in each treatment group; n: Number of observed values.*
LS mean: Least Square mean; *SE: Standard error.*
*95% CI: 95% confidence interval of the estimated difference.*
*μT – LS mean in LDL-c for the S05167 group.*
*μR – LS mean in LDL-c for the Coversyl® group*

[2] Here: $\mu_R$ – LS mean in SBP for the Lipitor® group.
[3] Here: $\mu_T$ – LS mean in SBP for the S05167 group.

The difference in LS means ($\mu_R$- $\mu_T$) with one-sided 95% CI was 0.445±0.0683 [0.3315; ∞], so the null hypothesis ($H_0$: $\mu_R$-$\mu_T \leq 0.3$) *could be rejected*. P-value was 0.018, so this difference was *statistically significant.* Therefore, S05167 was more effective (superior) in decreasing LDL-c level as compared to Coversyl® after 8-week treatment period for PPS population.
Results for this primary endpoint no. 2 for FAS and PPS populations were not similar.

SAFETY RESULTS

**Overall summary for TEAEs in the Safety Set**

| Parameter | S05167 N = 59 | | Lipitor® N = 59 | | Coversyl® N = 29 | |
|---|---|---|---|---|---|---|
| | Patients | Events | Patients | Events | Patients | Events |
| Any treatment-emergent AE (TEAE) | 4 (6.8%) | 9 | 9 (15.3%) | 14 | 2 (6.9%) | 2 |
| Treatment-emergent SAEs (TESAE) | 0 (0.0%) | 0 | 0 (0.0%) | 0 | 0 (0.0%) | 0 |
| Mild TEAE | 1 (1.7%) | 6 | 9 (15.3%) | 13 | 0 (0.0%) | 0 |
| Moderate TEAE | 3 (5.1%) | 3 | 1 (1.7%) | 1 | 2 (6.9%) | 2 |
| Severe TEAE | 0 (0.0%) | 0 | 0 (0.0%) | 0 | 0 (0.0%) | 0 |
| Treatment-emergent IMP-related AEs | 0 (0.0%) | 0 | 1 (1.7%) | 2 | 0 (0.0%) | 0 |
| Treatment-emergent IMP-related SAEs | 0 (0.0%) | 0 | 0 (0.0%) | 0 | 0 (0.0%) | 0 |
| Treatment-emergent study protocol procedures/conditions-related AEs | 0 (0.0%) | 0 | 0 (0.0%) | 0 | 0 (0.0%) | 0 |
| Treatment-emergent study protocol procedures/conditions-related SAEs | 0 (0.0%) | 0 | 0 (0.0%) | 0 | 0 (0.0%) | 0 |
| Treatment-emergent AEs/SAEs leading to withdrawal | 0 (0.0%) | 0 | 0 (0.0%) | 0 | 0 (0.0%) | 0 |

A total of 9 TEAEs were reported for 4/59 (6.8%) patients in the S05167 group, 14 TEAEs were reported for 9/59 (15.3%) patients in the Lipitor® group, and 2 events for 2/29 (6.9%) patients in the Coversyl® group.

The system organ classes affected by TEAEs were in the S05167 group: "Nervous system disorders" – 4 events in 1/59 (1.7%) patient, "Cardiac disorders" and "Infections and infestations" – 2 events each in 2/59 (3.4%) patients, "Gastrointestinal disorders" – 1 event in 1/59 (1.7%) patient; in the Lipitor® group: "Investigations" – 4 events in 3/59 (5.1%) patients, "Blood and lymphatic system disorders" – 2 events in 2/59 (3.4%) patients and "Vascular disorders" – 2 events in 1/59 (1.7%) patient; in the Coversyl® group: increased alanine aminotransferase from "Investigations" and dyslipidaemia from "Metabolism and nutrition disorders" – 1 event each in 1/34 (3.4%) patient.

The reported TEAEs had mild and moderate intensity, the majority of reported TEAEs had mild intensity. None of TEAEs had severe intensity. None of reported the TEAEs was serious.

Among the reported TEAEs, only 1 TEAE (alanine aminotransferase increased) in the Lipitor® group had a causal relationship with IMP as related, other 24 TEAE had a causal relationship with IMP as unrelated.

None of TEAEs led to study withdrawal.

The safety analysis demonstrated that during the study there was no clinically significant findings based on analysis of vital signs, ECG data, clinical laboratory tests including haematology and serum biochemistry.

The study results confirmed the safety profile of S05167 (fixed-dose combination of atorvastatin/perindopril), and detected no new safety signals.

CONCLUSION

This was a multinational, multicentre, randomised, double-blind, parallel, active-controlled phase 3 study conducted to demonstrate the superiority of the S05167 (fixed-dose combination of atorvastatin/perindopril) in terms of efficacy compared to atorvastatin reference drug alone and perindopril reference drug alone, and to assess the safety. The study population included adult patients with diagnoses of hypertension and dyslipidaemia who had or had not previously received treatment for hypertension and dyslipidaemia.

The study was early terminated by the sponsor. An abbreviated study report was written due to premature stopping the S05167 product development for the business reasons.

Although the randomised number of patients was 3 times less than planned (147 vs 545), efficacy analyses were performed on all planned primary and secondary endpoints.

The primary efficacy endpoint no. 1 (mean change from baseline in SBP at W008) in the S05167 group as compared with Lipitor® group was achieved both for the FAS (primary analysis population) and PPS (sensitivity analysis population).

The primary efficacy endpoint no. 2 (percent change from baseline in LDL-c at W008) in the S05167 group as compared with Coversyl® group was achieved only for the PPS (sensitivity analysis population), but not for FAS (primary analysis population). Hypothesis testing was performed while the number of patients was much lower than planned, the study was underpowered, therefore not statistically significant result for the primary efficacy endpoint no.2 in the FAS should be interpreted with caution.

Analysis of safety showed that the frequency of TEAEs in the group with fixed-dose combination of atorvastatin/perindopril (S05167) (4/59, 6.8%) was similar to that in the Coversyl® group (2/29, 6.9%) and much lower than in the Lipitor® group (9/59, 15.3%).

**The study results demonstrated that S05167 is an effective fixed-dose combination of atorvastatin/perindopril in terms of BP decrease and LDL-c decrease after 8-week treatment period, and also confirmed an acceptable safety profile of S05167 (fixed-dose combination of atorvastatin/perindopril), with no new safety signals.**

**Date of the report:** 18 September 2023

**Version of the report:** Final version 1.0