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Study Design and Protocol for a Randomized Controlled Trial to Assess Long-Term Efficacy and Safety of a Triple Combination of Ezetimibe, Fenofibrate, and Moderate-Intensity Statin in Patients with Type 2 Diabetes and Modifiable Cardiovascular Risk Factors (ENSEMBLE)

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Background: Atherogenic dyslipidemia, which is frequently associated with type 2 diabetes (T2D) and insulin resistance, contributes to the development of vascular complications. Statin therapy is the primary approach to dyslipidemia management in T2D, however, the role of non-statin therapy remains unclear. Ezetimibe reduces cholesterol burden by inhibiting intestinal cholesterol absorption. Fibrates lower triglyceride levels and increase high-density lipoprotein cholesterol (HDL-C) levels via peroxisome proliferator-activated receptor alpha agonism. Therefore, when combined, these drugs effectively lower non-HDL-C levels. Despite this, few clinical trials have specifically targeted non-HDL-C, and the efficacy of triple combination therapies, including statins, ezetimibe, and fibrates, has yet to be determined.

Methods: This is a multicenter, prospective, randomized, open-label, active-comparator controlled trial involving 3,958 eligible participants with T2D, cardiovascular risk factors, and elevated non-HDL-C (≥100 mg/dL). Participants, already on moderate-intensity statins, will be randomly assigned to either Ezefeno (ezetimibe/fenofibrate) addition or statin dose-escalation. The primary end point is the development of a composite of major adverse cardiovascular and diabetic microvascular events over 48 months.

Conclusion: This trial aims to assess whether combining statins, ezetimibe, and fenofibrate is as effective as, or possibly superior to,

statin monotherapy intensification in lowering cardiovascular and microvascular disease risk for patients with T2D. This could propose a novel therapeutic approach for managing dyslipidemia in T2D.

Keywords: Diabetes mellitus, type 2; Statin; Ezetimibe; Fibric acids; Dyslipidemias; Cardiovascular diseases

INTRODUCTION

Type 2 diabetes (T2D) is a progressive metabolic disorder that poses a significant risk for both microvascular and macrovascular complications [1]. Altered lipid metabolism in T2D, coupled with insulin resistance, manifests as elevated triglycerides (TGs), low high-density lipoprotein cholesterol (HDL-C), and an increase in small dense low-density lipoprotein particles, significantly contributing to the development of diabetic vascular complications [2,3]. Non-HDL-C levels, encompassing the atherogenic properties of circulating lipoproteins [4], emerge as a robust predictor of atherosclerotic cardiovascular disease (ASCVD), comparable in strength with low-density lipoprotein cholesterol (LDL-C), particularly in individuals with atherogenic dyslipidemia [5,6]. Current guidelines for dyslipidemia management endorse non-HDL-C levels as an alternative treatment goal for lipid management to reduce cardiovascular risk [7,8].

Ezetimibe primarily reduces the serum concentration of LDL-C by inhibiting cholesterol absorption from the intestine via blockade of the Niemann-Pick C1-like 1 protein [9]. Fenofibrate activates peroxisome proliferator-activated receptor-α [10], resulting in reduced TG and elevated HDL-C levels [11]. These drugs effectively lower non-HDL-C levels, and their combined effects are particularly potent [12-14]. Additionally, they offer multiple potential benefits for patients with T2D. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) highlighted significant cardiovascular benefits of ezetimibe in patients with T2D [15,16]. The randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease (RACING) trial demonstrated that a moderate-intensity statin plus ezetimibe combination was not inferior to high-intensity statin therapy in reducing cardiovascular events in patients with ASCVD [17,18]. Fenofibrate exhibits various beneficial effects on diabetic microvascular complications, including diabetic retinopathy and nephropathy, beyond its lipid-modifying effects [19-22].

Microvascular complications in T2D pose considerable health and economic burdens comparable with cardiovascular complications [23,24]. Recognizing dyslipidemia as a significant risk factor for both microvascular and macrovascular complications [25], the comprehensive objective of managing dyslipidemia in T2D is better aligned with the prevention or delay of all forms of vascular complications.

Therefore, this study aims to investigate the impact of a triple combination of ezetimibe, fenofibrate, and statins on microvascular and macrovascular endpoints in patients with T2D.

METHODS

Study design and overview

The Ezefeno (Hyundai Pharm, Seoul, Korea) dual or statin monotherapy for patients with type 2 diabetes and modifiable cardiovascular risk factors (ENSEMBLE) is an investigator-initiated, registry-based, pragmatic, multicenter, prospective, randomized, open-label, active comparator-controlled trial. This study was designed to compare the effects of triple combinations of ezetimibe, fenofibrate (administered as a fixed-dose combination, Ezefeno) and moderate-intensity statin versus statin monotherapy intensification on microvascular and cardiovascular outcomes in patients with T2D whose non-HDL-C was inadequately controlled with moderate-intensity statin. The primary objective of the study is to demonstrate a non-inferiority for incidence of predefined major adverse cardiovascular events and diabetic microvascular events in triple combination therapy group compared to high dose statin group. If non-inferiority is established, superiority of the triple combination therapy over high dose statin therapy will be determined under a gatekeeping procedure.

Fig. 1 illustrates the overall scheme of the study. The study protocol received approval from the Institutional Review Board of Korea University Anam Hospital (IRB number: 2023AN0429) and independent ethics committees at each site. The study protocol adheres to the principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. This trial was registered at ClinicalTrials.gov (registration no. NCT06293417).

Study population

The study participants will be recruited from 37 tertiary medical centers in South Korea. Eligible participants are adults (aged ≥

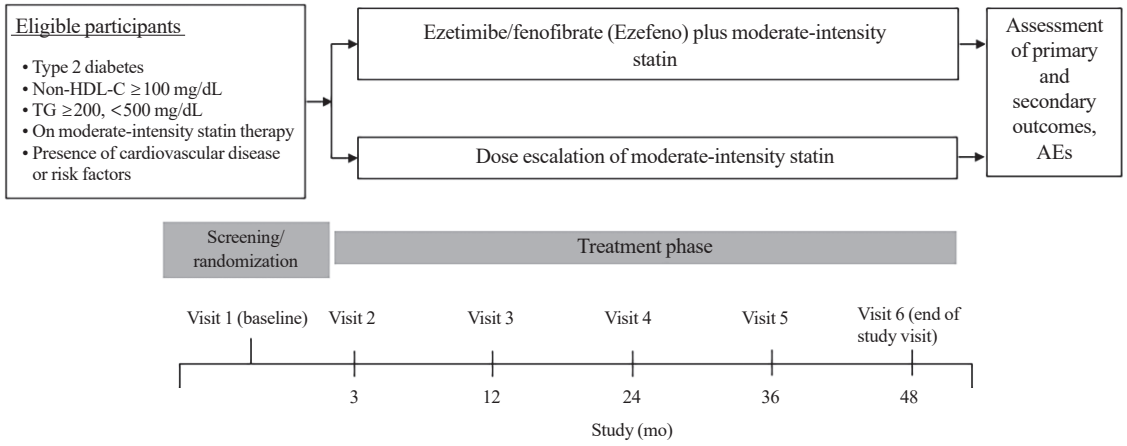

Fig. 1. Overall study design. HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; AE, adverse event.

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria
Patients diagnosed with type 2 diabetes according to American Diabetes Association criteria
Age ≥19 years
Non-HDL-C ≥100 mg/dL, TG ≥200, <500 mg/dL on moderate-intensity statins
Presence of cardiovascular disease or at least one of cardiovascular risk factors[a]
Exclusion criteria
Pregnant or breastfeeding women
Uncontrolled hyperglycemia (HbA1c >12.0%)
Serum creatinine >2.5 mg/dL or eGFR <30 mL/min/1.73 m^2
Gall bladder disease, myopathy, or rhabdomyolysis requiring treatment
Elevated liver enzymes (AST, ALT) >3 times the upper normal limit
Hypersensitivity to study drugs

HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]Cardiovascular diseases include coronary artery disease, ischemic stroke, transient ischemic attack, carotid artery disease, and peripheral artery disease. Cardiovascular risk factor includes abdominal aortic aneurysm, duration of diabetes ≥10 years, age (men ≥45 years, women ≥55 years), family history of premature atherosclerotic cardiovascular disease, hypertension, smoking, low HDL-C level (<40 mg/dL), albuminuria, chronic kidney disease (eGFR <60 mL/min/1.73 m^2), retinopathy, neuropathy, left ventricular hypertrophy.

19 years) with T2D who have a history of ASCVD or at least one of cardiovascular risk factors. Key inclusion criteria include a non-HDL-C level of ≥100 mg/dL, TG level of ≥200, <500 mg/dL on moderate-intensity statins. Further details on key inclusion and exclusion criteria are presented in Table 1.

Randomization

Participants meeting the eligibility criteria will undergo randomization into either the triple combination therapy or statin monotherapy intensification group in a 1:1 ratio. Randomization will be stratified based on the participating centers, and an interactive web response system provided by a central randomization service will be utilized.

Study procedures

The overall timetable of this study is presented in Table 2. During the initial visit, comprehensive data collection will be undertaken, encompassing demographic information, medical and medication history, physical examination, electrocardiogram, and laboratory tests (including hematology, blood chemistry, urinalysis, and lipid profile). The laboratory tests will be conducted on the basis of each participating center. Following a

Table 2. Timetable of the Study

Variable	Screening/ baseline[a] (visit 1)	Randomization	Visit 2 (3 mo)	Visit 3 (12 mo)	Visit 4 (24 mo)	Visit 5 (36 mo)	Visit 6 (48 mo)
Visit windows, day			±1 mo	±3 mo	±3 mo	±3 mo	±3 mo
Written informed consent	X						
Demographics[b]	X						
Physical examination	X						
Vital sign	X		X	X	X	X	X
Past medical history	X		X	X	X	X	X
12-lead ECG	X		X	X	X	X	X
Inclusion/exclusion criteria	X						
Randomization to treatment groups		X					
Laboratory test[c]	X		X	X	X	X	X
Assessment of trial outcomes/adverse events	X		X	X	X	X	X

ECG, electrocardiogram.
[a]Screening procedure and baseline measurements are conducted on the same day; [b]Demographic information includes age, date of birth, sex, height, weight, waist circumference, smoking history, alcohol consumption, and physical activity level; [c]Laboratory tests including hematology (red blood cell count, white blood cell [WBC] count, hemoglobin, hematocrit, platelet, WBC differential count, high-sensitivity C-reactive protein), blood chemistry tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, creatinine phosphokinase, total bilirubin, creatinine), urinalysis (pH, specific gravity, protein, WBC), urine albumin/creatinine, blood glucose test (glycosylated hemoglobin, fasting plasma glucose, fasting insulin), lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol [HDL-C], triglyceride, non-HDL-C) will be measured at the site visits or recorded from electronic medical records.

meticulous review of inclusion and exclusion criteria, eligible participants will be randomly assigned to one of the following groups:

• Group 1: will receive two tablets of the test drug (moderate-intensity statin+Ezefeno).

• Group 2: will receive one tablet of the active control drug (involving moderate-intensity statin dose escalation).

Throughout the trial, patient medical and medication histories, trial endpoint occurrences, and any adverse events (AEs) will be thoroughly assessed at each scheduled visit. Any events corresponding to pre-specified primary or secondary endpoints will be recorded. In line with the pragmatic nature of registry-based trials, participant electronic medical records and a nationwide medical registry provided by the National Health Insurance Service will also be utilized for assessing outcome measures. This approach will provide some benefits including profound retention of study subjects, detection of events occurred in other sites but not included in this trial, substantially low costs, and future long-term follow-up of the study cohort.

Two committees will be established to ensure a comprehensive evaluation of study end points and safety, each assigned distinct roles and responsibilities: the Adjudication Committee will comprise independent experts convened to assess and make decisions regarding critical events or outcomes within the clinical trial. These experts will remain blinded to the treatment assignments and results allocated to the participants. The Data and Safety Monitoring Board (DSMB) serves as an independent data monitoring committee with the primary responsibility of regularly evaluating the progress of the trial, data safety, and relevant evaluation variables. Its role extends to advising the investigator on key decisions, such as the continuation, modification, or termination of the trial.

Outcomes

The primary endpoint of the trial is the composite of major adverse cardiovascular or microvascular events within a 48-month period. Major adverse cardiovascular events include nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, heart failure, or peripheral artery disease, transient ischemic attack, coronary or peripheral revascularization (endovascular or surgical), and death from cardiovascular causes. Microvascular events include renal events (a sustained decline in estimated glomerular filtration rate [eGFR] of ≥40% from baseline, development of macroalbuminuria, onset of end-stage

kidney disease [dialysis for ≥28 days, kidney transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2], and death from renal causes) and retinopathy events (development of proliferative diabetic retinopathy, development of macular edema, blindness due to diabetic retinopathy, and surgical treatment of diabetic retinopathy [laser photocoagulation, vitrectomy, intravitreal injection therapy]). Death from renal causes is defined as death due to end-stage kidney disease.

Key secondary endpoints were (1) a composite of key adverse major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, death from cardiovascular causes, hospitalization for heart failure); (2) a composite of key adverse renal events (a sustained decline in eGFR of ≥40%, onset of end-stage kidney disease, death from renal causes); (3) death from any causes. Additional secondary endpoints include the percentages of participants maintaining non-HDL-C ≤100 mg/dL and LDL-C ≤70 mg/dL during the trial period, as well as mean changes in non-HDL-C, LDL-C, HDL-C, TG, LDL-C/HDL-C ratio, and total cholesterol (TC)/HDL-C ratio during the trial period.

Safety

An AE is defined as any unfavorable and unintended medical occurrence, encompassing signs, symptoms, or diseases in a study participant. AEs of special interest include myalgia, myopathy, myonecrosis, and acute kidney injury. Treatment-emergent adverse events (TEAE) refer to AEs either absent before medication or pre-existing events worsening in intensity or frequency post-treatment.

Throughout the study period, investigators will be recording AEs and TEAEs. The intensities of AEs and TEAEs will be categorized as mild, moderate, or severe based on factors such as frequency, duration, and tolerability of the signs or symptoms. Additionally, medical judgment will be employed to assess the relationship, considering all relevant factors.

Statistical consideration

The primary objective of this trial is to assess the noninferiority of the incidence of the composite of major adverse cardiovascular events or microvascular events within 48 months following randomization in the triple combination therapy group compared with the statin monotherapy intensification group. The primary efficacy analysis will utilize the confidence interval (CI) of the difference in incidence between the groups. Noninferiority will be determined by assessing the incidence difference and its confidence limits. The null hypothesis posits that the incidence difference is greater than or equal to the specified noninferiority margin ($\delta \geq 0.03$), whereas the alternative hypothesis sets that the incidence difference of the triple combination therapy group versus the statin monotherapy group is <0.03.

The selected noninferiority margin ($\delta = 0.03$) was established considering a 2% incidence difference observed in the IMPROVE-IT study, a 1% difference of composite of major adverse cardiovascular events during the 3-year follow-up RACING study, and clinical judgment favoring a broader primary composite of major adverse cardiovascular or microvascular events in this trial. Notably, a Korean targeted RACING study observed a 9% incidence of major adverse cardiovascular events after a 3-year follow-up in the moderate-intensity statin group. In this trial, participants will undergo follow-ups for up to 4 years, assuming a 10% incidence in the high-dose statin monotherapy group. An interim analysis, utilizing a group sequential design, is scheduled upon completing 50% of the intended follow-ups. To maintain an overall one-sided 2.5% significance level for multiple testing, the upper bounds of the 99.48% and 95.2% CI for the incidence difference will be compared with the noninferiority margin in the interim final analyses [26].

The estimated patient count was determined considering various factors, including the noninferiority margin, number of interim analyses, incidence in the control (monotherapy) group, significance level (type I error), power of the primary comparison (type II error), and dropout rate. Both interim and final analyses utilize O'Brian-Fleming boundaries, leading to a sample size inflation factor of 1.008 [26]. Assuming a noninferiority margin of 3% and a 10% incidence in the control group, a minimum of 3,958 participants (1,979 participants per group) were required to achieve 80% power in concluding the noninferiority of the triple combination therapy group over the monotherapy group at an overall one-sided 2.5% significance level. This calculation considers a 20% dropout rate and accounts for the sample size inflation factor.

In both interim and final analyses, if the noninferiority of the triple combination therapy group compared with the control group is confirmed for the primary efficacy endpoint, an additional assessment for the statistical superiority of the triple combination therapy group will be carried out. If both noninferiority and superiority are confirmed during the interim analysis, the possibility of early termination based on efficacy considerations may be considered, aligning with the recommendations of the DSMB. However, a futility analysis was not performed for the interim analysis.

For the secondary efficacy endpoints, the comparison between study groups regarding the percentages of participants maintaining non-HDL-C ≤100 mg/dL and LDL-C ≤70 mg/dL throughout the trial period will be assessed using the chi-square test or Fisher's exact test, as appropriate. Additionally, changes in non-HDL-C, LDL-C, HDL-C, TG, LDL-C/HDL-C ratio, and TC/HDL-C ratio will be evaluated using a mixed model for repeated measures (MMRM), followed by contrast tests for further analysis.

Safety evaluations of the triple combination therapy group will be compared with that of the monotherapy group in terms of AE and TEAE. Special attention will be given to the proportion of patients experiencing myalgia, myopathy, myonecrosis, and acute kidney injury in each treatment group. Comparisons of these proportions between groups will be conducted using the chi-square test or Fisher's exact test, as appropriate.

Furthermore, the MMRM method will be employed to compare mean differences in repeatedly measured laboratory test results both between and within groups. The test results will be categorized as normal, non-clinically significant abnormal, or clinically significant abnormal. Differences in proportions between groups and changes within groups will be assessed using the generalized estimating equation method.

The trial is not blinded concerning triple combination therapy or monotherapy. However, blinding will be maintained for all investigators, members of the coordinating center, operations committee, steering committee, event adjudication committee, and the sponsor with respect to treatment-level analyses of efficacy and safety. Access to the randomization code and treatment-related event information will be restricted to the DSMB and DSMB-associated biostatistician exclusively.

Following the intention-to-treat principle, all study endpoints will be examined using a full analysis set (FAS) population. This includes all randomized patients who received the study medication at least once, excluding those who did not undergo efficacy evaluation at all. Efficacy endpoints will also undergo analysis using a per-protocol set (PPS) population, encompassing all patients in the FAS population whose primary efficacy endpoints were observed according to the protocol without major violations. Instances of protocol violations will be identified during the analysis population review meeting before database locking. The safety set (SS) population consists of all participants who received at least one dose of the trial drug. Analyses of both primary and secondary endpoints will be carried out using both the FAS and PPS populations, with the conclusion of the trial based on the analysis results of the FAS. The SS population will be utilized for the analysis of safety endpoints.

No imputation for missing data will be performed for primary efficacy and safety endpoints, with the exception of the analysis of secondary efficacy endpoints using the FAS population, where last-observation-carried-forward imputation will be applied. All statistical analyses will be performed at a two-sided 5% level of significance, except for the evaluation of noninferiority in the primary efficacy endpoint, which will use a one-sided 2.5% level of significance.

DISCUSSION

To the best of our knowledge, the ENSEMBLE trial represents the first large-scale outcome trial to investigate the efficacy and safety of a triple combination of statins, ezetimibe, and fenofibrate in patients with T2D and cardiovascular risks. The primary focus of this trial is to compare the effects of triple combination therapy with intensified statin therapy on the development of both microvascular and cardiovascular events. A unique aspect of the trial is its primary outcome—a composite of adverse cardiovascular and microvascular events—which implies a potential shift in the perspective regarding the ultimate goal of dyslipidemia management in T2D. Although ASCVD remains a major health concern and leading cause of death in individuals with T2D, an increasing number of patients are experiencing and suffering from microvascular complications [27,28]. Given the scarcity of clinical evidence on whether dyslipidemia management truly contributes to the reduction of microvascular events in T2D, this trial aims to provide essential data on the microvascular effects of different dyslipidemia management approaches. Additionally, the trial will compare the safety and compliance of the two treatment strategies.

Undoubtedly, statin therapy remains the cornerstone of dyslipidemia management for individuals at risk of ASCVD, including those with T2D. However, a substantial risk of ASCVD persists even with appropriate statin therapy [29]. Moreover, achieving target LDL-C levels with optimal statin treatment poses a challenge in clinical practice [30,31]. In South Korea, despite the widespread use of statins, only 55.2% of individuals with T2D and ASCVD reach their target LDL-C levels [32]. Various factors contribute to this, including misunderstandings about statin therapy, side effects, and non-adherence or treatment intensification issues [33-36]. The combination of statins and ezetimibe has been proposed as a plausible strategy for stricter LDL-C management, potentially improving treatment compliance [37-39]. Additionally, concerns persist about resid-

ual cardiovascular risk even after effective LDL-C management. Elevated TG levels have emerged as potent markers of residual cardiovascular risk [40,41]. Although fenofibrates failed to further reduce cardiovascular risk when added to statin therapy in cardiovascular outcome trials [42], there remains a possibility of cardioprotective effectiveness in individuals with atherogenic dyslipidemia [43-45].

Therefore, we hypothesized that co-administering fenofibrate and ezetimibe would yield clinical benefits for patients still deemed at a high residual risk despite ongoing statin treatment. Ezefeno is a fixed dose drug combination of fenofibrate and ezetimibe, facilitating the formation of triple combination therapy with statins more conveniently. Given the low incidence of side effects associated with fenofibrate and ezetimibe, coupled with their potential advantages in addressing microvascular complications, we anticipate that this treatment strategy may offer a more promising option than statin intensification therapy.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception or design: K.C.W., Y.S.C., S.G.K. Revision of study protocol: N.H.K., J.L., S.C., J.M.Y., I.K.J., S.L., W.J.K., K.S., H.C.C., H.M.Y., K.A.K., S.S.K., S.H.L., C.H.K., S.H.K., Y.L., C.H.C., S.L., H.Y.J., J.H.L., G.K., S.Y.K., J.K., J.H.L., T.N.K., H.J.J., J.H.L., J.H.J., H.J.Y., H.K.K., H.K.P., I.S.N.G., S.H., C.W.A., J.H.Y., J.H.P., K.G.P., C.H.P., K.H.J., O.H.R., K.Y.P., E.G.H., B.S.C., K.C.W., Y.S.C., S.G.K. Drafting the work or revising: N.H.K., J.L., K.C.W., Y.S.C., S.G.K. Final approval of the manuscript: K.C.W., Y.S.C., S.G.K.

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