



Available online at  
**ScienceDirect**  
 www.sciencedirect.com

Elsevier Masson France  
**EM|consulte**  
 www.em-consulte.com



Original article

## Efficacy and safety of enavogliflozin versus dapagliflozin added to metformin plus gemigliptin treatment in patients with type 2 diabetes: A double-blind, randomized, comparator-active study: ENHANCE-D study

Kyung-Soo Kim<sup>a</sup>, Kyung Ah Han<sup>b</sup>, Tae Nyun Kim<sup>c</sup>, Cheol-Young Park<sup>d</sup>, Jung Hwan Park<sup>e</sup>, Sang Yong Kim<sup>f</sup>, Yong Hyun Kim<sup>g</sup>, Kee Ho Song<sup>h</sup>, Eun Seok Kang<sup>i</sup>, Chul Sik Kim<sup>j</sup>, Gwanpyo Koh<sup>k</sup>, Jun Goo Kang<sup>l</sup>, Mi Kyung Kim<sup>m</sup>, Ji Min Han<sup>n</sup>, Nan Hee Kim<sup>o</sup>, Ji Oh Mok<sup>p</sup>, Jae Hyuk Lee<sup>q</sup>, Soo Lim<sup>r</sup>, Sang Soo Kim<sup>s</sup>, Tae Ho Kim<sup>t</sup>, Kyu Chang Won<sup>u</sup>, Ki Young Lee<sup>v</sup>, Jae Hyoung Cho<sup>w</sup>, Ju Young Han<sup>x</sup>, So Hun Kim<sup>y</sup>, Jae Jin Nah<sup>z</sup>, Hwa Rang Song<sup>z</sup>, Si Eun Lee<sup>z</sup>, Sungrae Kim<sup>A,\*</sup>, for the ENHANCE-D Investigators<sup>a</sup>

<sup>a</sup> Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea

<sup>b</sup> Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University, Seoul, Republic of Korea

<sup>c</sup> Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea

<sup>d</sup> Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

<sup>e</sup> Department of Internal Medicine, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea

<sup>f</sup> Department of Internal Medicine, Chosun University Hospital, Chosun University School of Medicine, Gwangju, Republic of Korea

<sup>g</sup> Department of Internal Medicine, BunDang JeSaeng general Hospital, Seongnam, Republic of Korea

<sup>h</sup> Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Republic of Korea

<sup>i</sup> Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

<sup>j</sup> Department of Internal Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea

<sup>k</sup> Department of Internal Medicine, Jeju National University College of Medicine, Jeju, Republic of Korea

<sup>l</sup> Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Republic of Korea

<sup>m</sup> Department of Internal Medicine, Keimyung University School of Medicine, Dongsan hospital, Daegu, Republic of Korea

<sup>n</sup> Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea

<sup>o</sup> Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea

<sup>p</sup> Department of Internal Medicine, Soonchunhyang University Hospital Bucheon, Bucheon, Republic of Korea

<sup>q</sup> Department of Internal Medicine, Myongji Hospital, Goyang, Republic of Korea

<sup>r</sup> Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

<sup>s</sup> Department of Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea

<sup>t</sup> Department of Internal Medicine, Seoul Medical Center, Seoul, Republic of Korea

<sup>u</sup> Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Republic of Korea

<sup>v</sup> Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea

<sup>w</sup> Department of Internal Medicine, The Catholic University of Korea Seoul St. Mary's Hospital, Seoul, Republic of Korea

<sup>x</sup> Department of Internal Medicine, Central Hospital, Siheung, Republic of Korea

<sup>y</sup> Department of Internal Medicine, Inha University College of Medicine, Incheon, Republic of Korea

<sup>z</sup> Clinical Development Center, Daewoong Pharmaceutical Co., Ltd., Seoul, Republic of Korea

<sup>A</sup> Division of Endocrinology and Metabolism, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon, Republic of Korea

### ARTICLE INFO

#### Article History:

Received 19 November 2022

Revised 30 January 2023

Accepted 13 February 2023

Available online 9 March 2023

#### Keywords:

Enavogliflozin

### ABSTRACT

**Aims:** This study evaluated the efficacy and safety of enavogliflozin, a novel sodium-glucose cotransporter 2 inhibitor, versus dapagliflozin in Korean patients with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin and gemigliptin.

**Methods:** In this multicenter, double-blind, randomized study, patients with inadequate response to metformin ( $\geq 1000$  mg/day) plus gemigliptin (50 mg/day) were randomized to receive enavogliflozin 0.3 mg/day ( $n = 134$ ) or dapagliflozin 10 mg/day ( $n = 136$ ) in addition to the metformin plus gemigliptin therapy. The primary endpoint was change in HbA1c from baseline to week 24.

\* Corresponding author at: Division of Endocrinology and Metabolism, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 327 Sosa-ro, Wonmi-gu, Bucheon, 14647, Korea.

E-mail address: kimsunrae@catholic.ac.kr (S. Kim).

<https://doi.org/10.1016/j.diabet.2023.101440>

1262-3636/© 2023 The Author(s). Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

HbA1c  
Phase III study  
Randomized controlled study  
Sodium-glucose cotransporter 2 inhibitor  
Type 2 diabetes mellitus

**Results:** Both treatments significantly reduced HbA1c at week 24 ( $-0.92\%$  in enavogliflozin group,  $-0.86\%$  in dapagliflozin group). The enavogliflozin and dapagliflozin groups did not differ in terms of changes in HbA1c (between-group difference:  $-0.06\%$ , 95% confidence interval [CI]:  $-0.19, 0.06$ ) and fasting plasma glucose (between-group difference:  $-3.49$  mg/dl [ $-8.08; 1.10$ ]). An increase in urine glucose-creatinine ratio was significantly greater in the enavogliflozin group than in the dapagliflozin group ( $60.2$  g/g versus  $43.5$  g/g,  $P < 0.0001$ ). The incidence of treatment-emergent adverse events was similar between the groups ( $21.64\%$  versus  $23.53\%$ ).

**Conclusions:** Enavogliflozin, added to metformin plus gemigliptin, was well tolerated and as effective as dapagliflozin in the treatment of patients with T2DM.

© 2023 The Author(s). Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a major chronic metabolic disorder and over 460 million people are estimated to be living with diabetes [1–3]. The first-line therapy in patients with T2DM is metformin, but a combination treatment is needed for patients whose blood glucose levels are not controlled with metformin monotherapy [4–8]. Because dipeptidyl peptidase-4 inhibitors (DPP-4is) and sodium-glucose cotransporter 2 inhibitors (SGLT2is) exert different and complementary glucose-lowering effects, in patients in whom glycemic control is not successful with metformin plus a DPP-4i, adding SGLT2i is a good option [9–12].

Adding SGLT2i to combination therapy with metformin plus DPP-4i could be expected to have a complementary mechanism to improve several of the pathologic defects of T2DM without the burden of hypoglycemia or weight gain that one would expect with sulfonylurea or insulin regimens [6,7]. In addition, the DPP-4i could reduce the increase in glucagon secretion induced by the SGLT2i [13–15]. Compared with a DPP-4i, SGLT2i /DPP-4i combination therapy was significantly associated with a decrease in glycemic control (HbA1c,  $-0.71\%$ ) in a systematic review and meta-analysis of 14 randomized controlled trials involving 4828 patients [12]. However, experience with SGLT2is as an add-on to metformin plus DPP-4is in Asian patients with T2DM is limited [16]. Furthermore, there is no randomized clinical trial compared two different SGLT2is on top of metformin plus DPP-4i.

Enavogliflozin is a novel selective SGLT2i in the clinical development stage [17–20]. The efficacy and safety of enavogliflozin in patients with T2DM were demonstrated in a phase II study, in which enavogliflozin 0.3 mg monotherapy caused a significant reduction in HbA1c at week 12 by  $0.86\%$  [20]. The aim of this study was to evaluate the efficacy and safety of enavogliflozin versus dapagliflozin as an add-on to metformin and gemigliptin, a DPP-4i [21,22], in Korean patients with T2DM, using a non-inferiority design.

## 2. Materials and methods

### 2.1. Study design

This phase III study was designed as a 24-week, multicenter, double-blind, randomized study to evaluate the efficacy and safety of enavogliflozin 0.3 mg compared with dapagliflozin 10 mg in T2DM patients with inadequate glycemic control with dual therapy of metformin ( $\geq 1000$  mg/day) plus gemigliptin (50 mg/day) (NCT04654390). Eligible patients underwent a two-week placebo run-in period under a single-blinded (patient-only blinded) condition (Fig. 1). During the pre-screening period, a metformin titration period (up to four weeks) and/or a stabilization period (titrated metformin plus gemigliptin at 50 mg/day for eight weeks) were required for patients who were not under dual therapy of metformin plus gemigliptin. Patients with inadequate glycemic control (HbA1c between  $7.5\%$  [58 mmol/mol] and  $11.0\%$  [97 mmol/mol]) under metformin ( $<1000$  mg/day) plus another oral antihyperglycemic agent (OHA) underwent the titration period to reach a stable dose of metformin ( $\geq 1000$  mg/day) and thereafter the stabilization period, during which gemigliptin (50 mg/day) was added, and another OHA was withdrawn. Patients with inadequate glycemic control (HbA1c,  $7.5\%$ – $11.0\%$  [58–97 mmol/mol]) under metformin ( $\geq 1000$  mg/day) monotherapy or patients with inadequate glycemic control (HbA1c,  $7.0\%$ – $11.0\%$  [53–97 mmol/mol]) under dual therapy of metformin ( $\geq 1000$  mg/day) plus OHA other than gemigliptin underwent the stabilization period, during which gemigliptin (50 mg/day) was added and/or other OHA was withdrawn. During the run-in period, patients took two placebo tablets orally once a day (placebos of enavogliflozin and dapagliflozin each), in addition to the ongoing metformin plus gemigliptin treatment. If the compliances to each of the placebos, metformin, and gemigliptin were all between 70% and 130%, and the eligibility criteria were met, the patient was randomized either to the enavogliflozin group or dapagliflozin group at a 1:1 ratio. Throughout the study, the metformin ( $\geq 1000$  mg/day) and gemigliptin (50 mg/day) regimens were maintained without change, along with the ongoing diet and exercise routine. Follow-up assessments were

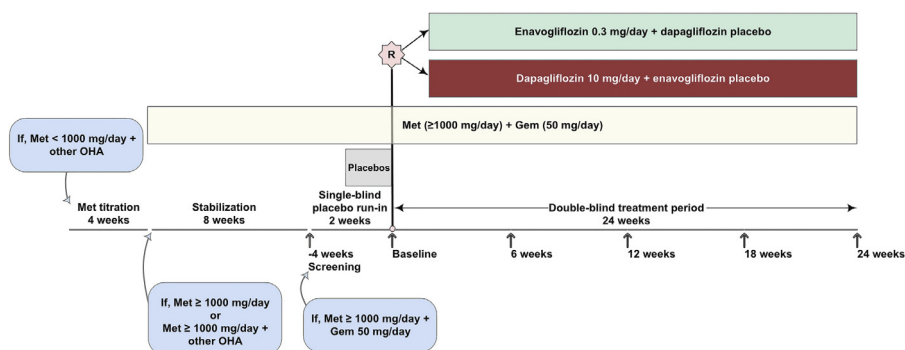


Fig. 1. Study scheme. Gem, gemigliptin; OHA, oral antihyperglycemic agent; Met, metformin; R, randomization.

made at six-week intervals (6, 12, 18, and 24 weeks). The study was conducted according to the principles of the Helsinki declaration and good clinical practice. The study was approved by the institutional review boards of each hospital and the Ministry of Food and Drug Safety of Korea. Before initiation of any study-related assessments, including pre-screening procedures, written informed consent was obtained from all patients.

## 2.2. Patients

Patients receiving dual therapy of metformin ( $\geq 1000$  mg/day) plus gemigliptin (50 mg/day) for at least eight weeks were considered for screening. Patients on other combinations of OHAs could be included in the screening after pre-screening procedures (Fig. 1). Eligibility criteria were as follows: age 19 to 80 years with body mass index between 20 and 45 kg/m<sup>2</sup>, HbA1c at screening between 7.0% (53 mmol/mol) and 11.0% (97 mmol/mol), and fasting plasma glucose (FPG) < 270 mg/dl. Major exclusion criteria were as follows: heart failure as per New York Heart Association classes II to IV; systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg; estimated glomerular filtration rate (eGFR) (< 60 ml/min/1.73 m<sup>2</sup>; aspartate aminotransferase or alanine aminotransferase > three times the upper limit of normal; triglyceride > 500 mg/dl, or other clinically significant conditions or diseases.

## 2.3. Randomization and study treatments

Randomization was done centrally via an interactive web response system using the stratified block randomization method. Stratification factors included the number of previous OHAs taken 24 weeks before screening ( $\leq 2$  versus  $\geq 3$ ) (Table S1; see supplementary materials associated with this article on line) and HbA1c level at screening ( $\geq 8\%$  [64 mmol/mol] versus < 8% [64 mmol/mol]). A randomized patient took two tablets (randomized drug, placebo of the other drug) orally once a day for 24 weeks. Other antihyperglycemic agents, unless a rescue drug was indicated (week 1–6: FPG > 270 mg/dl; week 7–12: FPG > 240 mg/dl; week 13–24: FPG > 200 mg/dl or HbA1c > 8% [64 mmol/mol]), were prohibited during the study. A list of other prohibited drugs included glucagon or glucose injection, weight-reduction medications, diuretics, immunosuppressants, iodized contrast media, and drugs that may interact with study treatment, such as inhibitors of organic cation transporters or CYP3A4 inducers.

## 2.4. Study endpoints

The primary endpoint was HbA1c change at week 24. Glycemic responses based on the following definitions were also evaluated: HbA1c < 7.0% (53 mmol/mol); HbA1c < 6.5% (48 mmol/mol); HbA1c < 7.0% (53 mmol/mol) or HbA1c reduction > 0.5%; HbA1c < 7.0% (53 mmol/mol) or HbA1c reduction > 0.7%; HbA1c < 7.0% (53 mmol/mol) or HbA1c reduction > 1.0%. Changes from baseline in body weight, urine albumin-to-creatinine ratio (UACR), urine glucose-to-creatinine ratio (UGCR), fasting C-peptide, homeostasis model assessment of  $\beta$ -cell function (HOMA-beta) and insulin resistance (HOMA-IR), leptin, adiponectin, fasting lipid profile, and blood pressure were evaluated as exploratory efficacy endpoints. Blood samples for efficacy parameters were analyzed in a central laboratory. As for safety endpoints, treatment-emergent adverse events (TEAEs) and results of complete blood count, serum chemistry, and 12-lead electrocardiogram were evaluated. Hypoglycemia, urinary tract and genital infection, pollakiuria, and polyuria were separately analyzed as adverse events of special interest.

## 2.5. Statistical analysis

A minimum sample size of 178 (89 per group) was calculated to provide 80% power at a one-sided significance level of 2.5% for the non-inferiority test on the primary endpoint, assuming the margin of non-inferiority of 0.35%, the true mean difference of 0%, and a standard deviation of 0.83%. Considering a potential drop-out rate of 30%, 256 patients were required for randomization (128 per group). The non-inferiority margin was set based on the margins suggested in the regulatory guidelines for the diabetes trial and those adopted in the clinical trials of dapagliflozin or DPP-4is.

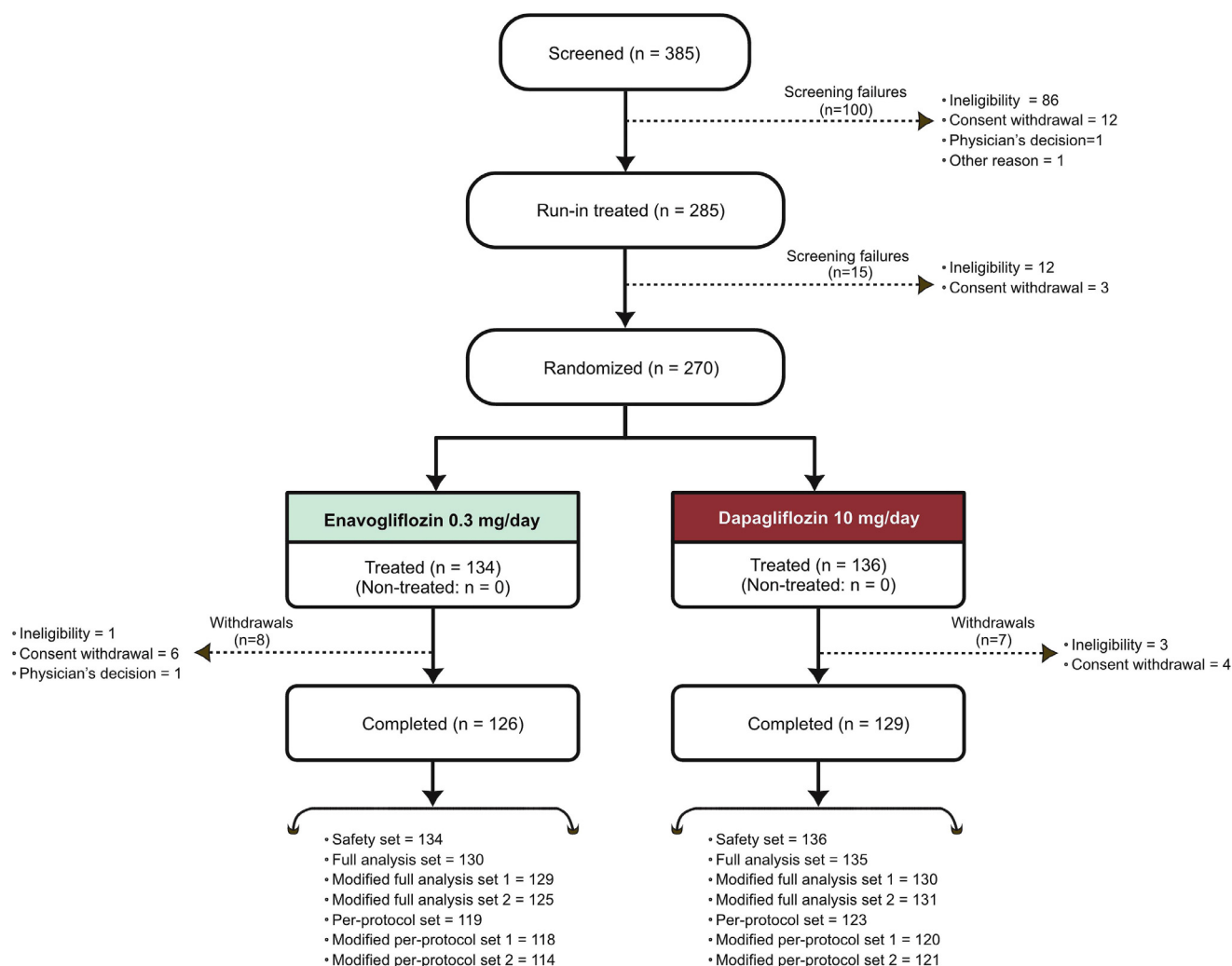
The full analysis set (FAS) consisted of patients who were exposed to at least one dose of the study drug and had at least one HbA1c result after randomization. The per-protocol set (PPS) consisted of patients who completed the 24-week treatment period without major protocol deviations, among patients included in the FAS. Most of the efficacy analyses were carried out both with the FAS and the PPS, with PPS as a primary analysis set. The safety analysis set included patients who received at least one dose of the study drug after randomization and had any post-randomization safety follow-up data (Fig. 2).

For the efficacy endpoints collected as continuous variables, between-group comparisons were made using analysis of covariance (ANCOVA), controlling baseline values and randomization stratification factors as covariates. Changes from baseline for those endpoints are all presented with adjusted mean changes and between-group differences with least square mean differences (enavogliflozin group – dapagliflozin group) in changes by ANCOVA. To test the robustness of the findings with HbA1c and FPG, sensitivity analysis was performed using a mixed model for repeated measures, in which fixed effects of the groups, visits, baseline values, randomization stratification factors, and treatment-by-visit interaction were included. As a pre-planned subgroup analysis, changes in HbA1c, FPG, UACR, and UGCR were evaluated in the subgroups per randomization stratification factors and per baseline eGFR (< 90 ml/min/1.73m<sup>2</sup> or  $\geq 90$  ml/min/1.73m<sup>2</sup>). UACR change in a subgroup of patients with albuminuria (UACR  $\geq 30$  mg/g) was evaluated as an ad hoc analysis. The between-group difference in the percentage of patients achieving various glycemic responses was evaluated based on the odds ratio and its 95% confidence interval (CI) calculated using logistic regression analysis. Except for the non-inferiority test for the primary endpoint, all statistical tests were two-sided at a significance level of 5%. All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc, Cary, North Carolina, USA). Verbatims of adverse events were coded using MedDRA version 24.0.

## 3. Results

### 3.1. Patient disposition and characteristics

The study was conducted from 30 December 2020 to 17 December 2021 in 28 hospitals in South Korea. Among 385 patients screened for the study, 285 entered the placebo run-in period, and 270 were randomized to one of the two treatment groups (134 to the enavogliflozin group, 136 to the dapagliflozin group) (Fig. 2). The demographics and baseline characteristics of the randomized patients were similar in the two groups (Table 1). Mean HbA1c at the screening was 7.98% (64 mmol/mol) and 8.00% (64 mmol/mol), in the enavogliflozin and dapagliflozin groups, respectively, and slightly more than 37% of patients in both groups (37.3% and 37.5%, respectively) had HbA1c  $\geq 8\%$  (64 mmol/mol). Mean diabetes duration was 10.2 years in the enavogliflozin group and 9.5 years in the dapagliflozin group.



**Fig. 2.** Patient disposition. The safety analysis set included patients who received at least one dose of the study drug after randomization and had any post-randomization safety follow-up data. The full analysis set (FAS) consisted of patients who were exposed at least one dose of the study drug and had at least one HbA1c result after randomization. The per-protocol set (PPS) consisted of patients who completed the 24-week treatment period without major protocol deviations, among patients included in the FAS. For the analyses of endpoints for lipid profile or blood pressure, patients who had any change (addition of new drug or regimen change) in antihyperlipidemic or antihypertensive treatment, respectively, were excluded from the FAS and PPS, thus the remaining patients composed respectively the modified FAS 1 and PPS 1 for lipid profile analysis and modified FAS 2 and PPS 2 for blood pressure analysis.

### 3.2. Efficacy

In both groups, a significant reduction in HbA1c was observed from week 6, and the decreasing trend was sustained until week 24 (Fig. 3A). The two groups had a similar level of HbA1c reduction at week 24 (−0.92% in the enavogliflozin group versus −0.86% in the dapagliflozin group), thus resulting in the between-group difference of −0.06% [95% CI: −0.19;0.06] (Table 2). As the upper end of the 95% CI was below the non-inferiority margin (0.35%), the non-inferiority of enavogliflozin 0.3 mg to dapagliflozin 10 mg was confirmed. FPG was also significantly reduced in both groups at week 24 (Fig. 3B). Proportions of patients achieving HbA1c < 7.0% (53 mmol/mol) at week 24 (−0.92% in the enavogliflozin group versus −0.86% in the dapagliflozin group) were 66.4% and 62.6%, respectively, (odds ratio=1.17 [95% CI: 0.66;2.09]) (Fig. 4). Glycemic response rates based on different definitions are presented in Fig. 4. Along with HbA1c reduction, a significant decrease in FPG was observed in both groups. No statistically significant between-group difference was detected in terms of HbA1c reduction, either in the sensitivity analyses or in the subgroups based on the number of previous OHAs ( $\leq 2$  versus  $\geq 3$ ) or HbA1c at screening ( $\geq 8\%$  [64 mmol/mol] versus < 8% [64 mmol/mol]) (Fig. S1; see supplementary materials associated with this article on line). Meanwhile, in a

subgroup of patients with baseline eGFR < 90 ml/min/1.73m<sup>2</sup>, HbA1c reduction tended to be greater in the enavogliflozin group at week 24 (−0.96% versus −0.72%,  $P = 0.0113$ ) (Fig. S1; see supplementary materials associated with this article on line).

Body weight gradually decreased in both groups (at week 24: −3.2 kg in the enavogliflozin group versus −3.0 kg in the dapagliflozin group,  $P = 0.6226$ ) (Table 2 and Fig. 3C). Systolic blood pressure was decreased 4.5 mm Hg in the enavogliflozin group and 4.3 mm Hg in the dapagliflozin group (Table 2). Diastolic blood pressure was decreased 2.6 mm Hg in the enavogliflozin group and 1.9 mm Hg in the dapagliflozin group (Table 2). Meanwhile, a significant increase in HOMA-beta and significant decreases in HOMA-IR and C-peptide were observed in both groups. No between-group differences were noted in lipid profile, adiponectin, leptin, or systolic or diastolic blood pressure.

A urinary glycemic index measured as UGCR also showed significant improvement. Of note was the greater increase in UGCR at week 24 in the enavogliflozin group than in the dapagliflozin group (60.2 g/g versus 43.5 g/g,  $P < 0.0001$ ) (Table 2 and Fig. 3D). The greater effect of enavogliflozin on UGCR was consistently observed in all subgroup analyses regardless of randomization stratification factors or baseline eGFR level (Fig. S2; see supplementary materials



**Table 1**  
Demographics and baseline characteristics.

	Enavogliflozin 0.3 mg (n = 134)	Dapagliflozin 10 mg (n = 136)
Age, years	58.1 (10.0)	59.1 (9.8)
Male, n (%)	73 (54.5)	68 (50.0)
Weight, kg	70.0 (12.0)	67.9 (11.3)
BMI, kg/m <sup>2</sup>	26.1 (3.7)	25.6 (3.0)
Duration of diabetes, years	10.2 (7.1)	9.5 (5.4)
OHA history, n (%)		
Metformin only (≥1000 mg/day)	0	1 (0.7)
Metformin (<1000 mg/day) + OHA	0	0
Metformin (≥1000 mg/day) + OHA other than gemigliptin	15 (11.2)	15 (11.0)
Metformin (≥1000 mg/day) + gemigliptin (50 mg/day)	119 (88.8)	120 (88.2)
HbA1c, %	7.98 (0.85)	8.00 (0.82)
HbA1c ≥8% (64 mmol/mol), n (%)	50 (37.3)	51 (37.5)
FPG, mg/dl	163.3 (33.8)	163.6 (32.2)
eGFR, ml/min/1.73m <sup>2</sup>	90.7 (19.1)	90.6 (17.5)
eGFR <90 ml/min/1.73m <sup>2</sup> , n (%)	68 (50.8)	72 (52.9)
SBP, mmHg <sup>†</sup>	126.9 (12.5)	124.1 (11.6)
DBP, mmHg <sup>†</sup>	76.2 (9.1)	74.1 (8.8)
Total cholesterol, mg/dl <sup>†</sup>	137.7 (27.8)	142.8 (35.4)
LDL-C, mg/dl <sup>†</sup>	74.0 (25.4)	77.4 (30.2)
HDL-C, mg/dl <sup>†</sup>	46.7 (10.1)	46.7 (10.6)
Triglyceride, mg/dl <sup>†</sup>	119.8 (59.4)	132.2 (92.8)

Continuous variables are presented as mean (standard deviation). Presented data are based on the data collected at the screening visit (−4 weeks from randomization) except those marked with dagger sign (†), which are based on the data collected on randomization day (Day 0). BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OHA, oral antihyperglycemic agent; SBP, systolic blood pressure.

associated with this article on line). Changes in UACR were generally in a decreasing direction in both groups but were statistically significant solely in the enavogliflozin group, although no between-group difference was detected at week 24 (−15.3 in the enavogliflozin group versus −16.1 in the dapagliflozin group,  $P = 0.8774$ ) (Table 2). In a subgroup of patients having albuminuria (≥ 30 mg/g) at baseline (mean baseline UACR: 151.9 mg/g in the enavogliflozin group [ $n = 30$ ] versus 144.9 mg/g in the dapagliflozin group [ $n = 22$ ]), UACR reduction at week 24 was significant in both groups without a significant between-group difference (−73.3 mg/g in the enavogliflozin group versus −67.7 mg/g in the dapagliflozin group,  $P = 0.8062$ ) (Table S2; see supplementary materials associated with this article on line).

### 3.3. Safety

The incidence rate of TEAEs was 21.6% in the enavogliflozin group and 23.5% in the dapagliflozin group (Table S3; see supplementary materials associated with this article on line). Among 39 and 46 TEAEs in the enavogliflozin and dapagliflozin groups, respectively, 37 and 40 were mild in intensity, six and seven were drug-related (adverse drug reactions, ADRs), and all ADRs were mild in intensity. Except for one TEAE in the dapagliflozin group, none of the TEAEs affected dosing of the study drug. Two serious TEAEs were reported in the enavogliflozin group (angina pectoris and intraductal papilloma of the breast) and six in the dapagliflozin group (angina pectoris, hepatocellular carcinoma, duodenal ulcer, pain, wrist fracture, and increased liver enzyme level), none of which were considered as an ADR. Except for one hypoglycemia, not assessed as an ADR, in the enavogliflozin group, all of the adverse events of special interest (two in the enavogliflozin group and five in the dapagliflozin group) were infections in the genital area. However, there was no urinary tract infection in either group.

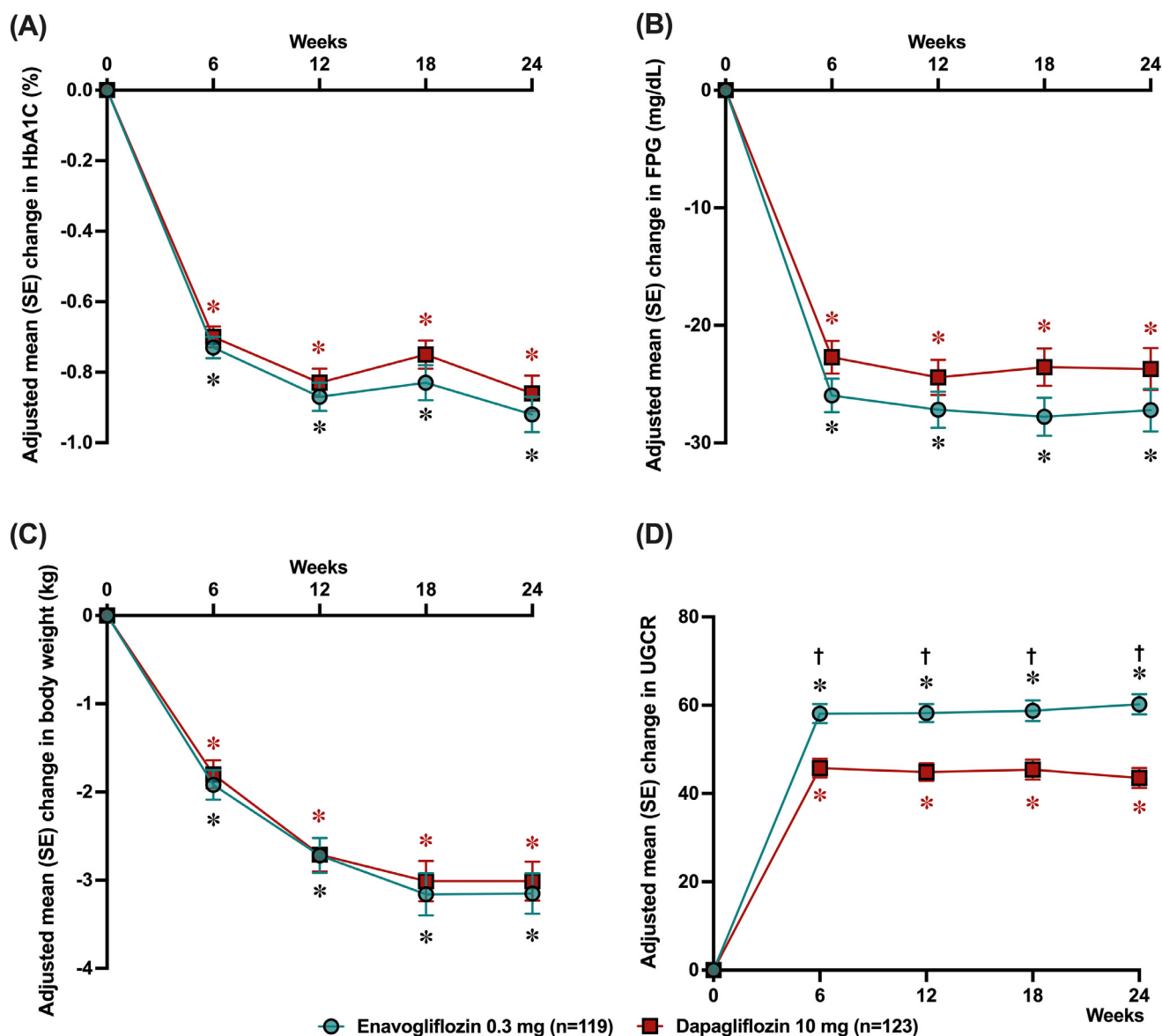
## 4. Discussion

This phase III clinical trial demonstrated that enavogliflozin 0.3 mg showed an effective glucose-lowering effect and was non-inferior to dapagliflozin 10 mg as an add-on in Korean patients with T2DM who had inadequate glycemic control on metformin plus gemigliptin. After 24 weeks of the treatment, enavogliflozin 0.3 mg and dapagliflozin 10 mg did not differ significantly in terms of the glycemic control indices, i.e. reductions in HbA1c, FPG, HOMA-IR and C-peptide, and increase in HOMA-beta, as well as in terms of body weight reduction, changes in lipid profile, adiponectin and leptin levels, and blood pressure. Enavogliflozin 0.3 mg and dapagliflozin 10 mg were tolerated well, with no significant between-group difference for TEAE occurrence.

Enavogliflozin is a novel selective SGLT2i developed in Korea. In the comparative pharmacokinetics and pharmacodynamics study, selective and competitive SGLT2 inhibition of enavogliflozin could potentiate the efficacy of enavogliflozin in coordination with the higher kidney distribution and retained SGLT2 inhibition of enavogliflozin relative to dapagliflozin and ipragliflozin [17]. Enavogliflozin induced glucosuria in a dose-dependent manner, and the steady state urinary glucose excretion was 50~60 g/d after multiple doses in the range of 0.3~2.0 mg in healthy volunteers [19]. The efficacy and safety of enavogliflozin were also demonstrated in patients with T2DM in a phase II trial, in which enavogliflozin monotherapy at 0.1, 0.3 and 0.5 mg caused a significant reduction in HbA1c at week 12, by 0.74%, 0.86% and 0.84%, respectively [20].

In this study, at week 24, the adjusted mean change from baseline in HbA1c was −0.92% in the enavogliflozin group and −0.86% in the dapagliflozin group. These values are within the range achieved in previous phase III studies analyzing dapagliflozin 10 mg as an add-on to saxagliptin 5 mg (−0.82%) [23] or sitagliptin 100 mg (−0.4%) [24]. The proportions of patients who achieved HbA1c < 7.0% (53 mmol/mol) at week 24 were 66.4% and 62.6% in the enavogliflozin and dapagliflozin groups, respectively. Although baseline HbA1c and duration of studies were different, these values tended to be higher than in the previous studies analyzing the efficacy of dapagliflozin 10 mg added to metformin plus saxagliptin 5 mg (38%) [23] or sitagliptin 100 mg (27.8%) [24]. The results mentioned above are also consistent with the findings of other studies analyzing triple therapies consisting of metformin, dapagliflozin 10 mg and a DPP-4i, regardless of the order in which the drugs were added [10,16,25–28]. However, there is no clinical trial providing head-to-head comparisons of the efficacy and safety between SGLT2is. In an indirect and network meta-analysis, dapagliflozin 10 mg produced a similar HbA1c reduction compared with empagliflozin 10 mg or canagliflozin 100 mg [29,30]. In addition, dapagliflozin 10 mg was as effective in reducing body weight and blood pressure as other SGLT2is except canagliflozin 300 mg. In a prospective, interventional, nonrandomized study conducted in India, the effect of different SGLT2is (canagliflozin, empagliflozin, dapagliflozin, and remogliflozin) on glycemic parameters and body weight was not different in patients with inadequately controlled T2DM receiving triple-drug therapy [31]. The present study would be valuable because it was a head-to-head randomized clinical trial and demonstrated that enavogliflozin 0.3 mg could be an effective add-on choice, as good as dapagliflozin 10 mg, in patients with T2DM inadequately controlled with metformin and a DPP-4i.

Interestingly, enavogliflozin caused a significantly more profound increase in urinary glucose excretion than dapagliflozin although UGCR increased from baseline in both enavogliflozin and dapagliflozin groups were statistically significant at all time points. The stronger effect of enavogliflozin on UGCR was observed consistently regardless of randomization stratification factors or baseline eGFR level. The higher UGCR of enavogliflozin seems to be associated with its greater affinity for SGLT2 inhibition compared with dapagliflozin.



**Fig. 3.** Least square mean change from baseline in major efficacy endpoints over 24 weeks (Per-Protocol Set). **A,** Glycated hemoglobin (HbA1c). **B,** Fasting plasma glucose (FPG). **C,** Body weight. **D,** Urine glucose-to-creatinine ratio (UGCR). An asterisk denotes statistically significant change from baseline within the group by paired *t*-test or Wilcoxon signed rank test (black asterisk=enavogliflozin group, red asterisk=dapagliflozin group). A dagger sign denotes a statistically significant difference between the groups by analysis of covariance. Error bars are standard errors of the mean (SE).

This might be because the values of the lowest half-maximal inhibitory concentration of enavogliflozin to SGLT2 were lower than those of dapagliflozin (0.8 nM versus 1.6 nM) [17]. Additionally, this also might be because enavogliflozin had higher kidney distributions and longer  $t_{1/2}$  in the kidney than dapagliflozin [17]. In a study of healthy volunteers, a dose-dependent increase in urinary glucose excretion was observed after a single dose of enavogliflozin and the mean urinary glucose excretion over 24 h at the steady state of the enavogliflozin 0.3 mg and dapagliflozin 10 mg was 48.3 g and 40.5 g, respectively [19]. These results implied that the effect of enavogliflozin on urinary glucose excretion is more potent than that of dapagliflozin, and enavogliflozin could have a better glucose-lowering effect than dapagliflozin. Indeed, enavogliflozin treatment tended to show a slightly better glucose response (HbA1c:  $-0.92\%$  in the enavogliflozin group vs.  $-0.86\%$  in the dapagliflozin group; FPG:  $-27.2$  mg/dL in enavogliflozin group versus  $-23.7$  mg/dL in the dapagliflozin group) and weight reduction ( $-3.2$  kg in the enavogliflozin group versus  $-3.0$  kg in the dapagliflozin group) than dapagliflozin treatment in

this study. However, these differences did not reach a significant level. This might be because the main mechanism of the two drugs is the same, but further studies are needed to explain the observed differences clearly.

The add-on treatments with enavogliflozin 0.3 mg and dapagliflozin 10 mg appeared to be safe and well tolerated in this study. The majority of the TEAEs were mild in intensity, and none affected dosing of the study treatments. These findings are consistent with the results of previous studies analyzing dapagliflozin 10 mg as an add-on treatment to metformin plus a DPP-4i [16,25–28] and suggest that enavogliflozin also could be well tolerated as an add-on treatment.

Several limitations need to be considered in the interpretation of this study. First, the relatively short study duration did not provide enough time to evaluate the long-term effect of enavogliflozin. Second, because this study was conducted in Koreans, the results might not be generalizable to other ethnicities. Asian patients have a different phenotype of T2DM with a more marked defect in insulin

**Table 2**  
Summary statistics of efficacy endpoints (Per-Protocol Set).

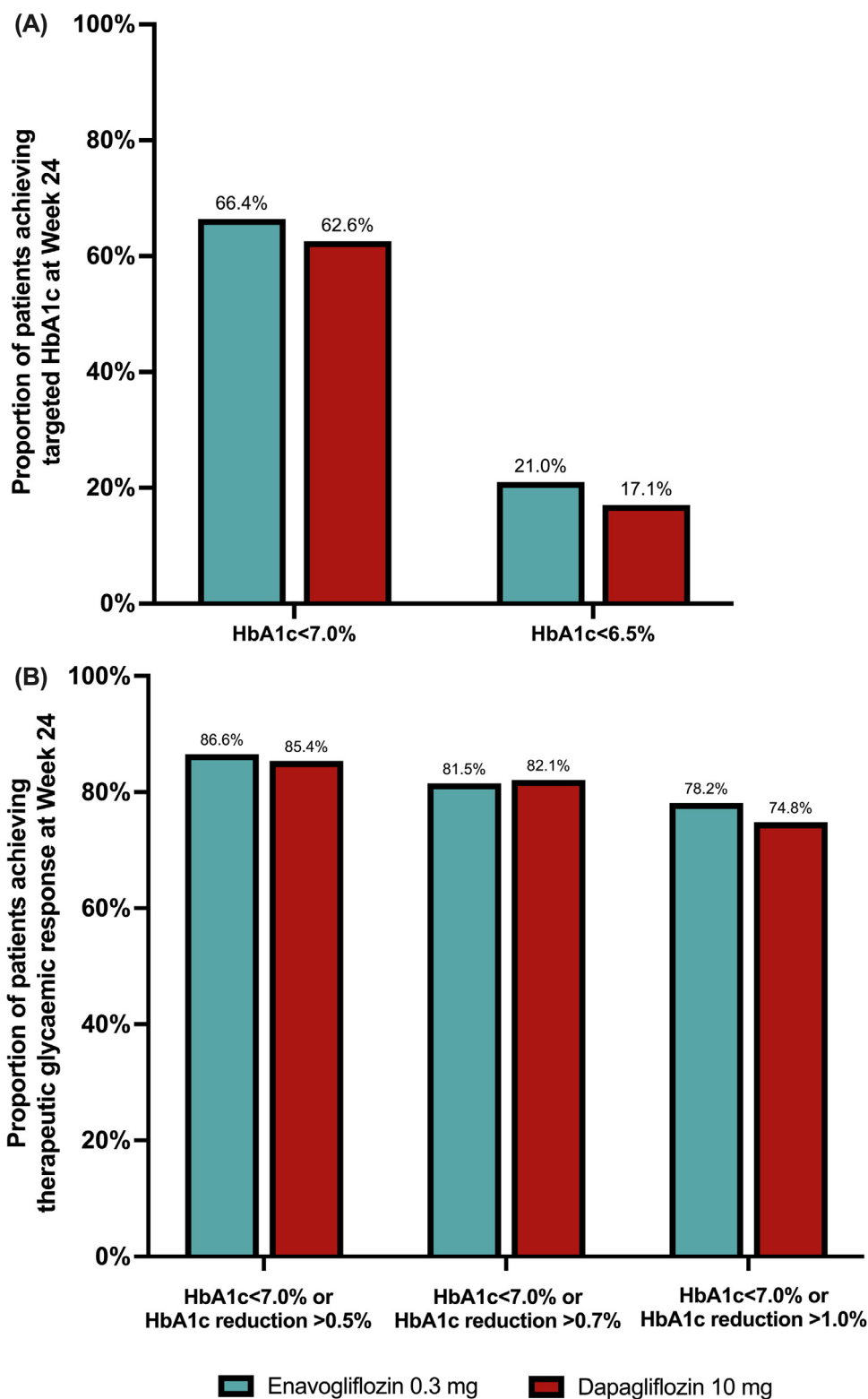
	Enavogliflozin 0.3 mg (n = 119)	Dapagliflozin 10 mg (n = 123)
<b>HbA1c, %</b>		
Baseline	7.79 (0.77)	7.83 (0.81)
Week 24	6.86 (0.54)	6.94 (0.64)
LS mean change (SE)	-0.92 (0.05)	-0.86 (0.05)
Between-group difference [95% CI]	-0.06 [-0.19, 0.06]	
<b>FPG, mg/dl</b>		
Baseline	139.3 (28.0)	140.5 (29.7)
Week 24	113.0 (17.6)	116.8 (21.3)
LS mean change (SE)	-27.2 (1.8)	-23.7 (1.8)
Between-group difference [95% CI]	-3.5 [-8.1, 1.1]	
<b>Body weight, kg</b>		
Baseline	69.3 (12.1)	67.2 (11.4)
Week 24	66.2 (11.6)	64.4 (11.0)
LS mean change (SE)	-3.2 (0.2)	-3.0 (0.2)
Between-group difference [95% CI]	-0.2 [-0.7, 0.4]	
<b>UACR</b>		
Baseline	47.2 (129.2)	34.7 (97.2)
Week 24	27.9 (53.7)	23.6 (47.4)
LS mean change (SE)	-15.3 (3.9)	-16.1 (3.8)
Between-group difference [95% CI]	0.8 [-9.3, 10.8]	
<b>UGCR</b>		
Baseline	0.7 (3.5)	1.5 (7.4)
Week 24	60.1 (24.6)	43.8 (22.2)
LS mean change (SE)	60.2 (2.3)	43.5 (2.3)
Between-group difference [95% CI]	16.7 [10.8, 22.6]*	
<b>HOMA-β</b>		
Baseline	42.9 (27.1)	40.5 (27.3)
Week 24	45.5 (67.0)	48.4 (31.9)
LS mean change (SE)	1.1 (4.8)	5.8 (4.7)
Between-group difference [95% CI]	-4.7 [-17.0, 7.6]	
<b>HOMA-IR</b>		
Baseline	2.90 (1.91)	2.86 (1.84)
Week 24	1.84 (1.10)	1.97 (1.49)
LS mean change (SE)	-1.09 (0.11)	-0.93 (0.11)
Between-group difference [95% CI]	-0.16 [-0.44, 0.13]	
<b>Adiponectin, mg/l</b>		
Baseline	6.22 (4.07)	6.34 (3.42)
Week 24	7.62 (4.55)	7.18 (3.53)
LS mean change (SE)	1.42 (0.35)	0.92 (0.35)
Between-group difference [95% CI]	0.49 [-0.42, 1.40]	
<b>Leptin, μg/l</b>		
Baseline	10.48 (10.49)	10.85 (9.19)
Week 24	8.95 (9.07)	10.10 (9.33)
LS mean change (SE)	-1.46 (0.52)	-0.57 (0.51)
Between-group difference [95% CI]	-0.89 [-2.21, 0.43]	
<b>C-peptide, nmol/l</b>		
Baseline	0.73 (0.25)	0.69 (0.21)
Week 24	0.64 (0.20)	0.62 (0.24)
LS mean change (SE)	-0.09 (0.02)	-0.08 (0.02)
Between-group difference [95% CI]	-0.01 [-0.05, 0.03]	
<b>Total cholesterol, mg/dl<sup>†</sup></b>		
Baseline	134.5 (24.9)	143.8 (35.5)
Week 24	140.1 (26.8)	148.5 (36.4)
LS mean change (SE)	4.5 (2.1)	5.6 (2.0)
Between-group difference [95% CI]	-1.1 [-6.4, 4.3]	
<b>LDL-C, mg/dl</b>		
Baseline	71.4 (22.8)	77.4 (29.4)
Week 24	73.2 (25.0)	80.1 (31.2)
LS mean change (SE)	0.9 (1.9)	3.1 (1.9)
Between-group difference [95% CI]	-2.3 [-7.1, 2.6]	
<b>HDL-C, mg/dl</b>		
Baseline	46.1 (9.9)	47.4 (10.8)
Week 24	50.6 (11.9)	51.9 (11.8)
LS mean change (SE)	4.3 (0.7)	4.4 (0.7)
Between-group difference [95% CI]	-0.1 [-1.9, 1.7]	
<b>Systolic blood pressure, mmHg<sup>‡</sup></b>		
Baseline	127.5 (12.7)	123.9 (11.7)
Week 24	122.3 (12.6)	120.2 (12.0)
LS mean change (SE)	-4.5 (1.0)	-4.3 (0.9)
Between-group difference [95% CI]	-0.2 [-2.7, 2.2]	
<b>Diastolic blood pressure, mmHg<sup>‡</sup></b>		
Baseline	76.6 (9.3)	73.9 (8.6)
Week 24	73.4 (9.4)	72.3 (9.1)
LS mean change (SE)	-2.6 (0.7)	-1.9 (0.7)
Between-group difference [95% CI]	-0.7 [-2.5, 1.2]	

Data are primarily based on the per-protocol set and presented as mean (standard deviation) unless otherwise specified.

<sup>†</sup> Lipid profile data are based on the modified per-protocol set 1 (enavogliflozin group=118, dapagliflozin group=120).

<sup>‡</sup> Blood pressure data are based on the modified per-protocol set 2 (enavogliflozin group=114, dapagliflozin group=121).

\* Statistically significant difference between the groups ( $P < 0.0001$ ). CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-β, homeostatic model assessment (HOMA) of beta-cell function; HOMA-IR, HOMA of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LS, least-square; SE, standard error of the mean; UACR, urine albumin-to-creatinine ratio; UGCR, urine glucose-to-creatinine ratio.



**Fig. 4.** Glycemic response at week 24 (Per-Protocol Set). **A,** Proportions of patients achieving HbA1c less than 7.0% or 6.5% at week 24. **B,** Proportions of patients achieving therapeutic glycaemic response at week 24.

secretion, so glucagon-like peptide-1 receptor agonists and DPP-4is exert a greater reduction in HbA1c in Asian than in non-Asian patients with T2DM. However, a systematic review showed that the clinical efficacy of SGLT2is added on to metformin was similar in Asian versus non-Asian patients [32]. Finally, gemigliptin and enavogliflozin are not commercialized worldwide. However, gemigliptin is

a potent, selective, and competitive DPP-4i, approved for clinical use in more than 11 different countries across the globe, including South Korea, India, and several Central American and South American countries [22]. Enavogliflozin was developed and approved in South Korea recently. Although it was not commercialized worldwide yet, the efficacy of enavogliflozin in patients with T2DM was demonstrated in



## Enavogliflozin added to metformin + gemigliptin: the ENHANCE-D study

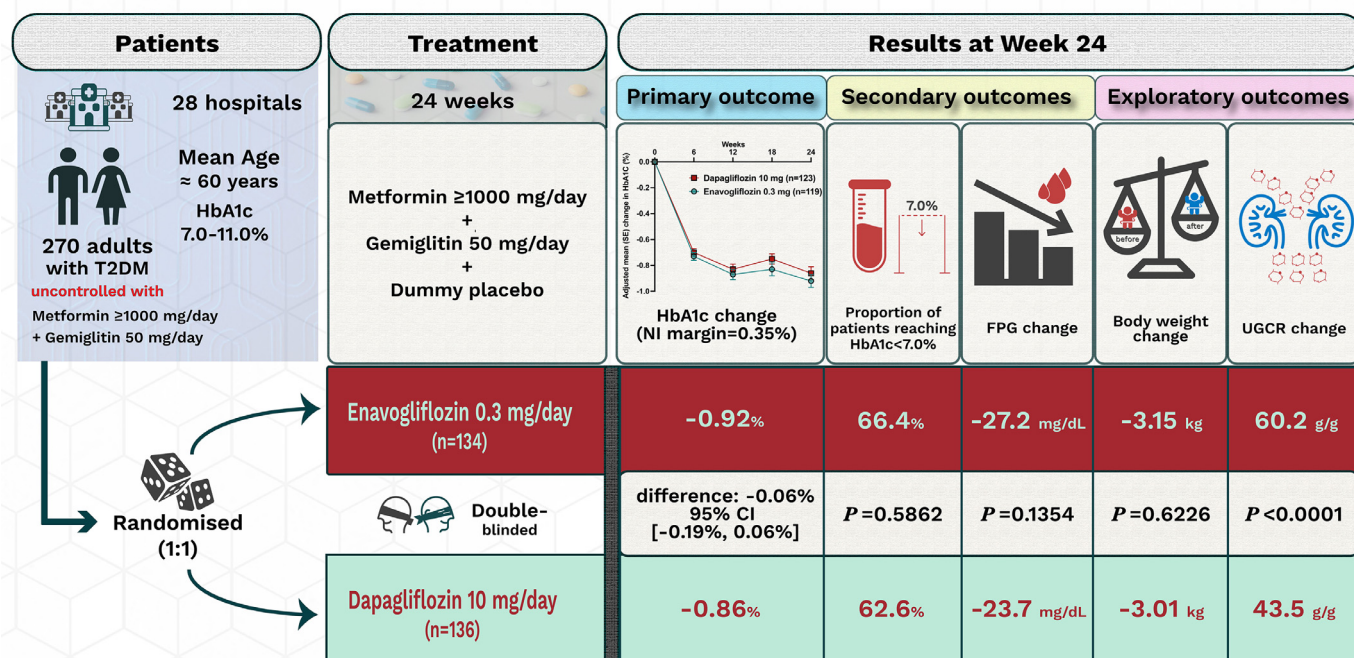


Fig. 5. Graphical abstract.

phase II and III studies. This study would be nonetheless valuable because there is no randomized clinical trial providing head-to-head comparisons of the efficacy and safety between SGLT2is on top of metformin plus a DPP-4i. In addition, the strengths of this study are high retention rates, good compliance with the study drugs, and the fact that the treatment groups were relatively well balanced in terms of demographic and baseline clinical characteristics.

In conclusion, this study showed that enavogliflozin 0.3 mg added to metformin and gemigliptin 50 mg significantly improved glycemic control in Korean patients with T2DM. Moreover, the glucose-lowering efficacy of enavogliflozin 0.3 mg was non-inferior to that of dapagliflozin 10 mg. Therefore, enavogliflozin could be an attractive and safe option as add-on therapy in patients controlled inadequately with metformin and DPP-4is (Fig. 5).

### Funding

This study was supported by Daewoong Pharmaceutical Co., Ltd., Seoul, Korea.

### Author contributions

K.S.K. was involved in patient enrolment, literature review and synthesis, data acquisition, detailed data analysis, statistical analysis, critical discussion, and drafting of the manuscript.

S.R.K, K.A.H., T.N.K., C.Y.P., J.H.P., S.Y.K., Y.H.K., K.H.S., E.S.K., C.S.K., G.P.K., J.G.K, M.K.K, J.M.H., N.H.K., J.O.M., J.H.L., S.L., S.S.K., T.H.K., K.C. W., K.Y.L., J.H.C., J.Y.H., S.H.K. was involved in the patient enrolment, critical discussion, data interpretation and revising of the manuscript.

J.J.N., H.R.S., S.E.L. was involved in the project conception, literature review and synthesis, data acquisition, detailed data analysis, statistical analysis, critical discussion, and drafting of the manuscript.

### Declaration of Competing Interest

Jae Jin Nah, Hwa Rang Song, and Si Eun Lee are full-time employees of Daewoong Pharmaceutical Co., Ltd. The other authors declare there are no potential conflicts of interest relevant to this article.

### Acknowledgments

We are grateful to all the patients, their families, and all study group members.

### Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.diabet.2023.101440](https://doi.org/10.1016/j.diabet.2023.101440).

### References

- [1] Saeedi P, Petersohn I, Salpea P, Malanda B, Karunranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2019;157:107843.
- [2] Jung CH, Son JW, Kang S, Kim WJ, Kim H-S, Kim HS, et al. Diabetes fact sheets in Korea, 2020: an appraisal of current status. *Diabetes Metab J* 2021;45:1-10.
- [3] American Diabetes Association Professional Practice Committee. 1. Improving care and promoting health in populations: standards of medical care in diabetes-2022. *Diabetes Care* 2022;45(Suppl 1):S8-16.
- [4] Neumiller JJ, Umpierrez GE. 2018 Standards of care update: pharmacologic approaches to glycemic management in people with type 2 diabetes. *Diabetes Spectr* 2018;31:254-60.
- [5] Matthews DR, Paldanius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S, VERIFY study group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet* 2019;394:1519-29.
- [6] Hur KY, Moon MK, Park JS, Kim S-K, Lee S-H, Yun J-S, et al. 2021 clinical practice guidelines for diabetes mellitus of the Korean diabetes association. *Diabetes Metab J* 2021;45:461-81.

- [7] American Diabetes Association Professional Practice Committee, B Draznin, Aroda VR, Bakris G, Benson G, Brown FM, et al. 9. pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2022. *Diabetes Care* 2022;45 (Suppl 1):S125–43.
- [8] Yu J, Lee SH, Kim MK. Recent updates to clinical practice guidelines for diabetes mellitus. *Endocrinol Metab (Seoul)* 2022;37:26–37.
- [9] Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. *Expert Opin Drug Metab Toxicol* 2016;12:1407–17.
- [10] Li D, Shi W, Wang T, Tang H. SGLT2 inhibitor plus DPP-4 inhibitor as combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2018;20:1972–6.
- [11] Rhee EJ, Kim MK, Lee WY. Best achievements in clinical medicine in diabetes and dyslipidemia in 2020. *Endocrinol Metab (Seoul)* 2021;36:41–50.
- [12] Moon JS, Suh S, Kim SS, Jin HY, Kim JM, Jang MH, et al. Efficacy and safety of treatment with quadruple oral hypoglycemic agents in uncontrolled type 2 diabetes mellitus: a multi-center, retrospective, observational study. *Diabetes Metab J* 2021;45:675–83.
- [13] Thornberry NA, Gallwitz B. Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4). *Best Pract Res Clin Endocrinol Metab* 2009;23:479–86.
- [14] Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014;124:499–508.
- [15] Rosenberg J, Jacob J, Desai P, Park J, Donovan L, Kim JY. Incretin hormones: pathophysiological risk factors and potential targets for type 2 diabetes. *J Obes Metab Syndr* 2021;30:233–47.
- [16] Kwak SH, Hwang YC, Won JC, Jc Bae, Kim HJ, Suh S, et al. Comparison of the effects of gemigliptin and dapagliflozin on glycaemic variability in type 2 diabetes: a randomized, open-label, active-controlled, 12-week study (STABLE II study). *Diabetes Obes Metab* 2020;22:173–81.
- [17] Choi MK, Nam SJ, Ji HY, Park MJ, Choi JS, Song IS. Comparative pharmacokinetics and pharmacodynamics of a novel sodium-glucose cotransporter 2 inhibitor, DWP16001, with dapagliflozin and ipragliflozin. *Pharmaceutics* 2020;12:268.
- [18] Kim JH, Kim DK, Choi WG, Ji H-Y, Choi J-S, Song I-S, et al. In vitro metabolism of DWP16001, a novel sodium-glucose cotransporter 2 inhibitor, in human and animal hepatocytes. *Pharmaceutics* 2020;12:865.
- [19] Hwang JG, Lee S, Huh W, Han J, Oh J, Jang I-J, et al. Dose-dependent glucosuria of DWP16001, a novel selective sodium-glucose cotransporter-2 inhibitor, in healthy subjects. *Br J Clin Pharmacol* 2022;88:4100–10.
- [20] Yang YS, Min KW, Park SO, et al. Efficacy and safety of monotherapy with enavogliflozin in Korean patients with type 2 diabetes mellitus: results of a 14 week, multi-center, randomized, double-blind, placebo-controlled, phase 2 trial. 2020 international congress of diabetes and metabolism. Korean Diabetes Association; 2020. 18–19 September.
- [21] Yang SJ, Min KW, Gupta SK, Jy Park, Shivane VK, Agarwal PK, et al. A multicentre, multinational, open-label, 52-week extension study of gemigliptin (LC15-0444) monotherapy in patients with type 2 diabetes mellitus. *Diabetes Metab J* 2021;45:606–12.
- [22] Dutta D, Agarwal A, Maisnam I, Singla R, Khandelwal D, Sharma M. Efficacy and safety of the novel dipeptidyl peptidase-4 inhibitor gemigliptin in the management of type 2 diabetes: a meta-analysis. *Endocrinol Metab (Seoul)* 2021;36:374–87.
- [23] Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirschberg B, et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. *Diabetes Care* 2015;38:2009–17.
- [24] Jabbour SA, Hardy E, Sugg J, Parikh S, Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care* 2014;37:740–50.
- [25] Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirschberg B, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care* 2015;38:376–83.
- [26] Matthaei S, Aggarwal N, Garcia-Hernandez P, Iqbal N, Chen H, Johnsson E, et al. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. *Diabetes Obes Metab* 2016;18:1128–33.
- [27] Mathieu C, Herrera Marmolejo M, González González JG, Hansen L, Chen H, Johnsson E, et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. *Diabetes Obes Metab* 2016;18:1134–7.
- [28] Zhuang Y, Song J, Ying M, Li M. Efficacy and safety of dapagliflozin plus saxagliptin vs monotherapy as added to metformin in patients with type 2 diabetes: a meta-analysis. *Medicine (Baltimore)* 2020;99:e21409.
- [29] Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *BMJ Open* 2016;6:e009417.
- [30] Pinto LC, Rados DV, Remonti LR, Viana MV, Leitão CB, Gross JL. Dose-ranging effects of SGLT2 inhibitors in patients with type 2 diabetes: a systematic review and meta-analysis. *Arch Endocrinol Metab* 2022;66:68–76.
- [31] Bhosle D, Indurkar S, Quadri U, Chandekar B. A comparative study of efficacy and safety of different sodium glucose co-transporter 2 (SGLT-2) inhibitors in the management of patients with type II diabetes mellitus. *J Assoc Physicians India* 2022;70:11–2.
- [32] Scheen AJ. SGLT2 inhibitors as add-on therapy to metformin for people with type 2 diabetes: a review of placebo-controlled trials in Asian versus non-Asian patients. *Diabetes Metab Syndr Obes* 2020;13:2765–79.