서울아산병원 Asan Medical Center

서울아산병원 임상연구심의위원회(AMC IRB)/기관생명윤리심의위원회

Protocol ID:

Multicenter, randomized, double-blind, placebo-controlled, phase 3 study to assess the efficacy of ertugliflozin on reduction of mitral regurgitation in patients with functional mitral regurgitation (stage B and C) secondary to left ventricular dysfunction

Ertugliflozin **F**or **F**uncti**O**nal mitral **R**egurgi**T**ation

The EFFORT trial

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ABSTRACT

Objectives	To assess the efficacy of ertugliflozin on reduction of functional mitral regurgitation after 12 months of treatment
Study Design	Multicenter, randomized, double-blind, placebo-controlled trial
Study Subjects	Patients with left ventricular dysfunction and secondary functional mitral regurgitation of stage B and C
Treatment arms	1. Ertugliflozin 2. Placebo
Sample Size	128 subjects
Duration	12 months following randomization
Participating Center	Asan Medical Center, Seoul National University Hospital, Samsung Medical Center, Seoul National University Bundang Hostpital, Severance Hospital, Inha University Hospital
Primary Endpoint	Change of effective regurgitant orifice area (EROA) of functional mitral regurgitation from baseline to 12 months follow-up
Secondary Endpoints	Change of regurgitant volume from baseline to 12 months follow-up Change of left ventricular end-systolic volume from baseline to 12 months follow-up Change of left ventricular end-diastolic volume from baseline to 12 months follow-up Change of NT-proBNP (N-terminal of the prohormone brain natriuretic peptide) from baseline to 12 months follow-up Change of left atrial volume index from baseline to 12 months follow-up

1 Title and phase of trial

1.1 Title

Multicenter, randomized, double-blind, placebo-controlled, phase 3 study to assess the efficacy of ertugliflozin on reduction of mitral regurgitation in patients with functional mitral regurgitation (stage B and C) secondary to left ventricular dysfunction

1.2 Development Phase: Phase 3

2 Name and addressof center

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Kyung A Song: Pharmacologist

5 Sponsor address

: Not applicable for investigator initiated study

6 Study Purpose and Background

6.1 Study Purpose

The primary objective of the EFFORT trial is to assess the efficacy of ertugliflozin on reduction of functional mitral regurgitation (MR) after 12 months of treatment. The secondary objective is to examine whether ertugliflozin is effective in reversing left ventricular remodeling (LV) and to evaluate whether reduction of MR and reversal LV remodeling by ertugliflozin improves cardiovascular outcomes.

6.2 Background

In patients with heart failure (HF) and LV dilation, adverse LV remodeling causes tethering of mitral valve (MV) preventing sufficient coaptation of normal leaflets and resulting in functional MR (1-4). Because secondary functional MR usually develops as a result of LV dysfunction, guideline-directed medical therapy for HF forms the mainstay of therapy (5). However, beta blockers, angiotensin-converting-enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB) fail to reverse adverse LV remodeling and functional MR (6-7), and the morbidity and mortality of patients with functional MR remain high despite standard medical therapy (8-10).

A recent randomized trial (11) (GW Stone et al. COAPT trial. NEJM 2018) proved that reduction of functional MR by transcatheter MV repair resulted in a lower rate of hospitalization for HF and lower mortality in patients with HF and significant secondary MR, and we recently demonstrated that the angiotensin receptor-neprilysin inhibitor (ARNI) is more effective in improving functional MR associated with HF than the ARB in a double-blind, randomized trial (12) (Kang et al. Circulation. 2019 Mar). In our trial, we enrolled 118 stable HF patients with functional MR, whose effective regurgitant orifice area (EROA) larger than 0.1 cm^2, lasting > 6 months despite standard medical treatment, and the primary end point of change in EROA was significantly different between the ARNI group and the ARB group (-0.058±0.095 versus -0.018±0.105 cm^2; P=0.032), and a decrease in end-diastolic volume index of the LV was also significantly greater in the ARNI group than in the ARB group (P=0.044).

6.3 Result of precedent study

Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce cardiac preload and afterload by natriuresis and lowering arterial stiffness, similar to the neprilysin inhibitor that facilitates sodium excretion and has vasodilating effects (13-16). In addition, effects on blood pressure reduction and weight loss may ultimately have a beneficial effect on LV remodeling. Recently it has been reported that SGLT2 inhibitors have a multifaceted effect on cardiac function including improvement in endothelial dysfunction and aortic stiffness (17), reduction in epicardial fat accumulation (18) as well as in visceral adipocyte hypertrophy (19).

In a prospective multicenter trial of 58 type 2 diabetes patients with stable HF in Japan, LV mass index (31 to

26 mL/m^2, p=0.001) and LA volume index (75.0 to 67.0 g/m^2, p <0.001) were significantly reduced 6 months after the administration of dapagliflozin (20). There were also significant decreases in markers of LA and LV end-diastolic pressures such as E/e' (9.3 to 8.5 cm/s, p=0.020) and BNP (168.8 to 114.3 pg/mL, p=0.012) in patients with baseline BNP ≥ 100 pg/mL. This association between SGLT2 inhibitors and improvements of LV diastolic function and LV remodeling has been reported in other SGLT2 inhibitors (21, 22). In our previous trial with ARNI (12), we also found significant differences in changes in LA volume index, LV end-diastolic volume index and E/e', and association between changes in these parameters and improvement of functional MR. With these results, SGLT2 inhibitor is expected to have a favorable effect on LV and LA remodeling, and improve cardiovascular (CV) outcomes by decreasing functional MR.

A few randomized trials (23-27) to explore CV benefit of the SGLT2 inhibitor have been performed and showed a significant reduction on the risk of CV death or hospitalization for HF. However, its effect on cardiac structure and function was not evaluated and further mechanistic studies are needed to interpret beneficial clinical effects of the SGLT2 inhibitors. Based on studies demonstrating SGLT2 inhibitors' favorable effects on LV and LA modeling, we hypothesize that SGLT2 inhibitor, ertugliflozin, is effective on improving MR in patients with functional MR secondary to LV dysfunction and try to examine this hypothesis in a multicenter, double-blind, randomized comparison study using echocardiography.

7 Name and characteristics of drugs

1) Study drug and matching placebo

① Trade name: Steglatro

② Generic name: Ertugliflozin

③ Appearance

- **5 mg: pink color, triangular shape and film coated tablet**

④ Drug contains: same as approval

8 Study indication

Patients with left ventricular dysfunction and secondary functional and ischemic mitral regurgitation

9 Inclusion / exclusion criteria and study population

9.1 Inclusion Criteria

To be included, patients must fulfill ALL of the following:

Inclusion Criteria:	
1.	Patients must agree to the study protocol and provide written informed consent
2.	Outpatients ≥ 20 years of age, male or female
3.	Non-diabetic or type2 DM patients with HbA1c 7.0-10.5%
4.	Patients with secondary functional MR (stage B and C) and LV dysfunction • Symptoms due to coronary ischemia or heart failure may be present but symptoms due to MR should be absent • Normal mitral valve leaflets and chords • Regional or global wall motion abnormalities with mild or severe tethering of leaflet • MR whose ERO > 0.10 cm^2 and which lasted > 6 months under medical treatment with a β-blocker and an ACE inhibitor (or ARB) • 35% < LV ejection fraction < 50%
5.	Dyspnea of NYHA functional class II or III
6.	Titration of HF medications should be completed and patients must take a stable, optimized dose of a β-blocker and an ACE inhibitor (or ARB) for at least 4 weeks prior to study entry

9.2 Exclusion Criteria

Exclusion Criteria	
1.	History of hypersensitivity or allergy to the study drug, drugs of similar chemical classes, or SGLT-2 as well as known or suspected contraindications to the study drug
2.	Current use or prior use of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor
3.	Known history of angioedema
4.	Any evidence of structural mitral valve disease, including prolapse of mitral leaflets and rupture of chords or papillary muscles
5.	Current acute decompensated heart failure or dyspnea of NYHA functional class IV
6.	Medical history of hospitalization within 6 weeks

7.	Symptomatic hypotension and/or a SBP < 100 mmHg at screening
8.	Estimated GFR < 45 mL/min/1.73m^2
9.	History of ketoacidosis
10.	Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 2 x upper limit of normal (ULN) at screening visit (Visit 0), history of hepatic encephalopathy, history of esophageal varices, or history of portacaval shunt.
11.	Acute coronary syndrome, stroke, major CV surgery, PCI within 3 months
12.	Substantial myocardial ischemia requiring coronary revascularization, a plan of coronary revascularization or mitral valve intervention within 1 year
13.	Indication of cardiac resynchronization therapy, a plan of heart transplantation or implantation of cardiac resynchronization therapy
14.	History of severe pulmonary disease
15.	Significant aortic valve disease
16.	Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using a barrier method plus a hormonal method
17.	Pregnant or nursing (lactating) women
18.	Any clinically significant abnormality identified at the screening visit, physical examination, laboratory tests, or electrocardiogram which, in the judgment of the investigator, would preclude safe completion of the study
19.	History of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption

9.3 Sample size calculation and basis of sizing

9.3.1 Target subject number: 224

9.3.2 Basis of calculation

We would like to have 90% power to detect a 0.05 cm^2 difference in EROA at 12 months between ertugliflozin and placebo group. Using a two-sided *t*-test with an alpha level of 0.05, sample size of 204 or 102 patients per treatment arm is required. In our previous trial (Kang DH, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation, Circulation 2019;139:1354-1365), change in effective regurgitant orifice area was significantly greater in the ARNI group than the ARB group (–0.058±0.095 versus –0.018±0.105 cm2; P=0.032) and difference in change between the two groups was 0.040±0.019. Based on our previous trial, we assume that a common baseline mean value is 0.21 cm^2 and a common SD of the change from baseline is 0.11

cm^2 in both groups, and SD of the difference in change between the two groups is 0.019 cm^2. Assuming a dropout rate of 10%, the target number of patients to be randomized is 224.

COVID-19 pandemic seriously affected enrollment of study patients. Although the rate of patient recruitment was much lower than expected, the sponsor made a decision to adhere to the original study timeline and provide new study drug no longer in 2022. According to expiration date of supplied study drug, the Executive Committee decided to stop enrollment in December 2022 without knowledge of any trial data and the actual number of study patients was 128, smaller than the target sample size of 224 patients. Although the smaller actual sample size may result in an underpowered study to provide the hazard ratio, this trial is still expected to show significant differences in primary or secondary endpoints with careful assessment of outcomes and follow-up of all study patients.

10 Study timeline

On the basis of a lower than expected rate of patient recruitment and a limited supply of study drug, the Executive Committee finished enrollment in December 2022 without knowledge of any trial data. Overall study will require 38 months to complete, including 26 months of recruitment and 12 months of follow up and close out

- First patient in: November 2020
- Last patient in: December 2022
- Last patient out: December 2023
- First results available: March 2024

11 Trial Design

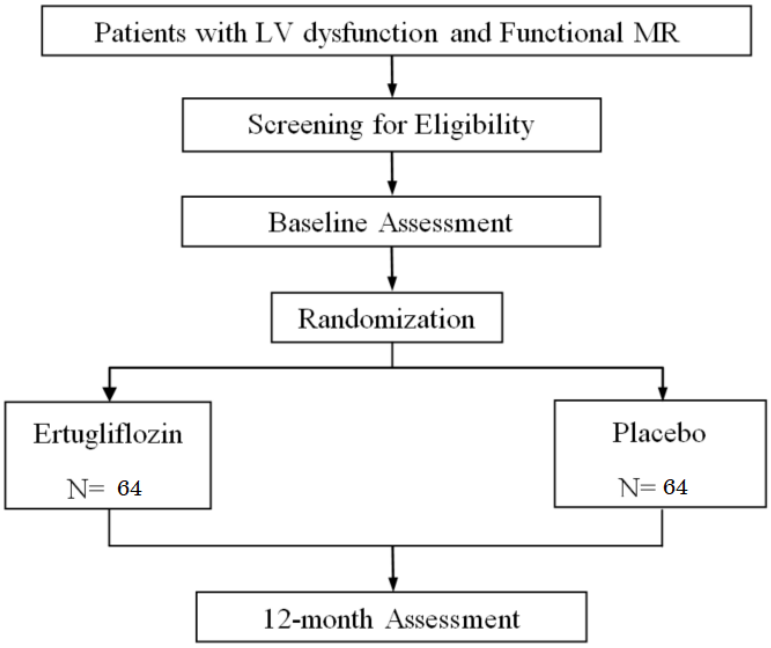
11.1 Study outline

This study is a prospective, multicenter, randomized, double-blind, two arm parallel group, placebo-controlled clinical trial involving patients with LV dysfunction and functional MR. Patients meeting inclusion criteria without any exclusion criteria will be randomized 1:1 to ertugliflozin 5mg or placebo therapy. Randomization will be stratified according to ischemic or non-ischemic cause of functional MR, presence of diabetes mellitus and cardiac rhythm, and the upper limit of randomized non-DM patients will be set as 90 patients (70%). The enrolment period was 26 months (n=128) and all patients will be followed for 12 months after randomization. Endpoints will be measured at 12 months. We design the protocol and conduct the trial in accordance with the principles of the Declaration of Helsinki, and the study protocol will be approved by the institutional review board (IRB).

11.2 Screening and recruiting protocol

The investigator at each clinical center will be responsible for case finding and subject recruitment. Echocardiographic studies performed as part of routine care before enrollment will be reviewed to determine if ERO of functional MR > 0.10 cm^2 and 35% < LV ejection fraction < 50% (inclusion criterion #4). For the purpose of screening, an echocardiogram performed within 24 months of enrollment, at a study center can be used. All eligible patients should be on standard medications for underlying heart failure (HF), which include an individually optimized dose of a beta-blocker and an ACE inhibitor (or ARB) at a stable dose for at least 4 weeks prior to study entry. After consultation with the patient's cardiologist, potential study participants will be approached about participation. At this time, a final determination about study eligibility will be made, and eligible patients will be asked to participate in the study.

Figure 1.Trial Flow



Primary end point: Change of effective regurgitant orifice area from baseline to 12 months follow-up

Secondary End Point: Change of regurgitant volume, end-systolic volume, end-diastolic volume, LA volume index, N-terminal of the prohormone BNP level, left ventricular global longitudinal strain from baseline to 12 months follow-up

11.3 Treatment

11.3.1 Investigational and Control Drugs

128 patients will be randomized at a ratio 1:1 to two arms:

a) Ertugliflozin

b) Placebo

All study patients will receive ertugliflozin or placebo in addition to their usual medications. Titration of HF medications should be completed and patients must take a stable, optimized dose of a β-blocker and an ACE inhibitor (or ARB) for at least 4 weeks prior to study entry.

The following doses of study drugs will be provided.

- ✓ Ertugliflozin 5mg qd or Placebo 5mg qd

11.4 Cautions for the prior and concomitant medications

① All study patients will receive ertugliflozin or placebo in addition to their usual prior medications. They will receive optimal medical treatment for their underlying disease such as hypertension, diabetes, arrhythmia and/or coronary artery disease.

② Any therapy started or stopped after randomization will be regarded as concomitant medications. All study patients will be educated to inform their concomitant therapy to the investigator before they start.

③ Hypoglycemia-associated agents, guanethidine, direct acting antiviral agents (HCV), alpha-lipoic acid, selective serotonin reuptake inhibitors, salicylates, prothionamide, pegvisomant, ,monoamine oxidase inhibitors, maitake, androgens (exceptions: danazol) may enhance the hypoglycemic effect of SGLT2 inhibitor.

④ SGLT2 Inhibitors may enhance the hypoglycemic effect of Insulins and sulfonylureas. Consider a decrease in insulin and sulfonylurea dose when initiating therapy with a sodium-glucose cotransporter 2 inhibitor and monitor patients for hypoglycemia.

11.5 Blinding and Unblinding Method

Investigational product will be administered in a double-blinded fashion. The identity of the treatment will be concealed by the use of study drugs that are identical in packaging, labeling, appearance and odor. Access to the randomization schedule and treatment codes will be maintained through the IWRS. Routines for this will be described in the IWRS user manual that will be provided to each site. All echo studies will be analyzed by core laboratory persons who will be blinded to treatment assignment. Patients and investigators will remain blind to the identity of treatment from the time of randomization until database lock. Treatment codes will not be broken

for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

In order to assure subject's safety, the study blind may be broken in emergency for the following reason:

1) in the opinion of the Medical Monitor and/or the PI, it is in the patient's best interest to do so

2) knowledge of the treatment will alter the clinical management of the patient

In the case of an emergency that requires unblinding, the Investigator can enter IWRS to unblind the patient without prior contact with the Medical Monitor although follow-up between the Investigator and Medical Monitor must occur so that all parties are aware of the unblinding. A series of questions must be answered to ensure that the Investigator does not accidently unblind a patient. Although it is recommended that the Investigator contact the Medical Monitor prior to unblinding any patient, in instances where this is not feasible or advisable the PI directly access the patient's treatment assignment using the IWRS. The emergency contact telephone number will be provided for each Medical Monitor.

12 Protocol Procedures

12.1 Measurement

Entry evaluation includes demographic data, medical history, clinical presentation, physical findings, medications, laboratory data and echocardiographic examinations. The blood test needs to be handled by each center's SOP t, and the collected blood does not require storage after analysis. The blood specimen handling and which collected for the study is responsible for the centers participated in the study All the specimens gathered for the study will be handled by the Experienced sonographers will perform comprehensive two- dimensional and Doppler echocardiographic examinations, and the pre-randomization baseline echo will be read by clinical site echocardiography investigator to assess the degree of MR which will determine echocardiographic eligibility for participation in the trial. After this initial assessment, the study echo will be sent to the Echocardiography Core Lab for centralized reading by a blinded investigator. Eligibility is determined after a patient undergoes a thorough evaluation of clinical and echocardiographic data. After the patient has signed informed consent, the randomization procedures will take place.

Each subject enrolled in the trial will be assigned a study identification (ID) number so that study information will be confidential. The link between subject name and ID number will be stored only at the site where the subject receives clinical care.

12.1.1 Schedule of Measurements

Visit number	**1**	**2**	**3**	**4**	**5**
Time of Visit*	**day 1**	**week 4**	**week 12**	**week 24**	**week 48**
Inclusion/Exclusion criteria	x				
Information & Informed consent	x				
Physical examination	x	x			x
Echocardiography‡	x				x
Dispense study medication	x		x	x	
Laboratory test†‡	x	x			x
Adverse events		x	x	x	x

* Time of visit: within +/- 7 days of the designated calendar day

** Visit 1, visit 5: CBC, blood chemistry, electrolytes, lipid battery, BUN, HbA1C, NT-pro BNP, Urine analysis, chest PA and EKG

Visit 2: CBC, blood chemistry and electrolytes, urine analysis

***Echocardiography and laboratory tests can be performed either on the day of visit 0 or within 30 days from visit 0.

12.2 Follow up: study patients will be follow up for 12 months after randomization

12.2.1 Clinical follow up

All subjects who participate in the study will be followed up in outpatient clinic on week 4, week 8, month 6 and month 12 after randomization. (All visits needs to be done within +/- 7 days of the designated calendar day). Investigator collects symptoms or clinical adverse events of the subjects and prescribes study drugs to them.

12.2.2 Echocardiographic follow up

Echocardiography will be performed on month 12(visit4) free of charge to all of the study patients.

12.2.3 Laboratory follow up

Laboratory tests include CBC, blood chemistry and urine analysis will be done on week 4(visit 1) and month 12(visit 4). Chest PA and EKG will be done on month 12(visit 4).

13 Risk benefit evaluation

13.1 Potential risk of the study participation

There are some risk or side effects that can be caused by study drug or for the consequence of blood sampling. Clinical trials have proven the safety and tolerability of ertugliflozin. The side effects of ertugliflozin is described below;

Genital mycosis, itching sense at the vagina, increased urine volume, thirsty, hypoglycemia, and weight loss at high doses. Even if it is very rare cases (0.1%), Ketoacidosis has been reported as a life threatening side effect. All the participants are required to be done the blood tests, echocardiography, and electrocardiogram at the beginning and the end of the trial period to evaluate the effects of treatment. The blood tests are performed in order to evaluate side effects of the study drug at the first month visit. Standard medical examinations are performed on every visit. Most significant discomfort which can be caused by participating in this study would be blood sampling. In rare cases, infection at the needle puncture site may occur. Blood collection is performed three times during the test. About 5 to 15 mL (1 to 3 teaspoons) of blood is taken depending on the type of laboratory test and it is required to monitor the safety and wellness of the subject. All collected samples are used only for the study purpose and are not stored and then discarded.

13.2 Potential benefit of the study participation

Up until now, there is no definitive drug treatment for functional mitral regurgitation, and furthermore, its effectiveness in surgical treatment is limited. On the other hand, ertugliflozin, a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, is a drug that is expected to have a therapeutic effect on left ventricular remodeling by reducing the preload and afterload of the heart through natriuresis. It can be expected to have a superior effect in improving functional mitral regurgitation compared to conventional heart failure medication if ertugliflozin has a therapeutic effect on left ventricular remodeling in patients with functional mitral regurgitation accompanied by left ventricular dysfunction.

Even if the subjects belong to the placebo group (control group), they continue to take the angiotensin receptor blocker (ARB), the medication which is expected to weaken left ventricular dilatation and remodeling, and the other treatments recommended within standard treatment for heart failure (beta blockers, diuretics) Etc.). Moreover the study team continues follow-up observations, so it is thought that it will be more advantageous in terms of long-term prognosis. Furthermore, the results of this clinical trial will contribute to the development of medical research both domestically and internationally.

13.3 Result of benefit analysis

The potential risk of the study is very low, and immediate action is possible even if it appears. It is thought that the benefit of participating in the study sufficiently outweight the risk since this study is expected to improve the long-term prognosis associated with cardiovascular complications in both the test and active control groups.

14 Predictable side effect and caution

The safety and efficacy of ertugliflozin have been studied in many present clinical trials, which reported side effects such as genitourinary fungal infection (females: 9% to 12%; males: 4%), headache (3% to 4%), hypovolemia (2% to

4%), hypoglycemia (3%), increased thirst (1% to 3%), weight loss (2%), severe hypoglycemia (1%), increased urine output (2% to 3%), vulvovaginal pruritus (2% to 3%), back pain (3%), renal insufficiency (1% to 3%), nasopharyngitis (3%). Increased LDL cholesterol, increased serum phosphate, decreased eGFR, increased serum creatinine, acute renal failure, increased hemoglobin, ketoacidosis, pyelonephritis, urinary tract infection, urinary tract infection with sepsis has been reported rarely.

15 Withdraw criteria

All patients have the right to withdraw at any point during the study without prejudice. The investigator may discontinue any patient at any time if medically necessary. However, it will be documented whether or not each patient completed the clinical study. If the study treatment(s) or observations are discontinued in any patient, the reason will be recorded and the executive committee must be notified promptly. It is imperative to obtain complete follow-up data for all patients, whether or not they receive their assigned treatment. Every attempt should be made to collect follow-up information, except for those patients who specifically withdraw consent for release of such information. All procedures and laboratory specimens or tests requested for evaluation following the assigned treatment should be carried out when possible, whether or not a patient continues to receive treatment according to the protocol. Patients will not be replaced in this trial.

1) Withdrawal of informed consent
2) Acute adverse drug reaction (ex. allergy, hypersensitivity to the drug)
3) Unable to continue participation due to unexpected medical illness
4) Any severe suspected drug-related adverse event
5) Not satisfactory to the inclusion/exclusion criteria
6) Any unexpected medical treatments or interventions that were performed during the trial without notice to investigators and have any possibility to affect the result of the trial.
7) Poor compliance to the investigator's request.
8) Pregnancy

16 Study Endpoint and data acquisition and analysis

16.1 Endpoint

16.1.1 Primary Endpoint

Change of effective regurgitant orifice area (EROA) of functional mitral regurgitation from baseline to 12 months follow-up

16.1.2 Secondary Endpoint

- Change of regurgitant volume from baseline to 12 months follow-up
- Change of left ventricular end-systolic volume from baseline to 12 months follow-up
- Change of left ventricular end-diastolic volume from baseline to 12 months follow-up
- Change of NT-proBNP (N-terminal of the prohormone brain natriuretic peptide) from baseline to 12 months follow-up
- Change of left atrial volume index from baseline to 12 months follow-up
- Change of left ventricular global longitudinal strain from baseline to 12 months follow-up

16.2 Echocardiographic Evaluation

Echocardiographic evaluation will be performed at baseline and 12 months follow-up. Echocardiographic evaluation should have a minimum window period of 6 weeks after discharge in patients hospitalized due to heart failure. Experienced sonographers who are unaware of the patients' clinical characteristics and treatment assignments will perform comprehensive two-dimensional and Doppler echocardiographic examinations. End-systolic dimension, end-diastolic dimension, end-diastolic interventricular septal and posterior wall thickness of the LV will be measured from parasternal M-mode acquisitions. End-systolic volume, end-diastolic volume and EF of the LV will be obtained using the biplane Simpson method. Incomplete leaflet closure area will be measured on apical 4-chamber view. Regional wall motion abnormalities will be analyzed using a 16-segment model. The following protocol is required for estimation of effective regurgitant orifice area and regurgitant volume (12).

Protocol for PISA (proximal isovelocity surface area) method

1. Optimize color flow imaging of mitral regurgitation from an apical window.
2. Expand the image by the zoom mode.
3. Shift the color flow zero baseline in the direction of flow to increase hemispheric PISA; the aliasing velocity should be set between 0.2 and 0.4 m/s.
4. Select the most satisfactory hemispheric PISA at mid-systole.
5. Record 3-5 cycle clip of PISA as well as still frame of an ideal PISA.
6. Measure the radius of the PISA at mid-systole from a frame with an ideal PISA.
7. Record a complete signal of the mitral regurgitation jet with continuous wave Doppler and capture a minimum of 3 consecutive cardiac cycles.
8. Measure the peak velocity and time-velocity-integral of the mitral regurgitation jet.

9. Determine EROA of the MR by dividing the regurgitant flow rate, calculated as $2\pi r^2 \times$ aliasing velocity, where r is the radius of PISA, by peak MR velocity.
10. Determine regurgitant volume by multiplying EROA by TVI of MR jet.

Echo study will be sent to the Echocardiography Core Lab for centralized analysis. The primary and secondary echocardiographic efficacy analyses will be done on off-line digital computerized review system by investigators who are blinded to treatment allocation and previous echocardiographic measures. Echocardiographic analyses will be done at baseline and 12 months.

16.3 Analysis of primary and secondary end point

All primary and secondary endpoints will be analyzed on an intention-to-treat basis (all patients analyzed as part of their assigned treatment group). For intention-to-treat analysis, all patients who sign the written informed consent form and are randomized in the study will be included in the analysis, regardless of whether or not they actually received the treatment to which they were assigned. The prespecified subgroups defined at baseline are ischemic versus nonischemic cause of functional MR, presence versus absence of DM, and sinus rhythm versus atrial fibrillation. The consistency of treatment effect will be assessed among prespecified subgroups with tests for interaction.

Baseline demographic and clinical variables will be summarized for each of the treatment groups. All continuous variables will be summarized as mean and SDs, or medians (with 95% confidence intervals [CIs]) as appropriate. Categorical variables will be summarized as frequencies and percentages and compared between treatment groups using chi-square test or Fisher's exact test.

The primary and secondary outcomes of this trial are the change of severity of functional MR and degree of left ventricular remodeling at 12 months after pharmacological treatment, assessed by EROA, regurgitant volume, LV end-systolic and end-diastolic volume and LV global longitudinal strain. The null hypothesis is that there is no difference in the EROA at 12 months after enrollment between patients treated with ertugliflozin compared to patients treated with placebo. The primary null hypothesis will be tested in an intention-to-treat analysis using a 0.05 level two-tailed t test if data are normally distributed, otherwise using the Mann-Whitney *U* test.

17 Participant Safety and Confidentiality

17.1 Guideline for safety evaluation

17.1.1 Definition

① Adverse event

For the purpose of this trial, an adverse event (AE) is defined as any untoward medical occurrence in a

patient enrolled in a clinical study and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational device or procedure.

② **Serious adverse event**

A SAE is any untoward medical occurrence that at any dose:

- results in death or is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or is otherwise a significant medical event.
- This includes any SAEs likely to arise from the trial indication or progression of underlying/concomitant illness (es) (e.g. progression of cancer in oncology trials), unless specified in the protocol as study specific exemptions.

③ **Unexpected adverse event**

Unexpected adverse event is defined as an event which occurred by the study drugs but differ from an expected side effect or severity according to medical information or investigator's brochure.

17.1.2 Evaluation guideline

① Intensity evaluation

Intensity of adverse event is evaluated

- Mild: the event may be noticeable to the subject. It does not influence daily activities, and usually does not require intervention
- Moderate: The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed
- Severe: The event may cause noticeable discomfort, and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

② Casualty evaluation

Casualty and severity are evaluated based on clinical decision of investigator. Causality of study drug cannot be ruled out when casualty is "possibly related" or "unknown, unassessable". Investigators

may use guideline below when he/she evaluates causality.

a. Definitely related

- Participant definitely took investigational medicinal product (IMP) and adverse event occurred after taking it.
- Adverse event is the most explainable with IMP administration
- Stopping IP is related to disappearance of AE
- Adverse event reappears with restarting IMP(when it is possible)

b. Probably related

- Participant definitely took IMP and adverse event occurred after taking it.
- Adverse event is the most explainable with IMP administration
- Stopping IMP is related to disappearance of AE

c. Possibly related

- Participant definitely took IMP and adverse event occurred after taking it.
- Adverse event is explainable with IMP administration but also with other possible cause.
- Adverse event disappears when stopping IMP

d. Probably not related

- Participant definitely took IMP.
- Other causes are more explainable than IMP administration.
- It is ambiguous that stopping IMP is related to disappearance of AE.
- It is ambiguous that restarting IMP is related to reappearance of AE.

e. Definitely not related

- Participant has never taken IMP.
- Occurrence of AE does not have sequential relationship to administration of IMP.
- There is other definite cause of AE.

f. Unknown, assessable

- There are not enough data to define relationship between AE and IMP.
- The data which is provided is low grade or inconsistent.

17.2 Method of evaluation

All kind of AEs observed during the trial should be recorded in EMR and CRF

17.3 Report of adverse event

17.3.1 Serious adverse event

Any SAE, and study drug misuse or abuse, irrespective of causality, occurring after the subject has provided informed consent and until four weeks after the subject has stopped study participation must be reported unless otherwise stated in the protocol. SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).In addition if required by the local health authority or ethics committee, the investigator should report appropriate safety information to the local health authority, the EC, DMC and the institutional review board at the study institution according to applicable law and regulations. Information about all SAE, misuse/abuse is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report Form in English, and send the completed, signed form with cover sheet to MSD Safety Desk. Any findings that might alter the current benefit-risk profile of the Study Drug or that would be sufficient to consider changes in the Study Drug's administration or in the overall conduct of the Study must be reported to MSD Safety Desk within 5 calendar days of becoming aware of such information.

17.3.2 Suspected unexpected serious adverse reaction

- Death or life threatening SUSAR: within calendar 7 days after learning of its occurrence
- Non-Fatal/LT SUSAR: within calendar 15 days after learning of its occurrence

Principle investigator and/or all other investigator must report SUSAR to IRB and KFDA. Investigator evaluate the event according to the IB to define weather the AE is expected or not.

17.3.3 Report to sponsor

All serious adverse events (SAEs) and study drug misuse or abuse from interventional clinical trials must be reported by the sites to Sponsor immediately after learning of its occurrence of the SAE. The timelines for investigator initiated trials reporting to MSD Safety Desk will be done as per Third Party Study/Investigator Initiated Trial Agreement within 15 day of learning by the investigator the SAE. The Cover Sheet must be submitted together with any individual safety cases to MSD.

17.3.4 Follow-up reports

SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome. The Sponsor shall support MSD in the following-up of all SAEs so that complete information is available to maintain patient safety and also as part of any commitments by MSD to any Health authority OR specific Health authority follow-up requests for the product under investigation.

17.3.5 Pregnancies

Any occurrences of a pregnancy in a patient (or a patients partner) during study participation will be collected. All pregnancies will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor, and the sponsor should forward that form to the local MSD Safety Desk according to agreed procedure with MSD within 15 days of learning by the investigator.

18 Elements of Informed Consent

We anticipate enrolling a total of 128 patients. We do not plan to enroll prisoners or institutionalized individuals due to logistical limitations in follow-up. Pregnant women and children are excluded from the trial for ethical and safety concerns.

Prior to collecting study data, the details of the study will be explained to the participant including: (1) that the study represents a research effort, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) any anticipated costs to the patient for participation, (4) potential risks and benefits for participation, and (5) contact information for additional concerns. Patients are informed of the purpose of the study, the treatment alternative, the random manner of assignment to treatment, the need to be available for telephone follow-up and return clinic visits at regular intervals for questionnaires and/or medical tests, and of their options to accept or refuse entry into the study without affecting their clinical care.

All sources of research materials will be in the form of medical records, echocardiograms, electrocardiograms and routine blood work. This material will be obtained both for routine medical care as well as for research purposes. In informed consent, we outline the potential risks, protection from these risks and potential benefits according to past experience and present knowledge. Informed consent will be obtained at least just before the subsequent randomly assigned procedure is to be performed. Part of the IRB/EC approval must include approval of an Informed Consent text

specific to the study. The investigator must administer this approved Informed Consent text to each prospective study patient and obtain the patient's signature on the text prior to enrollment in the study.

✓ Informed consent form is attached.

19 Insurance

Refer to attached insurance policy

20 Treatment of participant after termination of trial

The participants will be followed up and treated after termination of study according to therapeutic regimen of heart failure with functional/ischemic MR. Investigator need to guide the subject who is excluded from study or not respond to study drug to a proper treatment. Moreover, the subject is able to get a proper treatment after termination of study to prevent prolonged adverse event.

21 Ethics and Good Clinical Practice

The sponsor and investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the “Declaration of Helsinki” and with the laws and regulation of the country in which the research is conducted.

Investigators must have full understanding upon study drug and evaluate patient’s condition to decide whether the subject is eligible to the study. Moreover investigators are obligated to do their best to protect participants’ safety and right. Practically, the investigator will emphasize to the participants about the importance of informing investigator when they have any adverse event to protect safety. Especially after randomization, the investigator may stop the trial when he/she thinks this trial is harmful for the patient and lead him to a proper treatment. In addition, investigator will treat the subject properly until he/she recovers from an adverse event.

22 Study Organization

22.1 Executive Committee (EC)

The Executive Committee will approve the final trial design and protocol. Because of significant delay in enrollment of study patients and limited supply of study drug, this committee decided to stop enrollment in December 2022 without knowledge of any trial data. This committee will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications. Members of the committee will include the PI and persons who will organize this study.

22.2 Data Monitoring Committee (DMC)

An independent Date Monitoring Committee will review data periodically throughout the study and will have the ability to recommend stopping the study for safety and efficacy at any time. Details will be defined in the DMC charter.

22.3 Echocardiography (Echo) Core Lab

All echocardiograms will be performed according to a standardized protocol and will be centrally analyzed by the Network Echo Core Lab directed by Duk-Hyun Kang, MD, located at the Asan Medical Center.

22.4 Early Stopping Guideline

The IRB will be powered to recommend suspension of enrollment or termination of the study based on safety concerns. This study will not be stopped early based on efficacy results.

23 Publication Policy

No results will be released publicly before completion of the final analysis regarding the primary endpoint of this study. The statistical analysis will be performed according to the prespecified analysis plan as described in this protocol. The Executive Committee will review the primary outcome data according to the prespecified statistical analysis plan, and then will provide the data to the principal investigator which will in turn (a) first prepare a formal presentation to the Executive Committee members and (b) after taking under account the input and comments of the Executive Committee will proceed with submitting the manuscript .No study results will be released to the scientific or lay community without the approval of the Executive Committee. Authorship of the primary outcome paper will be credited collectively to the "Investigators."

24 Miscellaneous

24.1 Regulation

This study will be conducted in compliance with the protocol, local regulations where applicable, the International Conference on Harmonization (ICH) GCP guidelines and the Declaration of Helsinki.

24.2 Protocol adherence/compliance and amendment

The investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol and GCP requirements.

Any changes in protocol should be discussed with investigator and sponsor before it made. Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by IRB prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients

may be implemented before IRB approval even at this case immediate report to IRB should be made as soon as possible. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, study timing, etc.

24.3 Quality control and reliability assurance

Investigators and staffs should hold initiation meeting before starting the trial. A discussion about protocol, trial process, filling up CRF and et cetera will be done at this meeting. That investigator who could not participate at this meeting must be trained properly by principle investigator or who is delegated to.

24.4 Essential documents and retention of documents

Each investigator must maintain the following accurate, complete, and current records relating to the conduct of the investigation. Essential document are defined as documents which enables partial or overall evaluation and reconstruction of trial performance and its recording. Essential documents include all kinds of worksheet, source documents, all correspondence with another investigators and IRB and regulation documents and so on. All recordings need to be filed up including records of each subject's case history, study-required Case Report Forms, evidence of informed consent, all relevant observations of adverse drug effects, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, and the date of each study treatment.

Original data recording should be kept for source documents. All kinds of source documents, CRF and other trial related documents should be kept at site. Investigator should store all the documents until KFDA inspection after KFDA inspection, documents can be transfer to proper storage. Documents should be stored for 3 years after closure of study (studies for permission of articles should store them 3 years form permission).

24.5 Maintenance of data confidentiality

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study. However, authorized regulatory officials will be allowed full access to the records. Only initials and unique patient numbers in case report forms will identify patients. All medications provided and patient bodily fluids and/or other materials collected specifically for this trial shall be used solely in accordance with this protocol.

24.6 Reports

Below is a list of the reports which are the investigator's responsibility to generate. The table also shows to whom the report is to be sent and with what frequency or within what time constraints.

Reports Required from Clinical Investigators:

Type of Report	**Prepared by Investigator For:**	**Time Constraints of Notification**
Serious adverse event	IRB/EC	Per local regulations.
Annual progress report	EC	Submitted per 6 months.
Deviations from investigational plan	IRB/EC	Per local standard.
Informed consent not obtained	IRB	Notify within 5 days.
Final summary report	EC	Within 1 month.

24.7 Risk Management

The executive committee (EC) plays key roles in detecting any hazards the study may pose for its participants. Also, an independent Data Monitoring Committee (DMC) will review safety data and analyze efficacy periodically and may recommend stopping the study for safety and efficacy concerns at any time. Data are routinely collected and regularly monitored to document morbidity and mortality associated with study. Serious adverse events are reported to the EC and DMC within 24 hours. Timely reports will be made to the IRB. The IRB is responsible for advising early termination of the trial in the event if there are non-rectifiable, serious safety and efficacy concerns.

Appendix

List of Committee and Participating Center

	Center	Investigators
Executive Committee	Asan Medical Center	Duk-Hyun Kang, MD
		Jong-Min Song, MD
	Samsung Medical Center	Seung Woo Park, MD
		Sung-Ji Park, MD
	Severance Hospital	Suk-Min Kang, MD
	Inha University Hospital	Sung-Hee Shin, MD
	Seoul National University Hospital	Hyung-Kwan Kim, MD
	Seoul National University Bundang Hospital	Yeon-Yee Youn, MD
Participating Center	Asan Medical Center	Duk-Hyun Kang, MD
	Samsung Medical Center	Seung Woo Park, MD
	Severance Hospital	Geu-Ru Hong, MD
	Inha University Hospital	Sung-Hee Shin, MD
	Seoul National University Hospital	Hyung-Kwan Kim, MD
	Seoul National University Bundang Hospital	Yeon-Yee Youn, MD
Data Monitoring Committee	Asan Medical Center	Kee-Joon Choi, MD
		Ki Byung Nam, MD
		Ki Hoon Han, MD
		Joon Kim, MD

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