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PROTOCOL PAPER

Rationale and Design of the Efficacy and Safety of Esaxerenone in Hypertensive Patients With Left Ventricular Hypertrophy (ESES-LVH) Study

— Protocol for a Multicenter, Open-Label, Exploratory Interventional Study —

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Background: The complication of left ventricular (LV) hypertrophy (LVH) is associated with increased incidence of major cardiovascular events. Hypertension is an independent risk factor among several factors contributing to the development of LVH, and thus appropriate treatment of both hypertension and LVH reduces the risk of developing heart failure. Mineralocorticoid-receptor blockers (MRBs) have been reported to improve the prognosis of LVH, but use of currently available MRBs is limited by adverse events. Esaxerenone is a novel selective nonsteroidal MRB recently approved for treatment of hypertension. Although the renoprotective effect of esaxerenone has been demonstrated in both preclinical and clinical studies, little data is available in terms of its cardioprotective effects.

Methods and Results: This multicenter, open-label, exploratory interventional study was designed to evaluate the safety and efficacy of esaxerenone in combination with renin-angiotensin system (RAS) inhibitors or calcium-channel blockers (CCBs). Eligible criteria are hypertensive patients with LVH, and target blood pressure (BP) not reached with an RAS inhibitor or a CCB. The primary endpoints are change from baseline in seated home BP (early morning systolic/diastolic BPs), and change and %change from baseline in the LV mass index at the end of treatment.

Conclusions: This study will provide the first clinical evidence of the antihypertensive effect and safety of esaxerenone in hypertensive patients with LVH.

Key Words: Esaxerenone; Exploratory interventional study; Hypertension; Left ventricular hypertrophy; Mineralocorticoid-receptor blockers

In the Framingham Heart Study,[1] complication of left ventricular (LV) hypertrophy (LVH) was associated with increased incidence of major cardiovascular events such as ischemic heart disease, fatal arrhythmia, and sudden death. Among several factors contributing to the development of LVH, hypertension is an independent risk factor and approximately 40–60% of hypertensive patients have concomitant LVH.[2] The mechanism of cardiac hypertrophy induced by hypertension involves mechanical pressure overload caused by elevated blood pressure (BP), and neurohumoral factors centered on the renin-angiotensin system (RAS);[3] thus, appropriate treatment for hypertension inhibits the progression of cardiac hypertrophy and reduces the risk of developing heart failure.[4]

Regression of cardiac hypertrophy can be expected from continuous BP reduction by antihypertensive agents,[5] and

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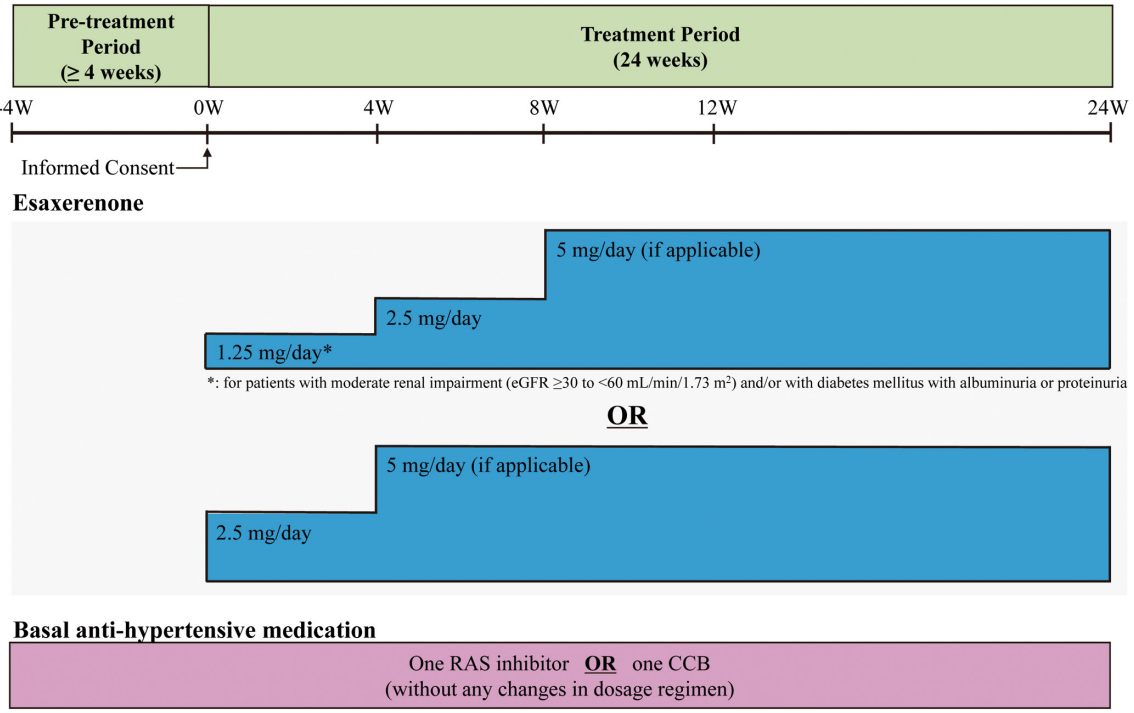

Figure. Study design. RAS inhibitor cohort (n=60): esaxerenone + RAS inhibitor; CCB cohort (n=60): esaxerenone + CCB. CCB, calcium-channel blocker; eGFR,estimated glemerular filtration rate; RAS, renin-angiotensin system.

RAS inhibitors and calcium-channel blockers (CCBs) have the most profound regressive effect of cardiac hypertrophy.[6] However, considering that the achievement rate for target BP in Japan is <40%,[7] these 2 drugs alone are insufficient to achieve the target BP in patients with cardiac hypertrophy. Furthermore, an aldosterone breakthrough phenomenon, in which blood aldosterone level initially decreases with dosing of RAS inhibitors and returns to or increases above the baseline through continuous dosing for 6–12 months, occurs with an incidence of ≥50% and eventually may be accompanied by LVH.[8]

Aldosterone not only adjusts BP through mineralocorticoid receptors (MRs) in the renal collecting duct, but also acts directly on the heart via MRs and enhances oxidative stress to provoke vasculitis and cause organ disorders such as fibrosis.[9] Thus, MR blockers (MRBs), which inhibit the action of aldosterone, have been used to treat hypertension and improve the prognosis of myocardial infarction and cardiac failure.[10] The Japanese Society of Hypertension (JSH) guidelines for the management of hypertension recommend combined use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), which are RAS inhibitors, and β-blockers or MRBs (spironolactone, eplerenone) as diuretics in patents with the complication of cardiac failure.[7] The RALES study, which investigated whether mortality risk was decreased by adding spironolactone to the standard of care treatment of patients with serious cardiac failure caused by LV failure, demonstrated that spironolactone improved the prognosis of cardiac failure.[11] Furthermore, studies in Japanese patients confirmed that concomitant use of MRBs with ACE inhibitors or ARBs achieved regression of cardiac hypertrophy.[12] Thus, cardioprotective effects are expected from MRBs prescribed as antihypertensive agents. However, spironolactone has low selectivity for MRs despite its potent inhibitory effect on them, and therefore is likely to cause side effects such as gynecomastia and menstrual abnormality via sex hormone receptors. Eplerenone has better selectivity in lieu of having relatively low potency against MR blockade, but it is contraindicated in hypertensive patients with moderate or severe renal impairment and in patients with diabetes mellitus-associated albuminuria.[13] For these reasons, currently available MRBs are impractical due to their side effects or contraindications.

Esaxerenone (CS-3150), a novel selective nonsteroidal MRB, was developed by Daiichi Sankyo Co., Ltd., and Exelixis, Inc.[13] In Japan, it was approved for the treatment of hypertension, and its pharmacological and clinical profiles, including renoprotective effects, have been well characterized.[13,14] However, even though its mechanism of action is expected to have cardioprotective effects such as cardiac hypertrophy regression,[9] little data is available compared with the renoprotective effects.

In this study, we examine the antihypertensive and LVH-regressive effects, and safety of esaxerenone in hypertensive patients with cardiac hypertrophy.

Methods

Study Design

The study is a prospective, multicenter, open-label, dose-

Table 1. Inclusion and Exclusion Criteria

Main inclusion criteria
(1) Age ≥20 years
(2) Hypertensive patients taking a RAS inhibitor or CCB at a fixed dosage regimen from 28 days or earlier before the start of esaxerenone administration, will be treated with esaxerenone if they meet the following registration criteria: **[Registration criteria]** Mean home BP values (early morning BP and bedtime BP) of systolic BP (SBP) and diastolic BP (DBP) measured in the past 7 days (at least 5 days) using an upper arm cuff sphygmomanometer are ≥135 to ≤159 mmHg, and/or ≥85 to ≤99 mmHg, respectively (2019 JSH guideline criteria), within 14 days before the start of esaxerenone administration
(3) Patients with LVH who meet any of the following criteria: • Thickening of the LV posterior wall or intraventricular septal wall of ≥12 mm on echocardiogram • LVH with Sv1 + Rv5 ≥35 mm on ECG • Patients with LVMI ≥125 g/m^2 for males and ≥110 g/m^2 for females
Main exclusion criteria
(1) Diagnosis of secondary hypertension (endocrine hypertension, preeclampsia, hypertension due to single kidney, etc.) or malignant hypertension
(2) With or have a history of orthostatic hypotension
(3) Cerebral cardiovascular disease that corresponds to any of the following: i) Patients who developed myocardial infarction, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or stroke of unknown type (TIA can be registered) within 6 months before written consent is obtained ii) Patients who have undergone PCI, CABG, ablation, etc. within 6 months before written consent is obtained iii) Patients scheduled to undergo PCI, CABG, ablation, etc. at the start of treatment iv) Patients with heart failure and LVEF has decreased to <50% v) Patients diagnosed with idiopathic cardiomyopathy vi) Patients with or have a history of congenital or rheumatic heart disease vii) Patients with unstable angina, severe arrhythmia (e.g., life-threatening refractory ventricular arrhythmias, arrhythmias with irregular R-R intervals such as sick sinus syndrome)
(4) Patients with symptoms or findings that are contraindicated in the package insert of esaxerenone (hyperkalemia, serum potassium level ≥5.0 mEq/L, severe renal impairment with eGFR <30 mL/min/1.73 m^2)
(5) Patients with type 1 diabetes

BP, blood pressure; CABG, coronary artery bypass grafting; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; JSH, The Japanese Society of Hypertension; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system; TIA, transient ischemic attack.

escalation, exploratory interventional study to evaluate the efficacy and safety of esaxerenone in combination with RAS inhibitors or CCBs, in hypertensive patients with cardiac hypertrophy who have had an inadequate antihypertensive response (**Figure**). Following the main purpose of the study, a comparison of the RAS inhibitor cohort and CCB cohort is not planned.

The study will consist of at least 4 weeks of pretreatment and a 24-week treatment period. Patients start esaxerenone at an initial dosage of 2.5 mg/day (1.25 mg/day for patients with moderate renal impairment, and/or diabetes mellitus with microalbuminuria or proteinuria). The dosage can be escalated to 5 mg/day (2.5 mg/day for patients with moderate renal impairment, and/or diabetes mellitus with microalbuminuria or proteinuria) at week 4. A subsequent dosage escalation to 5 mg/day esaxerenone occurs at week 8 only in patients who escalated to 2.5 mg/day esaxerenone at week 4. Dose escalation will be considered based on whether the patients have met the target BP defined in the JSH Guideline.[7] If the serum potassium level exceeds 5.0 mEq/L during treatment with esaxerenone, dose reduction should be considered; if it is ≥5.5 mEq/L, the dose should be reduced, or treatment withdrawn; if it is ≥6.0 mEq/L, treatment must be ceased immediately. During the study, basal antihypertensive medications (RAS inhibitor or CCB) are administered without any changes in dosage regimen. The intake timing of esaxerenone is not prespecified. The organization of the study is shown in the **Supplementary Table**. The study period will be March 2020 to October 2022.

All procedures will be conducted in accordance with the ethical principles of the Declaration of Helsinki and its amendments, and the Clinical Trials Act. In advance of commencement of the study, the ethical and safety aspects of the study plan and the protocol, and for informed consent were approved by the Kumamoto University Certified Clinical Research Review Board (approval no. CRB7180006). Written informed consent will be obtained from each patient prior to participation.

Eligibility Criteria

The study population is hypertensive patients with LVH who have been taking an RAS inhibitor or a CCB at a fixed dosage regimen from 28 days or earlier before the start of esaxerenone administration, and who have had an inadequate antihypertensive response. The main inclusion and exclusion criteria are listed in **Table 1**. To ensure enrollment of patients with LVH, the Echocardiographic Assessment Committee checks the echocardiographic data and reviews the results of analyses at each study institution.

BP Monitoring

Measurement of BP is performed twice, and the mean value is used as the value for early morning, bedtime, and office BPs, respectively. Home BP values are the mean of the past 7 days (at least 5 days). The measurement of home

Table 2. Study Procedures and Assessments

Procedures and assessments	Study period							
	Day 0	Week 2	Week 4	(Week 6)[a]	(Week 8)[a]	(Week 10)[b]	Week 12	Week 24
Informed consent	×							
Demographics and inclusion/exclusion criteria	×							
Enrollment	×							
Basal antihypertensive medication[c]	×	—	—	—	—	—	—	×
Esaxerenone administration	×	—	—	—	—	—	—	×
Esaxerenone dose increase decision			×		×			
Physical examination	×	×	×	×	×	×	×	×
Home blood pressure	×	—	—	—	—	—	—	×
Office blood pressure	×	×	×	×	×	×	×	×
Electrocardiography	×						×	×
Adverse events	×	—	—	—	—	—	—	×
Blood chemistry, hematology and urinalysis	×						×	×
Serum potassium/creatinine		×	×	×	×	×		
Clinical blood and urine markers[d]	×						×	×
Echocardiography	×						×	×
Vascular function evaluation[e]	×						×	×

[a]Applicable in the case of dose increase at week 4; [b]applicable in the case of dose increase at week 8; [c]renin-angiotensin system inhibitor or calcium-channel blocker; [d]N-terminal pro-B-type natriuretic peptide, C-reactive protein, plasma aldosterone concentration, plasma renin activity, urinary sodium, urinary potassium, albumin, creatinine, and urinary protein; [e]brachial-ankle pulse wave velocity and/or cardio-ankle vascular index.

Table 3. Primary Endpoints, Secondary Endpoints and Safety Evaluation

Primary endpoints
(1) Change from baseline in seated home BP (early morning SBP/DBP) at the end of treatment
(2) Change and %change from baseline in LVMI at the end of treatment
Secondary endpoints
(1) Change from baseline in seated home BP (early morning SBP/DBP) to week 12
(2) Change from baseline in seated BP (bedtime home SBP/DBP and office SBP/DBP) to week 12 and at the end of treatment
(3) Change over time in seated BP (early morning home BP, bedtime home BP, office BP: SBP, DBP, mean BP)
(4) Proportion of patients achieving target BP
(5) Change and %change from baseline in LVMI to week 12
(6) Changes from baseline in LVPWT to week 12 and at the end of administration
(7) Change and %change from baseline in vascular function evaluation (baPWV or CAVI) to week 12 and at the end of treatment
(8) Change and %change in myocardial strain
(9) Change from baseline in double product to week 12 and at the end of treatment
(10) Change from baseline in triple product to week 12 and at the end of treatment
(11) Change from baseline in heart rate variation coefficient to week 12 and at the end of treatment
(12) Changes over time, and change from baseline in urine and blood markers (N-terminal pro-B-type natriuretic peptide, C-reactive protein, plasma aldosterone concentration, plasma renin activity, urinary sodium, urinary potassium, albumin, creatinine, and urinary protein) to week 12 and at the end of treatment
Safety evaluation
(1) Adverse events, laboratory tests, vital signs (body temperature, pulse rate)
(2) Proportion of study subjects whose serum potassium levels are as follows:
≥5.5 mEq/L
≥6.0 mEq/L

baPWV, brachial-ankle pulse wave velocity; BP, blood pressure (DBP, diastolic blood pressure; SBP, systolic blood pressure); CAVI, cardio-ankle vascular index; LVMI, left ventricular mass index; LVPWT, left ventricular posterior wall thickness.

BP is instructed by the investigator and is performed by the patient or a family member using an upper arm cuff sphygmomanometer based on the cuff-oscillometric principle with the patient in a sitting position. Home BP is recorded in a BP diary. In order to encourage patients to record accurate BP values, the physicians will explain the importance of BP measurement when obtaining informed consent. Early morning BP is measured after 1–2 min of rest, within 1 h after arising and urination, before breakfast and taking any medicines. Bedtime BP is measured after

1–2 min of rest before going to bed, following at least 1 h after bathing and alcohol consumption. Office BP is measured in a seated position after a rest of at least 2 min at each standard clinic visit.

Ultrasonic Echocardiograms

Transthoracic echocardiography will be used to evaluate the degree of cardiac hypertrophy at baseline and after study treatment. Details are described in the **Supplementary Methods**.

Clinical and Biochemical Parameters

Details are described in **Supplementary Methods**.

Study Procedures and Assessments

Data will be collected every 12 weeks. Medication adherence, BP levels, and echocardiographic and laboratory data will be obtained at patients' visits of designated time points. Subjects will be instructed to maintain their normal lifestyle during the study period. Study procedures and assessment is detailed in **Table 2**.

Endpoints

Primary endpoints are (1) change from baseline in seated home BP (early morning SBP/DBP) at the end of treatment, and (2) change and %change from baseline in LV mass index (LVMI) at the end of treatment. Because BP-independent LVH reduction of MRBs has been reported in a variety of animal models,[15] and esaxerenone has high potency and selectivity for MRs compared with spironolactone and eplerenone in vitro,[13] the primary endpoints will be evaluated at week 24 considering the expected early onset of efficacy with esaxerenone based on the aforementioned reports. Secondary endpoints and safety evaluation are summarized in **Table 3**.

Sample Size

This study is not a confirmatory study but an exploratory study in patients in either a RAS inhibitor cohort or a CCB cohort (n=60 each, n=120 in total). Therefore, the sample size was determined not by statistical considerations but by practical considerations. Details of sample size, statistical analyses and data management are described in the **Supplementary Methods**.

Discussion

This is one of the first clinical studies to evaluate the efficacy and safety of a novel nonsteroidal MRB, esaxerenone, in clinical settings. This study will provide the first evidence on the antihypertensive and LVH-regressive effects as well as the safety of esaxerenone in hypertensive patients with LVH, who have not been studied in previous phase 3 clinical trials. The subjects are hypertensive patients taking an RAS inhibitor or a CCB as basal antihypertensive medication at a fixed dose for 28 days prior to the start of esaxerenone administration, and any change in the basal antihypertensive drug or its dose is not allowed during the study. Therefore, the efficacy and safety of esaxerenone should be clearly judged by the difference before and after its administration.

In the study, the primary endpoint is morning home BP, and the inclusion criteria are morning and bedtime home BP. It is known that the bedtime home BP value in Japanese is lower than that of the morning home BP because of lifestyle factors such as bathing and drinking,[7] as reported by the Ohasama study, which showed a difference of 10–20 mmHg.[16] In order to evaluate the antihypertensive effect of esaxerenone on home BP in Japanese, it is necessary to ensure the inclusion of hypertensive patients whose BP is not adequately controlled by either a RAS inhibitor or a CCB not only in the morning but also at bedtime. Therefore, we set the inclusion criteria to include not only morning home BP but also bedtime home BP. Morning and bedtime home BPs differ according to environmental and physiological conditions, and the JSH guideline states that they should be calculated independently because of their clinical significance.[7] Moreover, morning home BP is the time when antihypertensive drugs show their trough effect, and therefore is suitable for evaluating the persistence of drug efficacy. Hence, morning home BP is set as the primary endpoint and bedtime home BP as the secondary endpoint.

The limitation of the study is that it is a single-arm study. Thus, comparison with a historical control is necessary to elucidate the significance of the study. To clarify the differences between esaxerenone and existing steroidal MRBs such as spironolactone and eplerenone against the same patient background, the results of this study will need to be compared with those of for existing MRBs in hypertensive patients with cardiac hypertrophy. It is also necessary to compare the study with phase 3 trials of esaxerenone in patients with essential hypertension, hypertensive patients with moderate renal impairment, and hypertensive patients with diabetes mellitus accompanied by albuminuria. The comparison of studies with different patient backgrounds will clarify the significance of esaxerenone medication in hypertensive patients with cardiac hypertrophy.

Several studies have reported that combining a steroidal MRB with an ACE inhibitor or ARB has greater remarkable regressive effects on cardiac hypertrophy;[12] however, the number of such studies is few. Our present work will reinforce and confirm previous reports that the combination of MRB and an RAS inhibitor or a CCB exerts synergistic effects on LVH regression in hypertensive patients. If a regressive effect on LVH is demonstrated after concomitant use of MRB with an RAS inhibitor or a CCB, the study will have important clinical implications and will determine whether combination treatment is a promising therapeutic strategy for regression of LVH in hypertensive patients.

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Disclosures

K. Tsujita has received honoraria and grants from Daiichi Sankyo Co., Ltd. The remaining authors from Kumamoto University have nothing to disclose. T. Akasaka, K. Shiosakai and K. Sugimoto are employees of Daiichi Sankyo Co., Ltd.

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Certified Review Board Information

This protocol was approved by the Kumamoto University Certified Clinical Research Review Board (approval no. CRB7180006) and is

registered with the Japan Registry of Clinical Trials (jRCT ID: jRCTs071190043).

Data Availability

The datasets generated and/or analyzed during the current study will be available from the corresponding author and the study sponsor on reasonable request. The study results and findings will be disseminated in a peer-reviewed medical journal.

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Supplementary Files

Please find supplementary file(s);
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