2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor: LLS, 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 Ingredients:
Amlodipine 5mg/ Bisoprolol fumarate 5mg /Perindopril arginine 5mg (S05166)</td><td></td></tr>
<tr><td colspan="3">Title of study: Evaluation of the clinical efficacy and safety of Amlodipine 5mg/ Bisoprolol fumarate 5mg /Perindopril arginine 5mg fixed-dose combination in capsule and free monotherapy at the same dose in patients with uncontrolled essential hypertension (HT). A multicenter randomized, open-label, 12-weeks study.
Protocol No.: CL3-05166-003
EudraCT No.: Not applicable
The description of the study protocol given hereafter includes the modifications of the substantial amendment to the protocol.</td></tr>
<tr><td colspan="3">Main Investigator
The list of investigators is given in a separate document.</td></tr>
<tr><td colspan="3">Study countries:
150 patients included in the Russian Federation.</td></tr>
<tr><td colspan="3">Publication (reference):
Not applicable</td></tr>
<tr><td colspan="2">Studied period:
Initiation date: 14 May 2018 (date of first visit first patient)
Completion date: 18 December 2018 (date of last visit last patient)</td><td>Phase of development of the study:
Phase III</td></tr>
<tr><td colspan="3">Objectives:
The objective of this study was to evaluate the clinical efficacy and safety of the fixed-dose combination Amlodipine 5mg/ Bisoprolol fumarate 5mg /Perindopril arginine 5mg in single-capsule and of the free monocomponents, Amlodipine 5mg, Bisoprolol fumarate 5mg and Perindopril arginine 5mg, over 12 weeks, in patients having an uncontrolled HT defined by systolic blood pressure (SBP) ≥ 140 and < 160 mmHg and diastolic blood pressure (DBP) ≥ 90 and < 100 mmHg under ongoing treatment (anti-hypertensive monotherapy at maximal dose or either by a dual therapy at minimum dose, other than study treatment).</td></tr>
<tr><td colspan="3">Methodology:
This was a phase III, multicenter, randomized, open-label, controlled study, over a 12-week treatment period with a single-capsule of fixed dose combination (FDC) of Amlodipine 5 mg/ Bisoprolol fumarate 5 mg / Perindopril arginine 5 mg and a free monocomponents of Amlodipine 5 mg, Bisoprolol fumarate 5 mg and Perindopril arginine 5 mg given concomitantly, in 150 patients with uncontrolled essential HT.
Patients without any non-selection criteria, already treated by anti-hypertensive monotherapy at maximal dose or either by a dual therapy at minimum dose, other than study treatment, having an uncontrolled HT defined by SBP ≥ 140 and <160 mmHg and DBP ≥ 90 and <100 mmHg (in supine position) at 2 different visits (selection and inclusion) were to be selected in this study and randomized to one of two treatment groups: single-capsule combination or free therapy without any wash-out period.
For all patients, controlled blood pressure (BP) was defined as SBP < 140 mmHg and DBP < 90 mmHg.
This study was performed in strict accordance with ICH Good Clinical Practice.</td></tr>
<tr><td colspan="3">Number of patients:
Planned: 150 (75 per group) randomized patients
Included: 150 randomized patients: 77 patients in the group A – S05166 single-capsule of FDC of amlodipine 5 mg / bisoprolol fumarate 5 mg / perindopril arginine 5 mg; 73 patients in the group B – Free triple therapy of amlodipine 5 mg + bisoprolol fumarate 5 mg + perindopril arginine 5 mg, given concomitantly</td></tr>
<tr><td colspan="3">Diagnosis and main criteria for inclusion:
Selection criteria
– Men or women of any ethnic origin ≥18 years old who signed Informed consent form.
– Patients with uncontrolled HT defined by SBP ≥140 and < 160 mmHg and DBP ≥90 and < 100 mmHg already treated by anti-hypertensive monotherapy at maximal dose or either by a dual therapy at minimum dose, other than study treatment (amlodipine or bisoprolol or perindopril), for at least 4 weeks.
– Women of potential childbearing and men (and/or their partners) must agree to use appropriate contraceptive measures. This applies since signing of the Informed Consent form until the last study drug administration.
– Willing to provide signed and dated informed consent.</td></tr>
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Non-selection criteria

- Unlikely to co-operate in the study, to comply with study treatment or with the study visits.
- Pregnancy, breastfeeding.
- Current participation in another randomized study or within the preceding 3 months.
- Participant already enrolled in the study.
- Alcohol or drug abuse and/or dependence.
- Body mass index > 32 kg/m².
- Grapefruit juice was forbidden during the study (interaction with amlodipine).

Concerning HT

- DBP ≥100 mmHg and/or SBP ≥160 mmHg under treatment.
- Known or suspected symptomatic orthostatic hypotension.
- HT known to be resistant to Calcium Channel Blockers or ACE inhibitors or Beta Blockers.
- Secondary HT.
- Complicated HT: known stage III or IV hypertensive retinopathy, macroalbuminuria (patients with microalbuminuria could be selected).

Concerning concomitant diseases

- History of renal disease: Known renal impairment: Patients having a creatinine clearance value classifying them as moderate or severe renal failure (using national or international classification of chronic kidney disease), whatever the method for calculation used (MDRD or Cockcroft or any other eGFR formula), or bilateral renal artery stenosis or stenosis to a solitary kidney.
- History of cerebrovascular disease: ischemic stroke, cerebral hemorrhage, transient ischemic attack.
- History of heart disease: shock (including cardiogenic), myocardial infarction (within previous 6 months before selection), heart failure class II to IV NYHA (New York Heart Association), coronary revascularization (within the previous 6 months), severe aortic or mitral valve stenosis or hypertrophic obstructive myocardiopathy, unstable angina pectoris (including Prinzmetal's angina).
- History of recent (within previous 6 months before selection, accordingly to the doctor decision) ventricular rhythm disorders (except isolated extrasystoles), atrial fibrillation or atrial flutter, second or third degree atrioventricular (AV) block or other cardiac rhythm disorders leading to important beat-to-beat variations in BP (Left Ventricular Hypertrophy was authorized at selection and during the study).
- Known prolonged QT interval.
- Patients having resting HR <50 bpm.
- History of sick sinus syndrome.
- History of bradycardia clinically significant episode.
- Severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome.
- Severe bronchial asthma or severe chronic obstructive pulmonary disease.
- Severe gastro-intestinal tract disorders with possible influence on drug absorption or electrolytes.
- Known complicated liver disease (for example: chronic hepatitis, cirrhosis, hepatic encephalopathy…).
- Chronic pancreatitis.
- Endocrine diseases: uncontrolled dysthyroidia, Cushing's syndrome, acromegalia, hyperparathyroidia.
- Diabetes mellitus type I and type II under treatment (patients with diabetes type II well controlled at the selection visit by lifestyle and dietary rules alone could be selected).
- Any history or known severe disease likely to interfere with the conduct of the study, severe evolutive infection, evolutive malignant neoplasm.
- History of neutropenia.
- History of connective tissue disorders (systemic lupus erythematosus, progressive systemic sclerosis or other connective tissue disorders).
- History of severe mental or psychiatric disorder, severe depression or history of severe depression, e.g. requiring hospitalization or at high risk of suicide attempt.
- History of angioneurotic oedema.

Concerning concomitant medications

- β-blockers even if used for other reason than HT, in order to avoid the AE related to the immediate switch during selection visit.
- Antihypertensive treatments having central mechanism of action in order to avoid possible rebound effect at a full immediate stop at the randomization.
- Antiarrhythmic treatments in order to avoid possible interactions with bisoprolol.
- Inability to stop any of the medications listed in the prohibited concomitant medication list.
- Potassium supplement at selection and inclusion visit.
- Drugs contraindicated with the study treatments as defined in the Summaries of Product Characteristics of

each study drugs.

Concerning contra-indications to treatment with amlodipine, bisoprolol or perindopril

- Any history of angioedema, hereditary, idiopathic or associated with previous ACE inhibitor therapy.
- Allergy / hypersensitivity / history of intolerance or any contra-indications related to:
  - amlodipine or any other dihydropyridine and calcium inhibitors;
  - perindopril or any other ACE inhibitor;
  - bisoprolol or other beta-blockers;
  - any of the excipients of the study drugs.

Inclusion criteria

- Respect of the previous selection and non-selection criteria.
- Confirmed essential uncontrolled HT under patient's current treatment at W000 visit, defined as SBP ≥140 and < 160 mmHg and DBP ≥90 and < 100 mmHg, measured with a validated automatic device in supine position after at least 10 minutes of rest. There were 3 BP measurements at 2-3 minutes of an interval between each measurement. The mean of the two last values of the three measurements was taken.
- Normal or without any clinically significant abnormality 12-lead ECG (left ventricular hypertrophy and post-MI ECG-changes are authorized at selection and during the study).
- Normal or without clinically significant abnormality of laboratory examinations. Microalbuminuria was authorized.

Non-inclusion criteria

- As per non-selection criteria.
- Occurrence of an event requiring immediate notification since Selection.
- Laboratory results unavailable at the inclusion visit.
- Withdrawal of informed consent by patient.
- DBP ≥100 mmHg and/or SBP ≥160 mmHg under treatment since the selection visit.
- Positive orthostatic test at inclusion.
- Positive β-HCG pregnancy test (Blood test).
- Laboratory results unavailable at the inclusion visit or clinically significant abnormalities. Macroalbuminuria (>300 mg albumin/24h) was not authorized. ASAT or ALAT ≥ 2 UNL was not authorized.

If all Inclusion and non-inclusion criteria were satisfied, the patient was included and randomized to a treatment group.

Exclusion criteria (Withdrawal criteria):

- Patients whose BP was still uncontrolled at two consecutive visits (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) or whose SBP/DBP was above 160/100 mmHg (confirmed with 2 consecutive visits starting W004, at least 14 days apart).
- Onset of an adverse event (AE) which required prescription of a treatment incompatible with the protocol.
- Onset of an AE which, according to the investigator, makes it unsafe for the patient to continue with the study treatment. This includes clinically significant abnormal biochemical and haematological parameters, or clinically significant ECG abnormality.
- Pregnancy.
- Major protocol deviation preventing the analysis of the main endpoint, or which, in the opinion of the investigator, makes it unsafe for the patient to continue to take the study medication and to stay in the study.
- Non-medical reason (patient's personal decision to stop treatment).

Test drug:
S05166 FDC of Amlodipine 5 mg / Bisoprolol fumarate 5 mg / Perindopril arginine 5 mg; 1 capsule/day (oral administration) – Group A

Comparator (Reference product and/or placebo):
Norvasc® (Amlodipine) 5 mg 1 tab/day + Concor® (Bisoprolol fumarate) 5 mg 1 tab/day + Coversyl® (Perindopril arginine) 5mg 1 tab/day (oral administration) given concomitantly – Group B

Duration of treatment:
Run-in period on patient's current treatment: 1 week
***Study treatment period*:** 12 weeks

Criteria for evaluation:

Efficacy measurements:

- Supine BP (SBP/DBP) (all visits). BP lowering effects of anti-hypertensive therapy documented as the post treatment reduction of BP.
- Response criteria for antihypertensive therapy: rate of patients with supine BP normalized (SBP < 140 mmHg and DBP < 90 mmHg) and/or decrease of SBP ≥ 20 mmHg and/or decrease of DBP ≥ 10 mmHg from baseline, measured in supine position at W004, W008 and W012.
- Supine BP control rate (SBP < 140 mmHg and DBP < 90mmHg).

Safety measurements:

- Physical examination (all visits).
- Emergent adverse events (EAEs) (all visits).
- Orthostatic hypotension (all visits).
- Weight (at selection, W004 and W012 visit) and height (at selection).
- Heart rate (HR) (all visits).
- Complete laboratory examinations (at Inclusion and visit W012): haematology, blood biochemistry.
- Simplified laboratory tests (W004): creatinine clearance, serum potassium.
- 12-lead electrocardiogram (ECG) (at inclusion and visit W012).

Patient Reported Outcome:

- Assessment of patient treatment satisfaction using the TSQM-9 (Treatment Satisfaction Questionnaire for Medication) questionnaire (W012 visit).

Statistical methods:

A Statistical Analysis Plan was written after finalizing the protocol and definitively completed before the data review meeting. These specifications detailed the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol.

Efficacy analyses:

Efficacy analyses were carried out on the Full Analysis Set (FAS) and the Per Protocol Set (PPS).
BP efficacy parameters were analyzed using descriptive statistics by treatment group on the value at the visit and change from baseline to each post-baseline visit. A within group comparison on BP on the change from baseline to visit W012 was provided for each treatment group using a two-tailed Student's t test for paired samples and using Last Observation Carried Forward (LOCF) approach in the patients of the FAS. The percentage of responders/controlled at each post-baseline visit was described in each treatment group.

Safety analyss:

Safety analyses were carried out on the Safety Set (SS), by treatment group, for the W000-W012.
EAEs, clinical laboratory evaluation, vital signs and emergent ECG abnormalities were studied as safety parameters.

Patient reported outcome

Patient treatment satisfaction was assessed using the TSQM-9 questionnaire, which was analyzed using descriptive statistics by treatment group on the value at visit W012 or premature withdrawal for total transformed score of each domain (effectiveness, convenience and global satisfaction).

Study patients: disposition, baseline characteristics and treatments

Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Overall, 158 patients were selected for the study, of whom 150 were included and randomly assigned to one of the two treatment strategies.

A total of 145 patients (96.7%) completed the W000-W012 period and 4 patients (2.7%) were prematurely withdrawn: due to AE for 2 patients (1.3%), protocol deviation for 1 patient (0.7%) and uncontrolled BP for 1 patient (0.7 %). One patient (0.7%) in the S05166 Amlo/Biso/Per FDC was lost to follow up.

		All	S05166 Amlo/Biso/Per FDC	Amlo+Biso+Per free combination
Included	**N**	**150**	**77**	**73**
Lost to follow up	n (%)	1 (0.7%)	1 (1.3%)	-
Withdrawn due to	**n (%)**	4 (2.7%)	2 (2.6%)	2 (2.7%)
Adverse event	n (%)	2 (1.3%)	1 (1.3%)	1 (1.4%)
Protocol deviation	n (%)	1 (0.7%)	-	1 (1.4%)
Uncontrolled BP	n (%)	1 (0.7%)	1 (1.3%)	-
Completed	**n (%)**	**145 (96.7%)**	**74 (96.1%)**	**71 (97.3%)**
Full Analysis Set (FAS)	**n (%)**	149 (99.3%)	77 (100%)	72 (98.6%)
Per Protocol Set (PPS)	**n (%)***	144 (96.6%)	75 (97.4%)	69 (95.8%)
Safety set (SS)	**n (%)**	149 (99.3%)	77 (100%)	72 (98.6%)

N: Total number of patients included and randomized
n: number of patients in each category
% = (n/N)*100
*% of the FAS

BASELINE CHARACTERISTICS (RANDOMIZED SET (RS))

Characteristic	All (N = 150)	S05166 Amlo/Biso/Per FDC (N = 77)	Amlo+Biso+Per free combination (N = 73)
Mean HR, bpm			
Mean ± SD	72.84 ± 9.59	72.77 ± 8.77	72.91 ± 10.44
Mean Supine SBP, mmHg			
Mean ± SD	149.71 ± 5.09	150.19 ± 4.68	149.19 ± 5.48
Mean Supine DBP, mmHg			
Mean ± SD	94.92 ± 2.78	94.94 ± 2.67	94.9 ± 2.91

TREATMENTS FOR ESSENTIAL HT (RS)

Anti-hypertensive therapy		All (N = 150)	S05166 Amlo/Biso/Per FDC (N = 77)	Amlo+Biso+Per free combination (N = 73)
Previous treatments for essential HT before the selection period				
C02 Antihypertensives	n (%)	1 (0.7%)	1 (1.3%)	0 (0%)
C03 Diuretics	n (%)	29 (19.3%)	14 (18.2%)	15 (20.5%)
C07 Beta Blocking Agents	n (%)	3 (2%)	1 (1.3%)	2 (2.7%)
C08 Calcium Channel Blockers	n (%)	4 (2.7%)	1 (1.3%)	3 (4.1%)
C09 Agents acting on the Renin-Angiotensin System	n (%)	148 (98.7%)	75 (97.4%)	73 (100%)
Anti-hypertensive therapy during the selection period and before inclusion				
Monotherapy	n (%)	63 (42%)	35 (45.5%)	28 (38.4%)
Dual therapy	n (%)	87 (58%)	42 (54.5%)	45 (61.6%)

N: Total number of patients included and randomized
n: number of patients in each category
% = (n/N)*100

Demographic characteristics at baseline were generally well balanced between groups.
In the RS, patients had a mean age of 55.2 ± 10.1 years, with 34% aged 60 years or over.
All patients presented at selection an essential HT. The HT was reported in average since 7.7 ± 6.9 years.
Other personal medical histories in relation with HT reported were: dyslipidemia (32% of patients), cardiovascular disease (8.67%), diabetes mellitus (4.67%), dyslipidemia with a higher frequency reported in Group B than in Group A (29 patients [39.73%] versus 19 patients [24.68%], respectively); cardiovascular disease (5 patients [6.49%] in Group A versus 8 patients [10.96%] in Group B) reported with similar frequency in both treatment groups; diabetes mellitus reported with a higher frequency in Group A (5 patients [6.49%] in Group A versus 2 patients [2.74%] in Group B).
All patients received at least one treatment for essential HT started before inclusion, mainly agents acting on the renin-angiotensin system (98.7%) and diuretics (19.3%). 63 patients (42%) in the RS received anti-hypertensive monotherapy and 87 patients (58%) received dual anti-hypertensive before inclusion.
The supine SBP and DBP were at inclusion in average: 149.71 ± 5.09 mmHg and 94.92 ± 2.78 mmHg, clinically similar in both treatment groups. Standing SBP / DBP at 1 min and 3 min after standing up from supine rest were 149.1 ± 8.1 / 96.7 ± 7.5 and 148.6 ± 8.2 / 96.2 ± 7.5 respectively.
The supine HR in the RS was in average 72.84 ± 9.59 beats per minute (bpm) (ranging from 51.5 to 98 bpm).

EXTENT OF EXPOSURE
In the RS, treatment mean duration was 84.2 ± 7.3 days, ranging between 28 and 106 days (from W000 to W012). No relevant between-group difference was detected. The mean treatment compliance was good: 99 ± 2.3 % and all patients had an overall compliance between 80% and 120%.

EFFICACY RESULTS

- Office supine SBP/DBP: Change from baseline to last post-baseline value over the W000-W012 period

In the FAS, decrease in the **office supine SBP** was observed in both treatment groups from baseline to the last post-baseline value (LOCF). The changes were similar in both treatment groups: -22.01 ± 10.04 mmHg in S05166 Amlo/Biso/Per FDC group and -21.81 ± 9.41 mmHg in Amlo+Biso+Per free combination group.
A decrease over time was observed for office supine DBP in both treatment groups: -13.79 ± 7.47 mmHg in S05166 Amlo/Biso/Per FDC group and -15.06 ± 8.31 mmHg in Amlo+Biso+Per free combination group.
The results in the PPS were in the same line at W012(LOCF).

- Office supine SBP/DBP: Change from baseline to each post-baseline value at W004, W008 and W012

In the FAS, a decrease in the **office supine SBP and DBP** was observed in both treatment groups from baseline to each post-baseline value at W004, W008, W012 and W012 (LOCF), and results were similar in both treatment groups. The full effect on the office supine SBP and DBP was reached at W008 and maintained until W012.
Similar results were observed in the PPS.

- Response criteria for antihypertensive therapy

Response criteria were considered as rate of patients with supine BP normalized (SBP < 140 mmHg and DBP < 90 mmHg) and/or decrease of SBP ≥ 20 mmHg and/or decrease of DBP ≥ 10 mmHg from baseline, measured in supine position at W004, W008 and W012.
In the FAS, the rate of patients with supine BP normalized at the W004 visit was 72.73% in Group A and 84.51% in Group B. For visit W008, the rates were 92.11% in Group A and 95.77% in Group B. For visit W012 the rates were: 93.24% in Group A and 93.06% in Group B.
The response to the anti-hypertensive treatment at the last post-baseline value was observed for most of the patients in both treatment groups: 90.91% in Group A and 93.06% in Group B.
Similar results were observed in the PPS.

- Supine BP control rate

In the FAS, the control of the supine BP (defined as SBP < 140 mmHg and DBP < 90 mmHg) was obtained in the majority of the patients in both treatment groups, at each post-baseline value (at W004, W008, W012 and LOCF):

- W004: 62.34% in Group A and 74.65% in Group B.
- W008: 92.11% in Group A and 92.96% in Group B.
- W012: 91.89% in Group A and 87.5% in Group B.
- W012(LOCF): 89.61% in Group A and 87.5% in Group B.

Similar results were observed in the PPS.

SAFETY RESULTS

- **Main safety results - Safety Set (N=149)**

	S05166 Amlo/Biso/Per FDC (N = 77) n (%)	**Amlo+Biso+Per free combination (N = 72)** n (%)
Patients having reported at least one		
Emergent Adverse Event (EAE)	23 (29.9%)	27 (37.5%)
Treatment-related EAE	1 (1.3%)	5 (6.9%)
Hypotension	-	1 (1.4%)
Orthostatic hypotension		2 (2.8%)
Patients having experienced at least one		
Serious EAE (including death)	1 (1.3%)	-
Treatment-related serious EAE	-	-
Patients withdrawn due to		
EAE	-	1 (1.4%)
Serious EAE	-	-
Treatment-related EAE	-	1 (1.4%)
Treatment releated serious EAE	-	-
Patients who died	1 (1.3%)	-

31 EAEs were reported in 23/77 patients (29.9%) of the group A, and 30 EAEs were reported in 27/72 patients (37.5%) of the group B.
The SOCs most frequently affected were (clinically similar in both treatment groups) Infections and infestations (16 EAEs in 14 patients [9.4%]), Nervous system disorders (10 EAEs in 9 patients [6%]), Gastrointestinal disorders (6 EAEs in 5 patients [3.4%]), and Injury, poisoning and procedural complications (6 EAEs in 5 patients [3.4%]).

PTs of EAEs more frequently reported were:
- Headache (10 EAEs in 9 patients [6%]): 5 EAEs in 4 patients (5.2%) in Group A and 5 EAEs in 5 patients (6.9%) in Group B;
- Rhinitis (4 EAEs in 4 patients [2.7%]): 3 EAEs in 3 patients (3.9%) in Group A and 1 EAE in 1 patient (1.4%) in Group B.

These EAEs were not related to the study drug and occurred with different onset latency from the start of therapy.

Most of EAEs (65.57%) were mild in intensity: 67.74% of the total EAEs in Group A and 63.33% in Group B. The moderate EAEs were reported with a trend toward a lower rate in Group A (25.81%) than in Group B (36.67%).
The frequency of treatment related AEs tended to be greater in patients of the Amlo+Biso+Per free combination group as compared to the S05166 Amlo/Biso/Per FDC group: 5/72 patients (6.9%) and 1/77 patient (1.3%), respectively. EAEs considered as treatment-related according to the investigator's opinion, were in accordance with the known safety profile of the study treatments.
No treatment-related SAEs were reported.
Most of the EAEs were recovered without sequelae: 77.42% of the total EAEs in S05166 Amlo/Biso/Per FDC group and 99.67% in Amlo+Biso+Per free combination group. 6.45% of EAEs in Group A recovered with sequelae. 6.45% of EAEs in Group A were fatal. 3.23% of EAEs in Group A were recovering.

A total of 2 SAEs were reported in one patient in Group A: Road traffic accident and Injury (Trauma due to accident) and resulted in death. These two SAEs were not considered as treatment-related according to the investigator.

A particular focus was done on orthostatic hypotension, as it is an AE likely to occur with anti-hypertensive treatments. Three patients (4.17%) in Amlo+Biso+Per free combination group reported these EAEs (1 EAE of hypotension reported by 1 patient, and 2 EAEs of orthostatic hypotension reported by 2 patients) in the

Amlo+Biso+Per free combination group when no EAEs of hypotension were reported in the Amlo/Biso/Per FDC. All these EAEs were mild in intensity and resolved.

- **Laboratory tests**

For **biochemistry**, potentially clinically significant abnormal values (PCSA) were reported with a trend toward a lower frequency in Group B than in Group A.
Emergent PCSA **haematological** values were sparse in all groups and for each parameter and were reported with a trend toward lower in Group A than in Group B.
However, these results should be interpreted with caution due to low rate of patients presenting with PCSA values for biochemistry or hematology in both treatments groups (< 5% for each parameter).

- **Vital signs and ECG)**

A decrease of 6-7 bpm was observed at W004 and maintained until W012 in both treatment groups which was consistent with the known safety profile of the study treatments (bisoprolol).
Neither clinically relevant changes nor between-group difference over time were detected in body weight and physical examination.
None of the ECG abnormalities detected at post-baseline visit was considered as clinically significant by the investigator.

PATIENT REPORTED OUTCOME

A patient reported outcome, the TSQM-9 (Treatment Satisfaction Questionnaire for Medication) evaluated patients' treatment satisfaction at W012 (3 domains: Effectiveness, Convenience, and Global Satisfaction).

Characteristic	S05166 Amlo/Biso/Per FDC (N=73)	Amlo+Biso+Per free combination (N=69)
	TSQM-9: effectiveness	
Mean ± SD	72.755 ± 12.633	73.108 ± 12.111
Median	66.67	66.67
Min; Max	44.44; 100	50; 100
	TSQM-9: convenience	
Mean ± SD	78.463 ± 14.783	69.727 ± 13.012
Median	77.78	66.67
Min; Max	38.89; 100	33.33; 100
	TSQM-9: global satisfaction	
Mean ± SD	76.222 ± 13.886	76.709 ± 12.35
Median	78.57	71.43
Min; Max	42.86; 100	50; 100

Most of the patients were satisfied with the treatment in bot groups. A better convenience was observed for S05166 FDC group (78.463 ± 14.783) than for Amlo+Biso+Per free combination group (69.727 ± 13.012). No relevant between-group difference was detected for the results of the TSQM-9 questionnaire.

CONCLUSION

This randomized controlled phase III study aimed to evaluate the clinical effectiveness and safety of the FDC of Amlodipine 5mg/ Bisoprolol fumarate 5mg /Perindopril arginine 5mg in single-capsule (S05166) and of the free monocomponents, Amlodipine 5mg, Bisoprolol fumarate 5mg and Perindopril arginine 5mg given concomitantly, over 12 weeks, in patients having an uncontrolled HT defined by SBP ≥ 140 and < 160 mmHg and DBP ≥ 90 and < 100 mmHg under ongoing anti-hypertensive treatment (monotherapy at maximal dose or either by a dual therapy at minimum dose, other than study treatment).
Most of the patients in both treatment groups had their BP decreased, controlled and responded to the antihypertensive therapy.
The single-pill combination and the free triple therapy were well tolerated and the safety profile was in accordance with the SmPCs of amlodipine, bisoprolol and perindopril.
Most of the patients were satisfied with the treatment with similar results in effectiveness and global satisfaction in both treatment groups and with a better convenience for the patients exposed to the single pill combination.

Date of the report: 13 July 2021

Version of the report: 1.0