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Efficacy of Sevikar® compared to the combination of perindopril plus amlodipine on central arterial blood pressure in patients with moderate-to-severe hypertension: Rationale and design of the SEVITENSION study

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ABSTRACT

Background and rationale: To date, few studies have investigated the effects of combined renin-angiotensin system blockade/calcium channel blockade on central aortic blood pressure. The Conduit Artery Function Evaluation (CAFE) sub-study of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) investigated the effects of amlodipine/perindopril and atenolol/bendroflumethiazide on central aortic blood pressure (CABP). Similar brachial blood pressure levels were achieved; however, there was a significant difference, in favor of the amlodipine/perindopril combination, on the effects of CABP. No study has investigated the effects of a combination of an angiotensin receptor blocker/calcium channel blocker compared to those of a calcium channel blocker/angiotensin-converting enzyme inhibitor combination. To confirm and support previous findings, the SEVITENSION study will assess the effects on CABP of treatment with the high dose combination of perindopril plus amlodipine as used in ASCOT–CAFE compared with the high dose combination of olmesartan/amlodipine in patients with moderate-to-severe hypertension uncontrolled on amlodipine monotherapy.

Objective: To demonstrate non-inferiority of fixed-dose olmesartan/amlodipine combination therapy compared with the combination of perindopril plus amlodipine on the mean change from baseline in central aortic systolic blood pressure.

Design: A multicenter, double-blind, parallel-group, non-inferiority study comprising a 2–4-week open-label run-in period with amlodipine and a 24-week active treatment period. CABP will be measured by the SphygmoCor® Vx Pulse Wave Velocity System.

Patients: 720 moderate-to-severe hypertensive patients aged ≥40 to ≤80 years and ≥3 additional risk factors will be enrolled.

Interventions: Study treatment will comprise orally-administered combination of olmesartan/amlodipine (40/10 mg) or perindopril (8 mg) plus amlodipine (10 mg), and matching placebos. (EudraCT number: 2009-012966-30; ClinicalTrials.gov identifier: NCT01101009).

1. Introduction

The use of brachial BP measurement is based on the assumption that it accurately reflects the pressure in larger central arteries. However, pressure in the brachial and central arteries differs as systolic BP (SBP) and pulse pressure are amplified when pressure waves travel outwards from the aorta towards peripheral vessels [1,2].

Measurements of pulse wave velocity, a direct measure of arterial stiffness, show that central aortic BP (CABP) and brachial systolic and pulse pressures may differ considerably.

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CABP is affected by stiffening of the central arteries and may be a more direct reflection of loads imposed on the heart and cerebral arteries [3]. Furthermore, CABP may demonstrate a stronger correlation with organ damage and patient prognosis and be a stronger predictor of CV mortality and outcomes than brachial BP [3–6].

Despite producing similar changes in brachial BP, antihypertensive agents appear to differ in their ability to lower central BP [7–12], which may translate into differences in CV outcomes. Findings of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), demonstrated a reduced incidence of CV events, all-cause mortality and new-onset diabetes in patients who received the calcium channel blocker (CCB) amlodipine (5–10 mg) plus the angiotensin-converting enzyme inhibitor (ACEI) perindopril (4–8 mg) as required, compared with the β-blocker atenolol (50–100 mg) plus the thiazide diuretic bendroflumethiazide (1.25–2.5 mg) as required [13]. A sub-study of ASCOT, the Conduit Artery Function Evaluation (CAFE) study, investigated the effects of amlodipine–perindopril and atenolol–bendroflumethiazide on CABP and hemodynamics. Despite comparable brachial BP levels in the two groups, there were significant differences in the reduction of CABP, especially in the reduction of central aortic systolic pressure, which was significantly lower in the amlodipine–perindopril group [12].

To date, only a few studies have investigated the effects of combined renin angiotensin system (RAS) blockade/calcium channel blockade on CABP [8,10]. Furthermore, the implications of the differences between central and brachial pressures, and the use of tonometric CABP measurement as a tool for the management of hypertension have yet to be established [1].

Tolerability data from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) demonstrate that ARB (Angiotensin Receptor Blocker)-based combinations may be preferable to those based on an ACEI [14]. Combination therapy comprising the ARB olmesartan medoxomil plus amlodipine has been shown to effectively reduce BP and improve BP control in patients with mild-to-severe hypertension, including over 24 h [15–17]. To date, however, the effects of an ARB/CCB combination on CABP compared with those observed with the CCB/ACEI combination in ASCOT–CAFE have not been investigated.

To confirm previous findings, the efficacy of Sevikar® compared to the combination of perindopril plus amlodipine on central arterial blood pressure in patients with moderate-to-severe hypertension (SEVITENSION) study is being undertaken to assess the effects on CABP of treatment with the high dose combination of perindopril (8 mg) plus amlodipine (10 mg) used in ASCOT–CAFE compared with the high dose combination of olmesartan/amlodipine (40/10 mg) (Sevikar® [Daiichi Sankyo Europe]) in patients with moderate-to-severe hypertension and ≥3 additional risk factors whose BP is uncontrolled by amlodipine monotherapy.

2. Methods

2.1. Study design

The SEVITENSION study will be conducted in accordance with the principles specified in the Declaration of Helsinki, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines and the European Commission Directive, and all study participants will be asked to provide written informed consent.

Prior to study initiation, the study protocol, subject information and consent form, the respective Summaries of Product Characteristics, any written instructions to be given to the subject, available safety information, subject recruitment procedures, information regarding payments and compensation, and documented evidence of the Investigators' qualifications will be presented to the Regional Ethics Committees for ethical review and submitted for approval to the Independent Ethics Committee (IEC) according to local regulations.

2.2. Subjects

The multicenter, double-blind, parallel-group, non-inferiority SEVITENSION study will be conducted in approximately 20 centers in Spain. A total of 720 patients with moderate-to-severe hypertension are expected to undergo screening, with 576 patients randomized during an enrollment phase of approximately 24 months.

Male and female patients are being recruited if they fulfill the inclusion criteria: age ≥40–≤80 years at enrolment with moderate-to-severe hypertension defined as:

- For treatment-naïve patients, SBP ≥160 and ≤200 mm Hg or diastolic BP (DBP) ≥100 and ≤115 mm Hg.
- For inadequately controlled patients on current antihypertensive treatment, SBP ≥140 mm Hg or DBP ≥90 mm Hg.
- For inadequately controlled patients with diabetes or chronic kidney disease (CKD) on current antihypertensive treatment, SBP ≥130 mm Hg or DBP ≥80 mm Hg.

Furthermore, three or more additional risk factors should also be present, and these are listed in Table 1. The main study exclusion criteria are reported in Table 2. The selection criteria for the participating patients are as close as possible to those of the ASCOT–CAFE study to allow comparison of the results. As it is expected that the influence on CABP is a prognostic indicator for cardiovascular risk, the results obtained from this selective, high risk group of patients may provide some support for this hypothesis.

Table 1
Inclusion criteria–additional risk factors. (Patients will be required to have ≥3 additional risk factors to be eligible for inclusion.).

Age: male, >55 years; female, >65 years
Smoker (current or cessation for <1 year)
Dyslipidemia
Type 2 diabetes mellitus
Abnormal glucose tolerance test/increased fasting plasma glucose
Left ventricular hypertrophy
Cerebrovascular disease (ischemic stroke, cerebral hemorrhage, transient ischemic attack)
Heart disease (myocardial infarction, angina, coronary revascularization, heart failure)
Advanced retinopathy (hemorrhages/exudates, papilledema)
Atherosclerosis (including peripheral artery disease)
Renal disease (diabetic nephropathy, renal impairment, glomerular filtration rate <60 ml/min/1.73 m^2 or creatinine clearance <60 ml/min, microalbuminuria >30 mg/24 h, proteinuria >300 mg/24 h)

2.3. Open-label run-in phases

The study will commence with a 2–4-week open-label run-in period, consisting of two phases. As this study includes high risk patients, a placebo wash out is prohibited for ethical reasons. The run in phase is a stepwise, wash out phase for those patients who have been receiving antihypertensive medication other than amlodipine. During Run-in Phase I (Weeks −4 to −2), treatment-naïve or inadequately controlled patients on antihypertensive treatment other than amlodipine will receive orally-administered amlodipine 5 mg once daily for 2 weeks in addition to any existing antihypertensive treatment, with the exception of CCBs, which will be withdrawn. All patients who undergo Run-in Phase I will enter Run-in Phase II (Weeks −2 to 0), during which all other antihypertensive medication will be withdrawn and the dose of amlodipine increased to 10 mg orally once daily for a further 2 weeks. Prior to the run-in period, patients who are already receiving treatment with amlodipine 5 or 10 mg in combination with additional antihypertensive medication will directly enter Run-in Phase II and the additional antihypertensive medication will be withdrawn. Inadequately controlled patients receiving prior monotherapy with amlodipine 10 mg only will bypass the run-in period and enter active treatment directly.

Patients whose BP remains inadequately controlled on amlodipine 10 mg (defined as SBP ≥140 mm Hg [≥130 mm Hg for patients with diabetes or CKD], or DBP ≥90 mm Hg [≥80 mm Hg for patients with diabetes or CKD], based on conventional BP measurements) will enter Treatment Phase I (Weeks 0–4), and receive randomized treatment with either a fixed-dose combination of olmesartan/amlodipine (40/10 mg) or a combination of perindopril (8 mg) plus amlodipine (10 mg) once daily for 4 weeks.

2.4. Randomized, double-blind treatment phases

After the run-in period, patients will be randomly assigned to double-blind treatment with orally-administered once-daily olmesartan/amlodipine (40/10 mg) in a fixed-dose combination or perindopril (8 mg [2×4 mg]) plus amlodipine (10 mg), and matched placebos, during an active treatment period of 24 weeks (Fig. 1). Each blister comprises 28 tablets for seven days, i.e. every patient takes four tablets daily. Active olmesartan/amlodipine treatment comprises one olmesartan/amlodipine 40 mg/10 mg tablet, two placebo tablets matching perindopril 4 mg, and one placebo tablet matching amlodipine 10 mg. The corresponding blister with active perindopril and amlodipine consists of two perindopril 4 mg tablets, one amlodipine 10 mg tablet, and one placebo tablet matching olmesartan/amlodipine 40 mg/10 mg. Randomization will be performed independently using a randomized block design. If necessary after 4 weeks of active treatment, patients will receive once-daily open-label hydrochlorothiazide (HCTZ) 12.5 mg or, after 8 weeks, 25 mg to reach protocol-specific BP targets (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or CKD).

During Treatment Phase III (Weeks 8–12), those patients not yet receiving HCTZ and who have a conventional BP measurement of ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with diabetes or CKD) will commence HCTZ 12.5 mg add-on therapy for 4 weeks. Those patients already receiving HCTZ 12.5 mg will be uptitrated to HCTZ 25 mg. Patients reaching target BP will continue to receive the same dose of their study medication.

Finally, during Treatment Phase IV (Weeks 12–24), those patients not yet receiving HCTZ and who have a conventional BP measurement of ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with diabetes or CKD) will commence HCTZ 12.5 mg add-on therapy for a further 6 weeks. Those patients already receiving HCTZ 12.5 mg add-on therapy will be uptitrated to HCTZ 25 mg. Patients reaching target BP will continue to receive the same dose of their study medication, however, patients with BP measurements of ≥180/110 mm Hg, despite receiving HCTZ 25 mg, will be withdrawn from the study.

Table 2
Main exclusion criteria.

Secondary or malignant hypertension
Contraindication to any of the study medications
Creatinine clearance <40 ml/min
Patients receiving treatment with >3 antihypertensive agents
Myocardial infarction, percutaneous transluminal coronary angioplasty or cardiac bypass surgery <6 months prior to enrolment
Unstable angina pectoris
Stroke, transient ischemic attack or cerebrovascular surgery <3 months prior to enrollment
*Congestive heart failure (New York Heart Association [NYHA] classification II–IV)
Clinically relevant concomitant hematological, gastrointestinal, hepatic, renal, or other disease
History of alcohol or drug abuse
Pregnancy, women of childbearing potential without adequate contraceptive precautions for ≥3 months prior to enrollment, or nursing mothers

* The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Massachusetts: Little, Brown & Co; 1994:253–6.

2.5. Study assessment

2.5.1. Screening and study entry

After provision of written informed consent, a number of procedures will be performed during Run-in Phase I to determine a patient's eligibility for the study. These will include obtaining a medical history, performing a physical examination, laboratory assessments and 12-lead electrocardiogram (ECG), and checking vital signs and BP criteria.

Following study enrollment, assessments such as the evaluation of adverse events, vital signs and concomitant medication will be undertaken regularly at each visit.

2.5.2. Blinding and treatment compliance

The complete randomization code list was created before the study commenced by a data base manager of the entrusted CRO, who was not otherwise involved in the study, using an independent SAS, Proc PLAN and a ratio of 1:1 for the treatment groups. This list shows the relationship between the random number and treatment group. Based on this the study medication was labeled (coded) and emergency envelopes printed. The randomization code will be kept under safe conditions in an area with restricted access. All persons involved in the conduct of the study are kept blind to the treatment allocation. The block design enables treatment arms in each

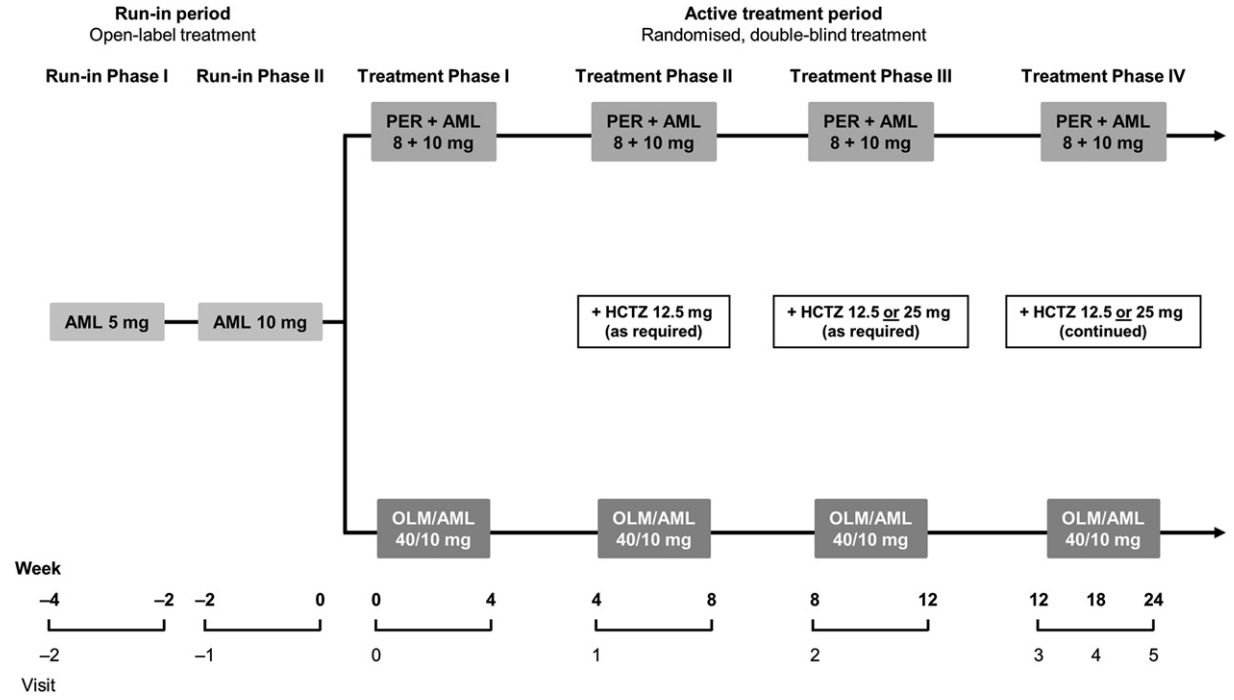

Fig. 1. Design of the SEVITENSION study. AML, amlodipine; HCTZ, hydrochlorothiazide; OLM, olmesartan; and PER, perindopril.

center to be balanced. Within a constant, default block size the random numbers will be assigned to treatment groups using a default ratio. The participating investigators will enroll patients using a sequence of random numbers, which are an integer multiple of the block size.

At each study visit, patients will receive medication sufficient to last until the next scheduled visit, during which they will be instructed to return any unused study medication dispensed at the previous visit for drug accountability as assessment of treatment compliance.

2.5.3. Measurement of CABP

Similarly to the CAFE sub-study of ASCOT, CABP will be measured by tonometry with the SphygmoCor® Vx Pulse Wave Velocity System by placing a Doppler probe over the radial artery. The Sphygmocor Software calculates central SBP, DBP and key heart function parameters deriving the calibrated BP wave form at the ascending aorta from a transcutaneous recording of the radial artery pressure wave form. Measurements will be performed at randomization (Week 0), Week 12 and at final examination (Week 24).

2.5.4. Measurement of brachial BP

Conventional trough SBP and DBP measurements over the brachial artery will be performed at each study visit (between 06:00 h and 11:00 h) using calibrated tensiometers (OMRON).

2.5.5. Ambulatory BP monitoring

Ambulatory BP (ABP) measurements will be performed at randomization and at final examination using standard measurement devices (Spacelabs) to record 24-hour BP profiles. Readings will be taken at 15-minute intervals during the daytime (between 06:00 h and 21:59 h) and at 30-minute intervals during the night-time (between 22:00 h and 05:59 h).

2.6. Study endpoints

2.6.1. Primary objective

The primary objective of the SEVITENSION study is to show non-inferiority of the fixed-dose combination of olmesartan/amlodipine 40/10 mg (Sevikar®) compared with the combination of perindopril (8 mg) plus amlodipine (10 mg) on the mean change in central aortic SBP from baseline (Week 0) to final examination (Week 24), based on a per protocol analysis using the last observation carried forward (LOCF) approach. As there is no experience of the effect of the fixed-dose combination of olmesartan/amlodipine on CABP measurements, a non-inferiority approach was chosen to determine the effects of treatment on this parameter.

The LOCF approach will be used for the per protocol set (PPS), that is patients without major protocol violations, as defined in the Statistical Analysis Plan (SAP). We expect to show an effect on CABP even if there are withdrawals or missing data for some patients since the per protocol definition will take account of this approach.

2.6.2. Secondary objectives

The secondary variables of SEVITENSION are as follows:

1) Changes in mean 24-hour, daytime and night-time systolic and diastolic ABP from baseline (Week 0) to final examination (Week 24).
2) Changes in mean seated brachial SBP and DBP from baseline (Week 0) to final examination (Week 24).

3) Changes in central aortic SBP from Week 12 to final examination (Week 24) in patients with stabilized BP (<140/90 mm Hg, or <130/80 mm Hg in patients with diabetes or CKD) between Week 12 and Week 18.
4) Changes in mean seated brachial SBP and DBP from Week 12 to final examination (Week 24) in patients with stabilized BP (<140/90 mm Hg, or <130/80 mm Hg in patients with diabetes or CKD) between Week 12 and Week 18.
5) The proportion of patients with controlled BP at final examination (Week 24) (defined as a brachial BP of <140/90 mm Hg, or <130/80 mm Hg in patients with diabetes or CKD).
6) The proportion of responders at final examination (Week 24) (defined as patients with controlled BP or a reduction in brachial SBP of ≥20 mm Hg or DBP of ≥10 mm Hg).
7) The relationship between mean seated brachial SBP, central aortic SBP and systolic ABP based on the changes in these parameters from baseline (Week 0) to final examination (Week 24).
8) The relationship between mean seated brachial DBP, central aortic DBP and diastolic ABP based on the changes in these parameters from baseline (Week 0) to final examination (Week 24).

The changes in BP between baseline and Week 24 for both treatment groups will be investigated to determine if these are comparable according to three methods of BP measurement (conventional, CABP and ABP).

2.6.3. Safety assessments

The safety and tolerability of each study medication will be assessed for the duration of the SEVITENSION study.

Information regarding AEs (Adverse Events— unexpected, expected and serious) will be collected and documented by the Investigator at each study visit by specific and non-specific questioning of patients, and AEs will be classed as mild, moderate or severe.

All AEs will be recorded and reported from the point of study initiation, including during the wash-out and run-in periods, until 2 weeks post-study termination. Serious AEs (SAEs) considered to be drug-related will be reported regardless of the time that has elapsed after study end.

Other assessments will include a complete physical examination undertaken at the first visit and at final examination, a 12-lead ECG performed at the first visit, and clinical laboratory assessments of hematology, biochemistry and urinalysis evaluated at the first visit.

3. Statistical methods

3.1. Determination of sample size

To achieve a statistical power of 90%, the sample size will assume a non-inferiority margin of 2.0 mm Hg (based on a one-sided *t* test and a significance level of 0.025) between the effects on mean change in central aortic SBP from baseline (Week 0) to final examination (Week 24) (LOCF approach) of olmesartan/amlodipine combination therapy and the combination of perindopril plus amlodipine, with a standard deviation of 7.0 mm Hg. Based on the assumption of a drop-out rate of 20% during the run-in period, a total of 720 patients will need to undergo Screening in order to achieve 576 randomized patients (288 patients per treatment arm). A total of 518 patients (259 patients per treatment arm) will remain in the PPS, assuming approximately 10% of major protocol deviations.

3.2. Statistical analysis

3.2.1. Analysis sets

The primary and secondary efficacy variables will be analyzed based on the PPS due to the non-inferiority study design. The use of well established compounds in this indication in both treatment arms is expected to show comparable anti-hypertensive efficacy. Based on experience of treating hypertension with ACE inhibitors and ARBs, and also in combination with other antihypertensive compounds, major imbalances resulting from premature termination or missing values due to e.g. adverse events, non-compliance, lack of efficacy, which may lead to implausible results by the described statistical methods are not expected. However, the main conclusions of the primary and secondary efficacy statistical analyses will be based on the PPS using the LOCF approach. The PPS will consist of all patients of the Full Analysis Set (FAS) without any major protocol deviations, which are defined as a lack of protocol compliance that interferes with efficacy assessment. Patients with major protocol violations will only be integrated in the Full Analysis (Observed Case [OC]) approach. Major protocol violations such as missing values, which are indispensable for the achievement of the primary objective, will be described in the SAP. Possible influence of age, sex, comorbidities and other known risk factors will be investigated as covariates in supportive/sensitivity analyses for the PPS (OC approach) and the FAS (LOCF and OC approaches) to gain insight into the robustness of the conclusions. In the case that there are relevant differences between the collectives this will be discussed in detail in the clinical study report.

Introduction of possible bias by the LOCF approach is not expected to affect estimation of the between-treatment comparison within the context of a randomized trial with active control.

The possible impact of various covariates will be investigated. The main model will be extended by baseline and post-baseline covariates e.g. the characteristics of central systolic BP in patients with stabilized BP values between weeks 12 and 18 (<140/90 mm Hg or <130/80 mm Hg for diabetics and chronic kidney disease). Results of these additional analyses and the impact of these covariates will be presented and discussed in detail in the clinical study report.

The FAS will be used to evaluate the robustness of the results for the primary and secondary efficacy parameters. The secondary parameter will be analyzed using the same analysis of covariance (ANCOVA) model, as used for the primary efficacy analysis, with the respective baseline values as covariates.

Any additional exploratory analyses of the primary and secondary variables will be performed on the PPS using an OC approach.

Safety analyses will be performed on Safety Sets 1 and 2, which are defined as all patients who receive at least one dose of open-label study medication and all randomized patients who

receive at least one dose of double-blind study medication, respectively.

3.2.2. Efficacy assessment

The primary objective of the SEVITENSION study is to show non-inferiority (one-sided, $\alpha = 0.025$) of olmesartan/amlodipine (40/10 mg) combination therapy compared with the combination of perindopril (8 mg) plus amlodipine (10 mg) using the change from baseline (Week 0) to Final Examination (Week 24) on central aortic SBP as the primary efficacy variable, based on the LOCF approach for the PPS.

Treatment with olmesartan/amlodipine (40/10 mg) will be considered non-inferior to perindopril (8 mg) plus amlodipine (10 mg) if the upper limit of the two-sided 95% CI for the difference in least squares means for the change from baseline of central aortic SBP between the two treatment arms is less than 2 mmHg. Additionally olmesartan/amlodipine (40/10 mg) will be considered superior to perindopril (8 mg) plus amlodipine (10 mg) if the upper limit of the 95% CI is <0 mm Hg.

Statistical analysis of the primary efficacy variable will be performed using the ANCOVA model with treatment as main effect and baseline central aortic SBP as covariate. Analysis of the secondary quantitative efficacy variables will also be performed using ANCOVA with the respective baseline values as covariates. The qualitative secondary efficacy variables will be analyzed by means of the χ^2 test.

If major deviations from parametric assumptions are detected the following tests will be considered for the primary efficacy analysis:

- G.G. Koch's non-parametric method to compare treatment groups.
- ANCOVA on the change in logarithmized CSBP. If this analysis is performed, exponentialized estimators of treatment effect (geometric means) and its 95% confidence interval will be displayed.

3.2.3. Safety assessment

AEs will be reported on a per-patient basis and these will be summarized for each treatment arm.

4. Study management

The conduct of this study will be monitored by APICES Soluciones, S.L. who will visit the sites at regular intervals throughout the study to verify adherence to the study protocol, completeness, accuracy and consistency of data, and adherence to ICH-GCP guidelines and local regulations. Data management will be performed by the CRO KantarHealth GmbH Munich (Germany) Daiichi Sankyo Europe will oversee the study by conducting regular co-monitoring visits at the study sites.

To ensure the quality of clinical data across all patients and sites, a Clinical Data Management review will be performed on subject data according to specifications provided by Daiichi Sankyo Europe, and data will be checked electronically and manually.

5. Discussion

Evidence suggests that CABP differs from conventional brachial BP. In particular, CABP is affected by the degree of stiffness of the large central arteries [3]. Therefore, in patients with hypertension, CABP may be superior to conventional brachial BP as a predictor of vascular damage basing on a loss of elasticity in the central artery. Therefore the confirmation of the clinical relevance of CABP as a prognostic indicator for cardiovascular risk factors and mortality in patients with hypertension is expected.

Furthermore, antihypertensive agents appear to have differential effects on central arterial stiffness, and therefore differ in their ability to reduce central aortic SBP and central PP. The findings of ASCOT and its sub-study CAFE demonstrate that this may translate into significant differences between treatments in their ability to reduce the risk of CV outcomes [12,13].

Since the ASCOT and CAFE studies have provided important information relating to CABP and CV risk, the aim of the SEVITENSION study is to show that the ARB/CCB combination of olmesartan/amlodipine (40/10 mg) is non-inferior to a combination of the ACEI perindopril (8 mg) plus amlodipine (10 mg) in terms of its effects on the stiffness of the large central arteries and, specifically, central aortic SBP. Therefore the inclusion criteria are as close as possible to those of the ASCOT–CAFE population as they seem to reasonably mirror a population with high CV risk. Identification of patients with possible prognostic factors resulting from CABP measurement may be beneficial. The results of the study may show the influence of possible differences in the populations, as the exclusion criteria were slightly less restrictive in the SEVITENSION study. Patients with myocardial infarction were only excluded if the event was within the last six months. Patients with unstable angina and congestive heart failure of NYHA II–IV were also excluded. There was no explicit exclusion criterion for patients with triglycerides ≥ 400 mg/dL; however patients with clinically relevant abnormal laboratory values, except those agreed as additional risk factors for inclusion criteria, were generally not accepted for participation in the study.

The rationale for comparing perindopril (8 mg) plus amlodipine (10 mg) and olmesartan/amlodipine (40/10 mg) is three-fold: perindopril (8 mg) plus amlodipine (10 mg) was the maximum dose of the RAS blocker/CCB combination used in the ASCOT study [13]; the use of perindopril (8 mg) plus amlodipine (10 mg) replicates the treatment used in ASCOT and CAFE, and this will enable simpler interpretation of the results of SEVITENSION; finally, the 40/10 mg formulation is the maximum permitted dose of the combination of olmesartan/amlodipine.

The SphygmoCor® device enables non-invasive measurement of CABP by analysis of radial pulse waveforms. Since this method has been validated independently [18] and used in previous clinical studies, including the CAFE sub-study of ASCOT and a study by Morgan et al. [11,12], it is rational to use this methodology in the SEVITENSION study.

The first patient entered the SEVITENSION study in April 2010, and the clinical phase of the study is expected to be completed by the end of 2012.. The primary results of SEVITENSION should become available by the middle of 2013.

It is expected that the SEVITENSION study will provide important insights into the vascular benefits of combined RAS blockade/calcium channel blockade with olmesartan/amlodipine in the management of hypertension. Furthermore,

confirmation of the clinical relevance of CABP as a prognostic indicator for cardiovascular risk factors and mortality in patients with hypertension is expected.

Conflict of interest

Dr Ruilope has served as an advisor and speaker for Daiichi Sankyo.

Dr Angie Schaefer is a current employee of Daiichi Sankyo Europe GmbH.

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