2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="2">Test drug
Name of Finished Product:
Not applicable
Name of Active Ingredient:
Atorvastatin/amlodipine/perindopril (S 5153)</td><td></td></tr>
<tr><td>Individual Study Table Referring to Part of the Dossier</td><td>Volume:</td><td>Page:</td></tr>
<tr><td colspan="3">Title of study: Efficacy and safety of fixed-dose combination atorvastatin/amlodipine/perindopril versus fixed-dose combination of atorvastatin/amlodipine in patients with hypertension and dyslipidaemia
Protocol No.: CL3-05153-006
EudraCT No.: 2014-005378-12
Universal Trial Number: U1111-1166-2705 (added by Amendment No. 1). The description of the study protocol given hereafter includes the modifications of the 3 substantial amendments to the protocol.</td></tr>
<tr><td colspan="3">International coordinator
Not applicable</td></tr>
<tr><td colspan="3">Study centres:
67 centres located in 8 countries included 849 patients: 8 centres in Argentina (90 patients included), 3 centres in Brazil (21 patients included), 6 centres in Bulgaria (41 patients included), 4 centres in Italy (17 patients included), 4 centres in Mexico (26 patients included), 10 centres in Poland (146 patients included), 24 centres in Russia (370 patients included) and 8 centres in Ukraine (138 patients included).</td></tr>
<tr><td colspan="3">Publication (reference): Not applicable</td></tr>
<tr><td colspan="2">Studied period:
Initiation date: 10/08/2015 (date of first visit first patient)
Completion date: 08/09/2016 (date of last visit last patient)</td><td>Phase of development of the study:
Phase III</td></tr>
<tr><td colspan="3">Objectives:
The primary objective was to demonstrate the superiority of atorvastatin/amlodipine/perindopril (S 5153) versus atorvastatin/amlodipine in lowering office sitting systolic blood pressure (SBP) after 12 weeks treatment versus baseline.
The secondary objectives were to assess:
- The efficacy of S 5153 versus atorvastatin/amlodipine in lowering diastolic blood pressure (DBP) after 12 weeks treatment versus baseline.
- The efficacy of S 5153 in lowering low density lipoprotein-cholesterol (LDL-c) after 12 weeks treatment versus baseline.
- The safety of each dose of S 5153 during the study and at the end of the treatment period.</td></tr>
<tr><td colspan="3">Methodology:
This was a phase III, randomised, double-blind, multi-centre, multinational, parallel-arm study, being conducted in patients with hypertension and dyslipidaemia. The randomisation was stratified by country.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.</td></tr>
<tr><td colspan="3">Number of patients:
Planned: 830 patients in total, 415 per treatment group (as modified by Amendment No. 3).
Included: a total of 849 patients were included: 426 in the S 5153 group and 423 in the atorvastatin/amlodipine group.</td></tr>
</table>

Diagnosis and main criteria for inclusion:
The main selection criteria were:

- Men or women of any ethnic origin aged 40 to 79 years (inclusive) with essential hypertension, defined as:
  - Hypertensive patients naïve of treatment:
    - 160 mmHg ≤ SBP < 180 mmHg and 100 mmHg ≤ DBP < 110 mmHg; or
    - isolated systolic hypertension: 160 mmHg ≤ SBP < 180 mmHg and DBP < 100 mmHg; or
  - Uncontrolled hypertensive patients under monotherapy treatment for ≥ 4 weeks
    - 150 mmHg ≤ SBP < 180 mmHg and 95 mmHg ≤ DBP < 110 mmHg; or
    - isolated systolic hypertension: 150 mmHg ≤ SBP < 180 mmHg and DBP < 95 mmHg.

  Note: the limit of DBP for isolated systolic hypertension was added by Amendment No. 2.
- Dyslipidaemic patients: naïve of treatment or uncontrolled with statin at lowest dose for ≥ 4 weeks with 130 mg/dL ≤ LDL-cholesterol < 190 mg/dL (equivalent to 3.36 mmol/L ≤ LDL-c < 4.91 mmol/L).
- 10-year atherosclerotic cardiovascular disease (ASCVD) risk ≥ 5%.

The main inclusion criteria were:

- Confirmed hypertension measured at W000 (the lower acceptable limits at this visit were 150 mmHg for SBP and 95 mmHg for DBP; upper limits were unchanged).
- Confirmed dyslipidaemia on lipid profile assessed at W000 visit.

The main non-selection/inclusion criteria were:

- Complicated hypertension, diabetes mellitus type I or type II, obesity (body mass index ≥ 32 kg/m²).
- Any history of stroke, transient ischemic attack, cerebrovascular surgery or history of coronary artery disease; heart failure, hypertrophic obstructive myocardiopathy or unstable angina.

Test drug:
S 5153 (atorvastatin/amlodipine/perindopril): 10/5/5 milligram (mg) tablets, 20/5/5 mg and 20/10/10 mg; oral administration, one tablet once daily (*o.d.*) before breakfast.
Batch No.'s: L0058845, L0058028, L0060897, L0059332.

Comparator (Reference product and/or placebo):
Atorvastatin/amlodipine: 10/5 mg, 20/5 mg and 20/10 mg capsules; oral administration, one capsule *o.d.* before breakfast.
Batch Nos.: L0058405, L0058466, L0058467, L0058494, L0059288, L0059320, L0059555, L0059558, L0059699, L0060055, L0060093, L0060104, L0060121, L0060126, L0060135, L0060316, L0060979, L0061000, L0061002, L0061004.
Placebo: tablets and capsules, matching the corresponding active drugs. Thus, all patients took one tablet and one capsule *o.d.* before breakfast.

Duration of treatment:
Wash-out period: 2 weeks (3 weeks maximum) without antihypertensive or lipid lowering drugs and without any IMP intake.
12-week double-blind treatment period:

- **The first 4-week period:** At inclusion, patients were randomised to receive the lowest dose of either S 5153 (10/5/5 mg) or atorvastatin/amlodipine (10/5 mg) *o.d.* for a period of 4 weeks.
- **The 8-week up-titration period:**
- At the W004 visit, the dose of atorvastatin was up-titrated for each patient and according to BP criteria, the patient was potentially up-titrated for perindopril and/or amlodipine in blinded fashion for the remaining 8 weeks:
  - If BP was not controlled (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg), the dose was increased to S 5153 20/10/10 mg o.d. or atorvastatin/amlodipine 20/10 mg o.d.
  - If BP was controlled (SBP < 140 mmHg and DBP < 90 mmHg), only the atorvastatin was up-titrated (to 20 mg for all patients), *i.e.* S 5153 20/5/5 mg *o.d.* or atorvastatin/amlodipine 20/5 mg *o.d.*

Criteria for evaluation:
The BP measurement was performed in the investigator's office using an automated validated device at trough of drug activity (*i.e.* within 24 ± 3 hours after the last drug intake at each visit).
The analyses of laboratory tests, including lipid profile and safety parameters were carried out in a central laboratory.
Efficacy measurements:
The **primary endpoint** was office sitting SBP, expressed mainly as change from baseline to last post baseline value over the W000-W012 period.
The **secondary endpoints** included office sitting DBP, lipid profile (LDL-c, total cholesterol, HDL-c) and triglycerides.

Safety measurements:
- Adverse events (AEs), vital signs including BP postural changes, clinical laboratory parameters (biochemistry and haematology) and an electrocardiogram (ECG).

Statistical methods:
Analysis Sets:
The Randomised Set (RS) was defined as all patients randomly assigned a therapeutic unit; the Full Analysis Set (FAS) as all patients of the RS having taken ≥ 1 dose of IMP and having an analysable value of mean sitting SBP at baseline and ≥ 1 post-baseline value over W0-W12 period; the Per Protocol Set (PPS), as all patients of the FAS without relevant deviation(s) which could affect the evaluation of sitting SBP; and the Safety Set (SS), as all patients having taken at least one dose of IMP.
A sub-group of patients having grade 2 systolic-diastolic hypertension at baseline was defined (post-hoc analysis; i.e. SBP ≥ 160 mmHg and DBP ≥ 100 mmHg), along with its complementary sub-group of patients. A Non Included Set (NIS) was constituted of all screened patients who were not selected or not included.
Efficacy analysis:
The primary efficacy endpoint was the office mean sitting SBP with the main analysis on the between group comparison (S 5153 *versus* atorvastatin/amlodipine) on the change from baseline to last post-baseline value over W000-W012 period using an analysis of covariance (ANCOVA) model, adjusted on fixed, categorical effects of treatment and country, as well as the continuous fixed covariate of baseline.
Secondary analysis included the change within each treatment group from W004 to W012 in patients with BP not controlled at W004 and treated with the highest possible dose at W004 (up-titration efficiency), using a paired Student's test.

Secondary criteria:
All analyses performed on the primary efficacy endpoint were realised on the mean sitting DBP.
For total cholesterol, LDL-c, HDL-c, and triglycerides, change from baseline to last post baseline value over W000-W012 was described within each treatment group using a paired Student's test. The same analysis was computed on change from baseline to value at W012.

Study outcome and safety analysis: Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 1481 patients were screened for the study and 1431 were selected (Table 1). Of them, 854 were randomised (429 patients to S 5153 and 425 to atorvastatin/amlodipine (ator/amlo) group), but only 849 were allocated treatment since 5 patients did not meet all inclusion criteria. The groups were well balanced with 426 *versus* 423 patients receiving treatment. A total of 803 patients (94.6% of included) completed the study.

The main reasons for not including patients who had been screened or selected (n = 632) were non-fulfilment of the dyslipidaemia criteria (379 patients), other non-selection criteria (114 patients), or the criterion for hypertension (38 patients).

Table 1 - Disposition of patients in Randomised Set

	S 5153	**Ator/amlo**	**All**
	n (%)	**n (%)**	**n (%)**
Randomised	**429**	**425**	**854**
Included*	**426**	**423**	**849**
Withdrawn due to	**24 (5.6)**	**22 (5.2)**	**46 (5.4)**
adverse event	9 (2.1)	11 (2.6)	20 (2.4)
non-medical reason	8 (1.9)	7 (1.7)	15 (1.8)
protocol deviation	7 (1.6)	4 (0.9)	11 (1.3)
Completed	**402 (94.4)**	**401 (94.8)**	**803 (94.6)**
Full Analysis Set (FAS)	423 (98.6)	420 (98.8)	843 (98.7)
Per Protocol Set (PPS)	374 (87.2)	358 (84.2)	732 (85.7)
Safety Set (SS)	425 (99.1)**	423 (99.5)	848 (99.3)

N: total number of patients randomised in considered group

n: number of patients in each category; % = (n/total number of included patients) x 100

** 5 patients were randomised but not included: 3 patients in S 5153 group and 2 patients in atorvastatin/amlodipine group. ** One patient excluded for not having taken IMP.*

BASELINE CHARACTERISTICS

The baseline characteristics are summarised in Table 2. No relevant differences between groups were observed for these parameters.

The overall mean hypertension duration was slightly longer in the S 5153 group (79.2 ± 92.2 months) as compared to the ator/amlo group (73.9 ± 83.2 months).

The overall mean SBP/DBP was 163.4 ± 7.3 / 95.4 ± 10.0 mmHg, and the mean values for LDL-cholesterol, HDL-c, total cholesterol and triglycerides were 4.02 ± 0.42 mmol/L, 1.42 ± 0.36 mmol/L, 6.27 ± 0.59 mmol/L, and 1.81 ± 0.74 mmol/L, respectively. There were no relevant differences between groups for these parameters.

The baseline characteristics in the FAS and PPS were similar to those observed in the RS. For the baseline data in the Non-Included Set, they were also comparable with the RS, except a small higher proportion of patients aged 65 years (29.4%) or older were observed, as compared to the RS population (25.9%).

BASELINE CHARACTERISTICS (Cont'd)

Table 2 - Demographics and baseline characteristics in the Randomised Set

		S 5153 (N = 429)	Ator/amlo (N = 425)	All (N = 854)
Age (years)	Mean ± SD	58.1 ± 8.7	57.7 ± 8.9	57.9 ± 8.8
	Median	58.0	58.0	58.0
	Min ; Max	40.0 ; 79.0	40.0 ; 79.0	40.0 ; 79.0
Female gender	n (%)	241 (56.2)	234 (55.1)	475 (55.6)
White Caucasian	n (%)	408 (95.1)	415 (97.7)	823 (96.4)
Reporting a normosodium diet	n (%)	340 (80.0)	329 (78.3)	669 (79.2)
Hypertension duration (months)	Mean ± SD	79.2 ± 92.2	73.9 ± 83.2	76.5 ± 87.8
	Min ; Max	0 ; 539	0 ; 436	0 ; 539
Dyslipidaemia duration (months)	Mean ± SD	32.8 ± 50.1	31.0 ± 45.8	31.9 ± 48.0
	Min ; Max	0 ; 369	0 ; 232	0 ; 369
Type of dyslipidaemia				
Hypercholesterolemia	n (%)	242 (56.4)	235 (55.3)	477 (55.9)
Mixed dyslipidaemia	n (%)	187 (43.6)	190 (44.7)	377 (44.2)
10-year ASCVD risk (%)	Mean ± SD	15.7 ± 8.8	15.7 ± 9.4	15.7 ± 9.1
	Min ; Max	5.0 ; 55.6	3.1 ; 69.0	3.1 ; 69.0
Main prescribed treatments before study				
Agents acting on the renin-angiotensin system	n (%)	267 (62.2)	243 (57.2)	510 (59.7)
Calcium channel blockers	n (%)	35 (8.2)	34 (8.0)	69 (8.1)
Lipid modifying agents	n (%)	23 (5.4)	38 (8.9)	61 (7.1)
Beta blocking agents	n (%)	27 (6.3)	32 (7.5)	59 (6.9)
Efficacy criteria				
Sitting SBP (mmHg)	Mean ± SD	163.1 ± 7.5	163.7 ± 7.1	163.4 ± 7.3
	Min ; Max	146.0 ; 184.0	150.5 ; 181.5	146.0 ; 184.0
Sitting DBP (mmHg)	Mean ± SD	95.2 ± 10.4	95.7 ± 9.5	95.4 ± 10.0
	Min ; Max	55.0 ; 109.5	59.5 ; 113.0	55.0 ; 113.0
LDL-cholesterol (mmol/L)	Mean ± SD	4.02 ± 0.42	4.03 ± 0.43	4.02 ± 0.42
HDL-cholesterol (mmol/L)	Mean ± SD	1.44 ± 0.38	1.39 ± 0.34	1.42 ± 0.36
Total cholesterol (mmol/L)	Mean ± SD	6.28 ± 0.60	6.25 ± 0.59	6.27 ± 0.59
Triglycerides (mmol/L)	Mean ± SD	1.80 ± 0.74	1.83 ± 0.75	1.81 ± 0.74
Weight (kg)	Mean ± SD	80.2 ± 11.3	80.7 ± 11.1	80.4 ± 11.2
	Min ; Max	44.0 ; 111.7	49.8 ; 116.6	44.0 ; 116.6

N: Total number of patients in the considered group
n: Number of patients concerned; % = (n/N or number of patients with available information) x 100
** The previous results within 12 months prior to selection visit were taken in account*

EXTENT OF EXPOSURE

The mean treatment duration was 81.2 ± 14.1 days in the RS; 81.8 ± 12.4 days in the Safety Set; and 82.3 ± 10.8 days in the FAS. The global compliance was good; the mean compliance in the RS was 97.4 ± 11.0%, with 97.4% of patients having a value between 70% and 130%.

At the W004 visit, 36.5% of patients in the S 5153 group were up-titrated compared with 41.8% of the atorvastatin/amlodipine group.

EFFICACY RESULTS

The mean change in sitting SBP (primary endpoint) over the 12-week treatment period is presented in Table 3, along with the results for the secondary endpoint of DBP change.

The between-group difference in sitting SBP change did not reach significance (p = 0.530), nor did the between-group difference in DBP change (p = 0.106).

Table 3 - Statistical analysis of blood pressure in the FAS over the period W000-W012

(mmHg)		**Sitting SBP** (primary endpoint)		**Sitting DBP**	
		S 5153 (N = 423)	**Ator/amlo (N = 420)**	**S 5153 (N = 423)**	**Ator/amlo (N = 420)**
Baseline	n	423	420	423	420
	Mean ± SD	163.2 ± 7.5	163.7 ± 7.1	95.2 ± 10.4	95.7 ± 9.5
Last post-baseline	Mean ± SD	131.5 ± 12.2	132.1 ± 12.6	79.3 ± 9.0	80.4 ± 8.8
Change	Mean ± SD	-31.7 ± 13.8	-31.6 ± 13.6	-15.9 ± 12.1	-15.3 ± 11.1
	Min, Max	-80.0 ; 25.5	-71.0 ; 8.5	-47.5 ; 28.0	-46.5 ; 26.5
Statistical analysis (between groups)					
	E (SE)	-0.52 (0.83)		-0.94 (0.58)	
	90% CI	[-2.14 ; 1.10]		[-2.08 ; 0.20]	
	p-value	0.530		0.106	

N: Total number of patients in the considered group; n: Number of patients with available value at baseline and during post-baseline period
E (SE): Estimate (standard error) of the difference (S 5153 - ator/amlo) in adjusted mean changes from baseline to last post-baseline value until W012, using the general linear model with treatment, baseline and country as covariates.
95% CI: Confidence interval of the estimate
P-value: According to general linear model

The mean changes in SBP and DBP over the following 8-week period in patients who were not controlled for BP and up-titrated correctly at W004 visit showed additional reductions in both groups by W012: -14.1 ± 12.5 / -7.8 ± 9.6 mmHg *versus* -13.9 ± 12.2 / -7.9 ± 7.8 mmHg, in S 05153 and atorvastatin/amlodipine groups, respectively.

A post-hoc analysis of the mean changes in SBP and DBP in patients with grade 2 systolic-diastolic hypertension at baseline is presented in Table 4. This analysis showed that S 5153 was relatively more efficient in BP reduction than the atorvastatin/amlodipine combination. In the complementary sub-group of patients without grade 2 systolic-diastolic hypertension, the 2 treatments were comparable.

Table 4 - Change in blood pressure in patients with grade 2 systolic-diastolic hypertension at baseline in the FAS (post-hoc analysis)

(mmHg)		**SBP**		**DBP**	
		S 5153	**Ator/amlo**	**S 5153**	**Ator/amlo**
	n	124	117	124	117
Baseline	Mean ± SD	168.2 ± 5.7	168.0 ± 5.3	104.4 ± 2.9	104.5 ± 2.8
	Min, Max	160.0 ; 184.0	160.0 ; 178.5	100.0 ; 109.5	100.0 ; 113.0
Last post baseline	Mean ± SD	131.6 ± 10.9	133.5 ± 11.8	79.8 ± 10.1	82.8 ± 9.7
	Min, Max	104.5 ; 168.0	105.5 ; 167.0	55.0 ; 105.5	59.0 ; 105.5
Change	Mean ± SD	-36.5 ± 10.8	-34.5 ± 12.5	-24.5 ± 10.0	-21.7 ± 9.8
	Min, Max	-66.0 ; -9.0	-71.0 ; -0.5	-47.5 ; -1.0	-46.0 ; 1.0
Statistical analysis (between group)					
	E (SE)	-2.32 (1.40)		-2.97 (1.23)	
	90% CI	[-5.08 ; 0.45]		[-5.38 ; -0.55]	
	p-value	0.101		0.016	

n: Number of patients with available information at baseline and during post-baseline period.
E (SE): Estimate (standard error) of the difference (S 5153 - ator/amlo) in adjusted mean changes from baseline to last post-baseline value until W012, using the general linear model with treatment, baseline and country as covariates.
95% CI: Confidence interval of the estimate
P-value: According to general linear model

EFFICACY RESULTS (Cont'd)

- **Secondary assessment criteria**

Regarding the lipid profile, statistical analyses were carried out within each group on the change from baseline to last post-baseline over the 12-week period. The mean changes in LDL-c were -1.47 ± 0.81 mmol/L in the S 5153 group *versus* -1.44 ± 0.84 mmol/L in the atorvastatin/amlodipine group ($p < 0.001$ for both groups); for HDL-c: -0.07 ± 0.37 mmol/L *versus* -0.07 ± 0.31 mmol/L, respectively; for total cholesterol: -1.70 ± 1.01 mmol/L *versus* -1.66 ± 0.99 mmol/L, respectively ($p < 0.001$ for both groups); and for triglycerides: -0.35 ± 0.76 mmol/L *versus* -0.31 ± 0.81 mmol/L, respectively ($p < 0.001$ for both groups).

SAFETY RESULTS

The observations of emergent adverse events (EAEs) during the study are summarised in Table 5. The results are presented by period to highlight potential differences between the prescribed doses, *i.e.* in the first 4 weeks, S 5153 10/5/5 mg is compared to atorvastatin/amlodipine 10/5 mg, and in the last 8 weeks, S 5153 20/5/5 mg, S 5153 20/10/10 mg, is compared to atorvastatin/amlodipine 20/5 mg and atorvastatin/amlodipine 20/10 mg, respectively.

- **Emergent adverse events**

Table 5 summarises the main results of adverse events in the Safety Set.

Table 5 - Overall summary for adverse events in the Safety Set

		Over W000-W004 period		Over W004-W012 period			
				Non-titrated		Up-titrated	
		S 5153 10/5/5 mg (N = 425)	Ator/amlo 10/5 mg (N = 423)	S 5153 20/5/5 mg (N = 259)	Ator/amlo 20/5 mg (N = 237)	S 5153 20/10/10 mg (N = 155)	Ator/amlo 20/10 mg (N = 177)
Patients having reported at least one:							
EAE	n (%)	23 (5.4)	32 (7.6)	30 (11.6)	34 (14.3)	28 (18.1)	38 (21.5)
Treatment-related EAE	n (%)	9 (2.1)	14 (3.3)	10 (3.9)	7 (3.0)	15 (9.7)	25 (14.1)
Oedema peripheral	n (%)	3 (0.7)	4 (0.9)	2 (0.8)	4 (1.7)	10 (6.5)	20 (11.3)
Peripheral swelling	n (%)	-	-	-	1 (0.4)	2 (1.3)	2 (1.1)
Blood CPK increased	n (%)	1 (0.2)	-	3 (1.2)	1 (0.4)	1 (0.6)	2 (1.1)
Cough	n (%)	-	-	1 (0.4)	-	1 (0.6)	-
Patients having reported at least one:	n (%)						
SAE	n (%)	1 (0.2)	2 (0.5)	3 (1.2)	-	2 (1.3)	1 (0.6)
Serious EAE	n (%)	1 (0.2)	2 (0.5)	3 (1.2)	-	2 (1.3)	1 (0.6)
Treatment-related SAE	n (%)	-	1 (0.2)	-	-	1 (0.6)	-
Patients with treatment withdrawal due to:	n (%)						
EAE	n (%)	3 (0.7)	3 (0.7)	3 (1.2)	1 (0.4)	4 (2.6)	7 (4.0)
Treatment-related EAE	n (%)	3 (0.7)	3 (0.7)	2 (0.8)	-	3 (2.0)	5 (2.8)
Oedema peripheral	n (%)	1* (0.2)	-	1* (0.4)	-	1 (0.6)	3 (1.7)
Serious EAE	n (%)	-	1 (0.2)	-	-	-	1 (0.6)
Treatment-related serious EAE**	n (%)	-	1 (0.2)	-	-	-	-

N: total number of exposed patients in the treatment group
n: number of affected patients; % = (n/N) x 100
** The patient withdrawn due to oedema peripheral on S 5153 10/5/5 mg and on S 5153 20/5/5 mg referred to the same patient, for this event occurred during the W000-W004 period as moderate event and worsened to severe in the W004-W012 period, and subsequently led to IMP withdrawal.*
*** Bronchospasm*

During the study period (W000-W012), 172 patients (20.3% of Safety Set, N = 848) reported a total of 231 EAEs, with a lower proportion in the S 5153 group than in the atorvastatin/amlodipine group: 74 patients (17.4%) with 107 events *versus* 98 patients (23.2%) with 124 events. The most frequently affected SOC was general disorders and administration site conditions (3.8% *versus* 6.6%, respectively); the difference was mainly due to the incidence of oedema peripheral: 11 patients (2.6%) *versus* 23 (5.4%). The second most frequent affected SOC was infections and infestations (4.2% *versus* 5.0%); mainly nasopharyngitis (1.9% *versus* 3.1%). The SOC investigations affected 4.9% *versus* 3.8% of patients respectively, mainly increased blood CPK (2.1% *versus* 1.9%) or increased ALT levels (1.9% *versus* 0.9%).

SAFETY RESULTS (Cont'd)

During the first 4-week treatment period, there were 28 events in 23 patients (5.4%) receiving S 5153 10/5/5 mg *versus* 37 events in 32 patients (7.6%) receiving atorvastatin/amlodipine 10/5 mg. The most frequently reported event in both groups was oedema peripheral (3 patients [0.7%] *versus* 4 patients [0.9%]), followed by headache and nasopharyngitis (2 [0.5%] *versus* 4 [0.9%] for each preferred term). The majority of EAEs were rated mild in both groups (64.3% of all events *versus* 75.7%) and none were severe.

Emergent AEs **led to IMP withdrawal** during this period of 3 patients in each group. In the S 5153 10/5/5 mg group: peripheral oedema (emergent in this period, but worsened and leading to IMP withdrawal after W004), urticaria and, for one patient, drug intolerance, facial swelling and hot flush. In the atorvastatin/amlodipine 10/5 mg group: myalgia, dizziness and bronchospasm.

During the 8-week titration period, there were, in patients who were not-titrated, a total of 45 EAEs in 30 patients (11.6%) on S 5153 20/5/5 mg *versus* 39 EAEs in 34 (14.3%) patients on atorvastatin/amlodipine 20/5 mg. Whereas in patients who were titrated to the higher antihypertensive posology there were 36 EAEs in 28 (18.1%) patients on S 5153 20/10/10 mg *versus* 49 EAEs in 38 (21.5%) patients on atorvastatin/amlodipine 20/10 mg.

The most frequently reported PT was oedema peripheral, although this was less frequent on the non-titrated patients (2 patients [0.8%] *versus* 3 [1.3%]) as compared to the titrated patients (8 [5.2%] *versus* 17 [9.6%]). In addition, there were a few cases of peripheral swelling (1 in the combined S 5153 groups *versus* 4 in the combined atorvastatin/amlodipine groups). All cases of oedema peripheral and peripheral swelling were considered related to the treatment. The occurrence of increased blood CPK was similar across treatment groups: in the non-titrated patients, 1.9% *versus* 2.1% and in the titrated patients, 1.9% *versus* 1.7%. 3 EAEs during this period were rated as severe: in the S 5153 20/5/5 mg group: oedema peripheral (emergent in the previous period); in the atorvastatin/amlodipine 20/10 mg group: acute myocardial infarction and angina pectoris (both serious events in the same patient).

Emergent AEs **led to IMP withdrawal** during this period of 4 patients who were not-titrated (3 [1.2%] *versus* 1 [0.4%]): oedema peripheral, increased CPK and urticaria *versus* headache; and 11 patients who were titrated (4 [2.6%] *versus* 7 [4.0%]): oedema peripheral, peripheral swelling, increased CPK and haemorrhagic diathesis *versus* oedema peripheral [3], asthenia [2], decreased BP, tremor, and acute myocardial infarction.

Serious emergent AEs were uncommon, affecting 9 (1.1%) patients and there were no deaths. During the study, there were 7 events in 6 patients (1.4%) in the S 5153 group *versus* 8 events in 3 patients (0.7%) in the atorvastatin/amlodipine group. These were distributed between the study periods and treatment doses as follows:

- In the first 4-week period:
  - On S 5153 10/5/5 mg (1 event in 1 patient): hydrocele.
  - On atorvastatin/amlodipine 10/5 mg (2 events in 2 patients): bronchospasm and carotid artery stenosis.
- In the 8-week titration period:
  - On S 5153 20/5/5 mg (3 events in 3 patients): lower respiratory tract infection, oeritonsillar abscess and thrombocytopenia.
  - On S 5153 20/10/10 mg (3 events in 2 patients): GGT increased in one patient, and hypertensive crisis and blood potassium increased in the other patient.
  - On atorvastatin/amlodipine 20/10 mg (2 events in 1 patient): acute myocardial infarction and angina pectoris.

After the end of the treatment period. 1 patient randomised to the atorvastatin/amlodipine 20/10 mg group reported 4 serious events: pericarditis, anaemia, respiratory tract infection and post procedural haematoma.
2 serious events were considered related to treatment (bronchospasm and GGT increased), and 2 led to treatment withdrawal (bronchospasm and acute myocardial infarction).

Laboratory tests
The incidence of emergent potentially clinically significant abnormal (PCSA) values on treatment was infrequent. PCSA values most frequently concerned low HDL-c determinations, affecting 4.1% of patients in the S 5153 group *versus* 2.4% in the atorvastatin/amlodipine group (these were mostly values of around 0.7 mmol/L *versus* a threshold of 0.8 mmol/L); high CPK affecting 2.1% *versus* 1.9%; high GGT affecting 1.7% *versus* 2.0%; or high potassium affecting 1.2% *versus* 1.4%. No relevant difference was observed between the two treatment periods or between treatment doses.

SAFETY RESULTS (Cont'd)

Other safety evaluations

The standing BP (after 1 minute upright) showed mean changes (SBP/DBP) of -31.2 ± 16.3 / -15.1 ± 13.6 mmHg in S 5153 group *versus* -29.7 ± 16.7 / -15.1 ± 11.7 mmHg in the atorvastatin/amlodipine group. The changes after 3 minutes in an upright position were similar. No adverse event of orthostatic hypotension was reported during the study. The heart rate and weight remained stable in both groups.

There was no increase in the incidence of significant ECG abnormalities during the study.

CONCLUSION

This was a phase III study designed to compare the efficacy of S 5153, a fixed-dose combination product comprising atorvastatin, amlodipine and perindopril, in lowering office sitting SBP *versus* a combination of atorvastatin plus amlodipine in hypertensive, dyslipidaemic patients over 12 weeks. Following a 2-3 week wash-out period for previous antihypertensive and lipid-lowering therapies, patients were randomised to one of the 2 treatment groups. A dose titration of the antihypertensive constituents was made after 4-week treatment, for patients whose BP was not controlled, *i.e.* in the S 5153 arm, the dose of amlodipine and perindopril was increased from 5 mg to 10 mg and in the atorvastatin/amlodipine arm, amlodipine was increased from 5 mg to 10 mg. In patients whose BP was controlled the anti-hypertensive dose was not increased. At the same visit and in all patients, the dose of atorvastatin was increased from 10 mg to 20 mg.

The included population conformed well to the target population and the two treatment groups were well-balanced in terms of demographics, baseline characteristics, concomitant medications and study duration.

There was no significant between-group difference in SBP change after 12 weeks of treatment: -0.52 mmHg (95% CI [-2.14 ; 1.10], p = 0.530; general linear model), while a substantial decrease in mean sitting SBP in both groups was observed: -31.7 ± 13.8 mmHg in the S 5153 group and -31.6 ± 13.6 mmHg in the atorvastatin/amlodipine group. The between-group difference in DBP change showed a trend towards greater efficacy in the S 5153 group, but statistical significance was not reached (estimate: -0.94 mmHg, 95% CI [-2.10 ; 0.20], p = 0.107). Mean within group decreases of SBP and DBP at W012 in patients whose BP not controlled, showed statistically significant differences as compared to the values at the W004 visit. Post-hoc analyses showed that in patients with grade 2 systolic-diastolic hypertension at baseline the antihypertensive efficacy of S 5153 was relatively greater than the atorvastatin/amlodipine treatment, with a difference of -2.32 mmHg for SBP (p = 0.101) and of -2.93 for DBP (p = 0.016). The planned analyses of lipid profiles, notably LDL-c, total cholesterol and triglycerides, over the treatment period (W000-W012) showed statistically significant decreases in both treatment groups.

The safety profile of S 5153 was good, with incidences of EAEs being generally similar or lower than in atorvastatin/amlodipine group. In particular, it may be noted that the incidence of oedema peripheral under S 5153 (2.6%) was lower than under atorvastatin/amlodipine (5.4%), which probably reflects the protective effect of perindopril on amlodipine-related oedema. No new safety concern was identified.

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