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Efficacy and safety of a fixed-dose combination of dapagliflozin and linagliptin (AJU-A51) in patients with type 2 diabetes mellitus: A multicentre, randomized, double-blind, parallel-group, placebo-controlled phase III study

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Abstract

Aims: To evaluate the efficacy and safety of add-on dapagliflozin in patients with type 2 diabetes mellitus (T2D) who had inadequate glycaemic control with metformin and linagliptin.

Materials and Methods: A total of 235 patients with inadequate response to metformin (≥1000 mg/day) plus linagliptin (5 mg/day) were randomized to receive either dapagliflozin/linagliptin fixed-dose combination (FDC [AJU-A51]) 10/5 mg/day

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($n = 117$) or linagliptin 5 mg plus placebo ($n = 118$) for 24 weeks. After the main treatment period, patients who received linagliptin plus placebo were treated with AJU-A51 for an additional 28 weeks. Change in glycated haemoglobin (HbA1c) from baseline to Week 24 was the primary endpoint.

Results: AJU-A51 significantly reduced HbA1c levels (from 7.93% ± 0.82% to 7.11% ± 0.61%) compared with linagliptin plus placebo (from 7.80% ± 0.71% to 7.87% ± 0.94%), with a least squares mean difference of −0.88% (95% confidence interval −1.07 to −0.68; $p < 0.0001$) at 24 weeks. The AJU-A51 group had a significantly higher proportion of patients who achieved HbA1c <7.0% at Week 24 than the control group (44.8% vs. 18.6%; $p < 0.001$). The AJU-A51 group maintained glycaemic efficacy up to 52 weeks, whereas the control group showed a substantial reduction in HbA1c after switching to AJU-A51 in the extension study period. Both groups had similar incidence of treatment-emergent and serious adverse events, and no cases of symptomatic hypoglycaemia were reported.

Conclusions: Dapagliflozin and linagliptin FDC (AJU-A51) showed potent glucose-lowering effects, with good tolerability, in patients with T2D who had poor glycaemic control on metformin and linagliptin (ClinicalTrials.gov [NCT06329674]).

KEYWORDS
dapagliflozin, linagliptin, randomized controlled trial, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes mellitus (T2D) is a chronic disease that affects millions of individuals worldwide.[1] Based on its long-standing evidence of efficacy, cost, weight neutrality, and favourable safety profile, metformin is traditionally recommended as the first-line oral antidiabetic medication for T2D.[2] Since 2010, metformin has consistently been the most prescribed antidiabetic medication.[3] However, because T2D has a progressive course,[4] many patients need multiple antidiabetic medications to achieve their glycaemic goals.[5] Clinical guidelines provide several recommendations for second-line drugs after metformin, each considering the individual's clinical characteristics, including cardiovascular risk, weight management goals, side effects, and preferences.[5,6] The combination of metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor is predominantly used as dual therapy for T2D in Korea.[3,7] Linagliptin is one of the most frequently prescribed DPP-4 inhibitors.[8] Compared with other DPP-4 inhibitors, linagliptin is mainly eliminated through nonrenal pathways.[9] Thus, dosage adjustments are unnecessary for patients with impaired renal function.[10]

Despite the widespread use of dual therapy, the rate of glycated haemoglobin (HbA1c) control has not significantly improved.[11] Various medications can be added as a third option when glycaemic control with metformin and a DPP-4 inhibitor is inadequate (HbA1c > 7%). However, there is no consensus regarding the optimal choice for third-line therapy because there is insufficient evidence supporting the use of one medication over another. Although previous studies have demonstrated the efficacy of triple combinations involving a sodium-glucose cotransporter 2 (SGLT2) inhibitor with metformin and a DPP-4 inhibitor,[12–17] the specific effect of adding dapagliflozin to linagliptin and metformin remains unknown. Additionally, the efficacy of dapagliflozin and linagliptin fixed-dose combination (FDC) has not yet been evaluated in patients with dual antidiabetic therapy.

In this phase III trial, the efficacy and safety of add-on dapagliflozin in the form of a dapagliflozin/linagliptin FDC in patients with T2D who had inadequate glycaemic control with metformin and linagliptin were investigated.

2 | MATERIALS AND METHODS

2.1 | Study details

This study was a multicentre, randomized, double-blind, parallel-group, placebo-controlled phase III study. The trial (ClinicalTrials.gov [NCT06329674]) was conducted at 30 centres in Korea between May 2021 and June 2023. This study was conducted in compliance with the Helsinki Declaration (2013) and the International Conference on Harmonization Good Clinical Practice guidelines. The protocol was approved by the institutional review board (IRB) of each centre (Asan Medical Center IRB no. 2021-0216). All eligible patients provided written informed consent before enrolment. AJU-A51 (dapagliflozin/linagliptin 10/5 mg FDC tablet) was provided by AJU PHARM Co., Ltd. (Korea) and taken orally once daily in the morning.

2.2 | Study participants

Patients with T2D who were aged between 19 and 75 years, had a body mass index (BMI) of <40 kg/m^2 and were using one to three oral hypoglycaemic medications were considered eligible. The glycaemic criterion for enrolment was as follows: (a) 7% ≤ HbA1c ≤ 10.5% and fasting plasma glucose (FPG) ≤270 mg/dL in those with one or two oral hypoglycaemic agents before screening or (b) 6.5% ≤ HbA1c ≤ 9.5% and FPG ≤270 mg/dL in those with three oral hypoglycaemia agents before screening.

The key exclusion criteria included patients with type 1 or secondary diabetes (i.e., pancreatic surgery, steroid use, pancreatic disease) and those who had experienced metabolic acidosis, including diabetic ketoacidosis or lactic acidosis, or history of severe heart and/or brain disease in the preceding 6 months, ongoing treatment of acute haemorrhagic or necrotic pancreatitis, severe infection, history of malignancy 5 years prior to screening, and/or bariatric surgery 1 year prior to screening. The inclusion and exclusion criteria are described in detail in the Supporting Information, Table S1.

2.3 | Study design

The study period comprised two phases: a 24-week main treatment period conducted in a double-blind setting, followed by an additional 28-week extension period with open-label treatment (Supporting Information, Figure S1). After screening, patients who met the inclusion criteria were stabilized with metformin (over 1000 mg) and linagliptin 5 mg daily for 8 weeks. Subsequently, there was a 2-week run-in period with metformin (over 1000 mg), linagliptin 5 mg, and an AJU-A51 placebo in single-blind conditions. Following this period, patients who had an HbA1c of ≥7.5% to ≤10.5% with metformin and linagliptin were randomly assigned 1:1 to one of two treatment arms: the experimental group received metformin, AJU-A51, and a linagliptin placebo (referred to as the AJU-A51 group hereafter), while the control group received metformin, linagliptin, and an AJU-A51 placebo (referred to as the linagliptin plus placebo group hereafter). Randomization was stratified by HbA1c level (<8.0% or ≥8.0%) and estimated glomerular filtration rate (eGFR; <90 or ≥90 mL/min/1.73 m^2). Participants were administered the clinical trial drugs according to their assigned groups for 24 weeks, and planned efficacy and safety assessments were conducted at 12 and 24 weeks. All participants who completed the main treatment period were administered AJU-A51 and metformin for an additional 28-week extension period, with no dose adjustments of either medication.

During the main treatment and extension period, rescue therapy was permitted based on the investigator's judgement. The criteria for rescue therapy are provided in the Supplementary Methods.

2.4 | Study endpoint

The primary endpoint was the changes in HbA1c (%) from baseline to 24 weeks of treatment. The secondary endpoints were the (a) change in HbA1c from baseline to 12 weeks of treatment, (b) change in glycaemic parameters (FPG, homeostatic model assessment index of insulin resistance [HOMA-IR], homeostatic model assessment index for beta-cell function [HOMA-β], quantitative insulin sensitivity check index [QUICKI]) at 12 and 24 weeks, (c) changes in lipid parameters (total cholesterol [TC], triglycerides [TG], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]) at 12 and 24 weeks, (d) changes in body weight and waist circumference at 12 and 24 weeks, and (e) proportions of participants who reached target HbA1c below 6.5% and 7% at 24 weeks. In addition, changes in blood pressure and biochemistry profiles of special interest were investigated at 12 and 24 weeks. Additional information about the laboratory measurements is available in the Supplementary Methods.

The safety profile was assessed by recording any adverse events, the incidence of symptomatic hypoglycaemia (<70 mg/dL), variations in liver and renal function, vital signs, physical examination results, and electrocardiogram findings.

2.5 | Statistical analysis

The sample size of participants was calculated assuming an HbA1c difference of 0.4% and a standard deviation (SD) of 1.0% between the experimental and the control groups. The 0.4% decrease in HbA1c was chosen based on the results of a previous study with a similar design, in which dapagliflozin significantly decreased HbA1c compared to placebo when added to sitagliptin plus metformin, with a mean difference of −0.4% between the two groups.[18] The calculated sample size was 198 (99 in each arm) with a power (1 − β) of 0.8 and a significance level of 0.05 (two-tailed test). Considering a dropout rate of 15%, the final required sample size was 234 (117 per group).

Baseline demographic, clinical, and laboratory data are presented as mean ± SD for continuous variables and number and percentage for categorical variables. Differences in baseline characteristics between treatment groups were compared using a two-sample *t*-test or Wilcoxon rank sum test for continuous variables and chi-squared or Fisher's exact tests for categorical variables.

The primary efficacy analysis was performed in the full analysis set (FAS), which included all randomized patients who had baseline and at least one follow-up HbA1c measurement. The data collected after initiating rescue medication were treated as missing values in all efficacy analyses. To analyse the primary endpoint, a mixed-effect model repeated measure (MMRM) analysis was used to estimate the differences in means and their 95% confidence intervals (CI) between two groups. The model included treatment group, visit, visit-by-treatment interaction, and stratification factor (eGFR group) as fixed effects and baseline HbA1c value as a covariate. The MMRM was also used to analyse other secondary endpoints in continuous variables, with each baseline parameter included as an additional covariate. To assess the achievement rate of HbA1c levels ≤6.5% or 7% at Week 24, differences between groups were evaluated using the Cochran–Mantel–Haenszel test, with stratification factors (HbA1c and eGFR group) as covariates. To control the overall type 1 error rate, the statistical significance

for the primary endpoint and the key secondary endpoints related to HbA1c and FPG were evaluated using a stepwise testing procedure. The testing sequence was as follows: (1) change in HbA1c at 24 weeks; (2) change in HbA1c at 12 weeks; and (3) change in FPG at 12 and 24 weeks. For the remaining secondary endpoints, including changes in HOMA-IR, HOMA-β and QUICKI at 12 and 24 weeks, the proportion of patients achieving target HbA1c, changes in lipid parameters (TC, TG, LDL-C, HDL-C), and changes in body weight and waist circumference, statistical significance was assessed using MMRM analysis.

Safety outcomes were assessed in the safety set, which included all participants who took the trial drug at least once after being randomized. The frequency of adverse reactions was presented as number and percentage for each treatment group, and differences between groups were evaluated using the chi-squared test or Fisher's exact test. Two-sided p values <0.05 were taken to indicate statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Subject disposition

A total of 318 patients were screened in the endocrinology departments of 30 centres in Korea. Sixty-five patients who did not meet the inclusion criteria were excluded. Eighteen patients withdrew their agreement to participate in the study during the screening and run-in period. Finally, 235 patients with T2D were enrolled and allocated to the AJU-A51 group ($N = 117$) and the linagliptin plus placebo group ($N = 118$). During the main treatment period, 25 participants were withdrawn from the study (13 from the AJU-A51 group and 12 from the linagliptin plus placebo group), resulting in 210 participants completing the main treatment period. During the extension period, 194 participants entered the study. The AJU-A51 group ($N = 97$) maintained their medication until study completion, whereas the linagliptin plus placebo group (N = 97) switched regimen to metformin plus AJU-A51. Finally, 188 participants completed the extension period, with a dropout of six participants (Figure 1).

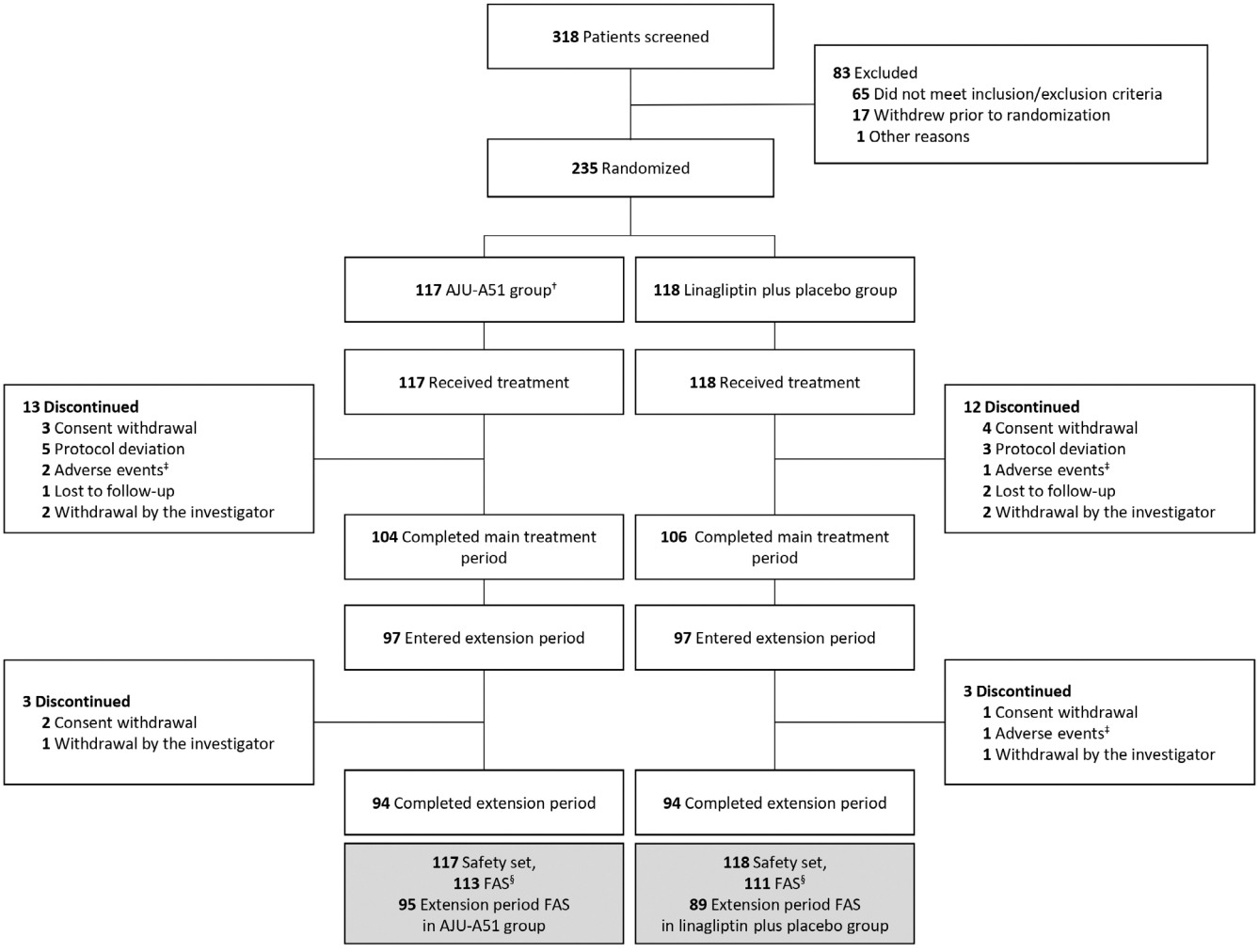

FIGURE 1 Study enrolment flowchart. †AJU-A51 refers to dapagliflozin/linagliptin fixed-dose combination. ‡Adverse events other than hypoglycaemia and abnormal liver enzyme levels. §All 13 subjects were excluded from the full analysis set (FAS) because of the absence of follow-up glycated haemoglobin results after baseline examination.

3.2 | Baseline characteristics

The baseline characteristics in the two treatment groups are shown in Table 1. The mean age and baseline BMI of participants were balanced across treatment groups: 58.7 ± 10.5 years and 26.1 ± 3.8 kg/m^2 in the AJU-A51 group and 57.8 ± 10.4 years and 26.0 ± 4.2 kg/m^2 in the linagliptin plus placebo group. No significant differences were observed in most of the biochemical profiles between the groups, except for systolic blood pressure ($p = 0.011$). The mean baseline HbA1c was comparable: 7.93% ± 0.82% in the AJU-A51 group and 7.80% ± 0.71% in the linagliptin plus placebo group.

3.3 | Glycaemic efficacy outcomes

During the 24-week main trial period, AJU-A51 treatment showed significantly greater decreases in HbA1c compared with linagliptin plus placebo (Figure 2A). The least squares means ± standard error of HbA1c changes from baseline at Week 24 were −0.77 ± 0.07% in the AJU-A51 group and +0.10 ± 0.07% in the linagliptin plus placebo group, and the least squares mean difference between the groups was −0.88% (95% CI −1.07, −0.68) in MMRM analysis ($p < 0.0001$). The AJU-A51 group constantly showed lower HbA1c and FPG levels than the linagliptin plus placebo group at each time point of evaluation during the main treatment period ($p < 0.0001$; Figure 2A,B). The AJU-A51 group

TABLE 1 Demographic and baseline characteristics at randomization.

	AJU-A51[a] ($n = 117$)	Linagliptin plus placebo ($n = 118$)	*p* value
Age, years	58.66 ± 10.48	57.75 ± 10.44	0.407
Male, *n* (%)	54 (46.15)	72 (61.02)	0.022
Height (cm)	162.26 ± 9.20	165.11 ± 8.60	0.015
Weight (kg)	68.96 ± 12.73	71.21 ± 14.45	0.251
BMI (kg/m^2)	26.12 ± 3.84	26.01 ± 4.22	0.612
Duration of diabetes (years)	9.97 ± 6.94	9.80 ± 6.41	0.987
SBP (mmHg)	127.25 ± 13.19	130.93 ± 13.16	0.011
DBP (mmHg)	75.52 ± 10.48	76.99 ± 9.62	0.177
Biochemistry profile			
HbA1c, %	7.86 ± 0.72	7.86 ± 0.65	0.766
FPG, mg/dL	161.20 ± 34.72	158.99 ± 32.74	0.733
AST, IU/L	28.03 ± 16.44	27.33 ± 12.75	0.305
ALT, IU/L	30.09 ± 20.09	29.56 ± 16.43	0.427
Total bilirubin, mg/dL	0.82 ± 0.35	0.78 ± 0.27	0.493
BUN, mg/dL	14.18 ± 3.85	14.92 ± 3.79	0.124
Creatinine, mg/dL	0.78 ± 0.17	0.79 ± 0.19	0.554
eGFR, mL/min/1.73 m^2	92.52 ± 14.37	94.31 ± 14.74	0.347
Total cholesterol, mg/dL	145.09 ± 30.36	140.80 ± 31.71	0.182
Triglycerides, mg/dL	141.19 ± 78.05	136.00 ± 75.46	0.525
HDL-C, mg/dL	48.50 ± 11.37	48.45 ± 10.43	0.703
LDL-C, mg/dL	79.05 ± 26.08	75.79 ± 27.98	0.221
HOMA-IR	4.10 ± 4.07	3.60 ± 2.26	0.363
HOMA-β, %	45.15 ± 41.78	45.28 ± 31.24	0.253
Dyslipidaemia, *n* (%)	94 (80.3)	99 (83.9)	0.477
Hypertension, *n* (%)	53 (45.3)	58 (49.2)	0.554
Dose of metformin (mg)	1365.1 ± 448.9	1319.9 ± 400.2	0.435

Note: Values are presented as mean ± standard deviation and *n* (%) for categorical variables, where appropriate.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment index of insulin resistance; HOMA-β, homeostatic model assessment index of beta-cell function; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

[a]AJU-A51 refers to dapagliflozin/linagliptin fixed-dose combination.

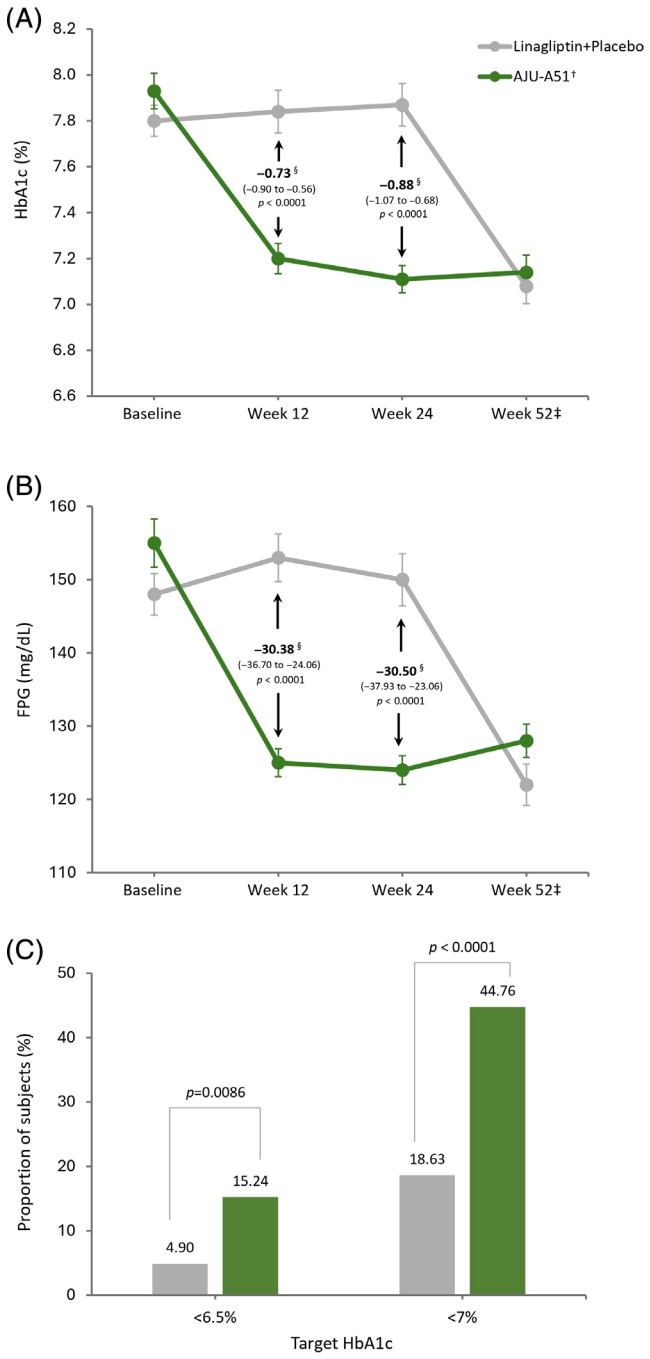

FIGURE 2 Glycaemic outcomes. (A) Changes in glycated haemoglobin (HbA1c) and (B) fasting plasma glucose (FPG) levels from baseline. (C) Achieved target glycaemic goals of HbA1c at Week 24. (A and B) Values at each time point are presented as mean ± standard error. (C) Values are presented as percentage (%). †AJU-A51 refers to dapagliflozin/linagliptin fixed-dose combination. ‡Extension study: participants were additionally administered with AJU-A51 for 28 weeks regardless of the group assigned in the main study. §Differences in changes between the two groups are reported as least squares mean (95% confidence interval).

maintained glycaemic efficacy up to 52 weeks, whereas the linagliptin plus placebo group showed substantial reduction in HbA1c and FPG levels after switching to AJU-A51 in the extension study period.

The proportion of patients who achieved target HbA1c at Week 24 is presented in Figure 2C. Among the subjects included in FAS, the proportion of target HbA1c achievement was evaluated only for patients who had HbA1c values available at 24 weeks (105 and 102 patients in the AJU-A51 and linagliptin plus placebo groups, respectively). The reasons for exclusion from the analysis at 24 weeks are detailed in the Supporting Information, Table S2. The AJU-A51 group had a significantly higher proportion of patients who achieved HbA1c levels below 6.5% (16 out of 105, 15.2%) compared with the linagliptin plus placebo group (5 out of 102, 4.9%; $p = 0.0086$). When the target was set at HbA1c levels below 7.0%, the AJU-A51 group also had a higher proportion of patients who met this goal compared with the linagliptin plus placebo group (44.8% vs. 18.6%; $p < 0.001$).

Considering that sex and systolic blood pressure showed statistically significant differences between groups at baseline, we conducted additional MMRM analyses including these two factors as covariates (Supporting Information, Table S3). The reanalysed p values for the primary and secondary outcomes in the two groups were generally consistent with our original results.

During the main treatment period, 4.5% of participants (5 out of 111) in the linagliptin plus placebo group were indicated for rescue therapy, while no participant in the AJU-A51 group was indicated for rescue therapy. Of the five participants in the linagliptin plus placebo group who received rescue therapy, three were given rescue medication and two were advised on lifestyle improvements at the investigator's judgement.

3.4 | Other clinical outcomes

The major metabolic and lipid outcomes are presented in Figure 3. AJU-A51 significantly reduced HOMA-IR, body weight and TG, and increased HDL-C compared with linagliptin plus placebo at Week 24. No significant changes were observed in HOMA-β or LDL-C levels in the two groups.

The outcomes for other anthropometric and biochemical variables are presented in Table 2. At Week 24, AJU-A51 significantly decreased BMI, body weight, systolic/diastolic blood pressure, uric acid, aspartate aminotransferase and alanine aminotransferase, which all showed statistically significant improvements compared with the control group. Regarding renal function, AJU-A51 and placebo did not demonstrate significant changes in creatinine levels and eGFR.

3.5 | Safety outcomes

Among the 234 patients included in the safety set, overall treatment-emergent adverse events (TEAEs) were reported in 24 patients (20.5%) in the AJU-A51 group and 25 patients (21.2%) in the linagliptin plus placebo group, which showed no significant difference between groups ($p = 0.8989$; Table 3). The incidence rates of adverse drug reactions, serious adverse reactions, and adverse reactions that caused trial discontinuation were similar in the two groups. The details

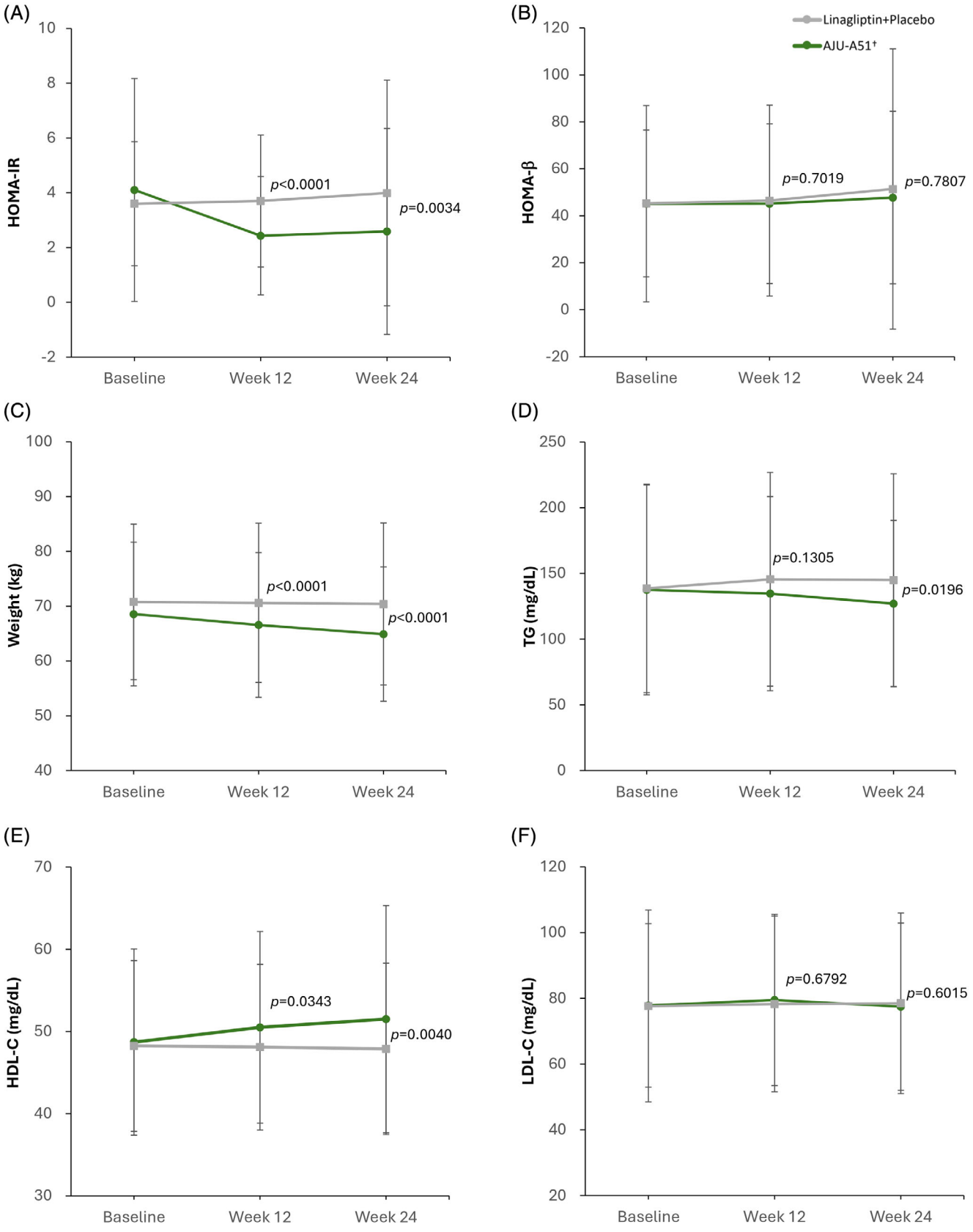

FIGURE 3 Metabolic and lipid outcomes. Changes in (A) homeostatic model assessment of insulin resistance (HOMA-IR), (B) homeostatic model assessment index of beta-cell function (HOMA-β), (C) body weight, (D) triglycerides (TG), (E) high-density lipoprotein cholesterol (HDL-C), and (F) low-density lipoprotein cholesterol (LDL-C) levels from baseline to 24 weeks. Values at each time point are presented as mean ± standard deviation. †AJU-A51 refers to dapagliflozin/linagliptin fixed-dose combination.

TABLE 2 Changes in metabolic, glycaemic, and other clinical variables during the main treatment period.

	AJU-A51[a] ($n = 113$)			Linagliptin plus placebo ($n = 111$)			
	Baseline	24 weeks	*p* value	Baseline	24 weeks	*p* value	*p* value[b]
BMI	26.00 ± 3.95	25.00 ± 3.92	<0.001	25.86 ± 4.13	25.64 ± 4.09	0.004	<0.001
Body weight	68.56 ± 13.09	64.89 ± 12.25	<0.001	70.78 ± 14.19	70.39 ± 14.77	0.014	<0.001
Waist circumference	89.77 ± 9.25	87.57 ± 8.82	0.002	88.59 ± 10.06	89.40 ± 9.22	0.071	<0.001
SBP	128.97 ± 13.86	123.62 ± 12.04	<0.001	127.86 ± 13.39	128.27 ± 12.87	0.648	<0.001
DBP	76.24 ± 10.37	72.89 ± 9.45	<0.001	74.78 ± 9.43	75.37 ± 9.52	0.545	0.001
HbA1c, %	7.93 ± 0.82	7.11 ± 0.61	<0.001	7.80 ± 0.71	7.87 ± 0.94	0.196	<0.001
FPG, mg/dL	155.36 ± 34.85	124.11 ± 20.11	<0.001	148.62 ± 29.91	150.66 ± 35.97	0.269	<0.001
HOMA-IR	4.10 ± 4.07	2.59 ± 3.76	0.003	3.60 ± 2.26	3.99 ± 4.12	0.307	0.003
HOMA-β	45.15 ± 41.78	47.75 ± 36.73	0.162	45.28 ± 31.24	51.41 ± 59.67	0.359	0.781
QUICKI	0.33 ± 0.05	0.35 ± 0.06	<0.001	0.32 ± 0.04	0.32 ± 0.05	0.470	<0.001
Total cholesterol, mg/dL	145.58 ± 30.47	146.34 ± 27.76	0.179	141.59 ± 32.06	144.54 ± 32.95	0.376	0.906
TG, mg/dL	140.66 ± 79.28	127.20 ± 64.41	0.082	136.55 ± 76.64	144.84 ± 80.59	0.238	0.020
HDL-C, mg/dL	48.35 ± 10.96	51.42 ± 13.69	0.001	48.63 ± 10.50	48.10 ± 10.51	0.493	0.004
LDL-C, mg/dL	79.81 ± 26.16	78.28 ± 25.38	0.947	76.40 ± 28.24	77.89 ± 26.99	0.697	0.602
Creatinine, mg/dL	0.77 ± 0.17	0.78 ± 0.17	0.380	0.80 ± 0.19	0.83 ± 0.23	0.097	0.330
eGFR	101.19 ± 8.02	101.25 ± 7.89	0.935	100.76 ± 8.36	100.74 ± 8.61	0.367	0.488
Uric acid, mg/dL	4.67 ± 1.44	4.36 ± 1.25	<0.001	4.86 ± 1.29	4.88 ± 1.31	0.882	0.002
AST, IU/L	26.82 ± 14.42	22.30 ± 8.90	<0.001	27.10 ± 12.50	26.65 ± 13.00	0.488	0.007
ALT, IU/L	30.54 ± 20.74	21.52 ± 13.00	<0.001	30.55 ± 19.23	28.56 ± 17.78	0.122	0.003

Note: Values are presented as mean ± standard deviation.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment index of insulin resistance; HOMA-β, homeostatic model assessment index of beta-cell function; LDL-C, low-density lipoprotein cholesterol; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; TG, triglycerides.

[a]AJU-A51 refers to dapagliflozin/linagliptin fixed-dose combination.

[b]Between-group significance at 24 weeks.

TABLE 3 Summary of adverse events.

	AJU-A51[a] ($n = 117$)			Linagliptin plus placebo ($n = 118$)			
	N (%)	95% CI	Events	*N* (%)	95% CI	Events	*p* value
Any TEAE	24 (20.51)	13.20, 27.83	30	25 (21.19)	13.81, 28.56	41	0.8989
Any ADR	4 (3.42)	0.13, 6.71	5	5 (4.24)	0.60, 7.87	6	1.0000
Any SAE	3 (2.56)	0.00, 5.43	3	2 (1.69)	0.00, 4.02	3	0.6835
AE leading to discontinuation	2 (1.71)	0.00, 4.06	2	1 (0.85)	0.00, 2.50	1	0.6218

Abbreviations: ADR, adverse drug reaction; AE, adverse event; CI, confidence interval; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]AJU-A51 refers to dapagliflozin/linagliptin fixed-dose combination.

of the TEAEs in each treatment group are described in the Supporting Information, Table S4. Gastrointestinal and nervous system disorders were the most common TEAEs in the AJU-A51 group, whereas hyperglycaemia was the most common TEAE in the linagliptin plus placebo group. No cases of symptomatic hypoglycaemia were reported in either group. The adverse reactions that caused trial discontinuation were dyspepsia and hyperhidrosis (two cases, 1.71%) in the AJU-A51 group and cardiac failure (one case, 0.85%) in the control group (data not shown).

4 | DISCUSSION

In this study, the addition of dapagliflozin to metformin and linagliptin showed significant glucose-lowering efficacy with good tolerability in participants with uncontrolled T2D on metformin and linagliptin compared with placebo. This beneficial glycaemic efficacy was evidenced by significantly higher reduction in HbA1c (−0.77% vs. +0.10%; $p < 0.001$) and a higher proportion of participants achieving target

HbA1c below 7% (44.8% vs. 18.6%; $p < 0.001$) at 24 weeks. This is the first study to investigate the efficacy and safety of add-on dapagliflozin, particularly in the form of dapagliflozin/linagliptin FDC, in patients with T2D who had inadequate glycaemic control with metformin and linagliptin.

As demonstrated in the UK Prospective Diabetes Study and Steno-2 Study, early intensive glucose control provides durable and sustained protection against diabetes-related complications, including microvascular complications and myocardial infarction.[19–21] Based on these data, the treatment of patients who are not meeting their treatment goals needs to be promptly intensified.[5,22] Although the recent American College of Physicians guideline recommends against adding DPP-4 inhibitors to metformin,[23] the combination of metformin and a DPP-4 inhibitor is the most commonly used dual therapy in Asian countries,[3,7,24] with a wide range of third-line options available, including SGLT2 inhibitors, thiazolidinediones, and sulphonylureas. Among them, SGLT2 inhibitors, which control plasma glucose levels by promoting urinary glucose excretion, have a distinct mechanism of action from that of metformin and DPP-4 inhibitors,[25] with the mechanisms potentially complementing each other. This insulin-independent mechanism of SGLT2 inhibitors minimizes the risk of hypoglycaemia while providing additional metabolic benefits that are difficult to achieve with metformin and DPP-4 inhibitors.[26,27]

In previous clinical studies on SGLT2 inhibitors as add-on therapy to metformin and DPP-4 inhibitors, the addition of SGLT2 inhibitors resulted in additional HbA1c reductions ranging from −0.34% to −0.89% across 16–26 weeks.[12,13,15–17,28] The findings of the present study (−0.88% additional reduction of HbA1c compared with the control group) are generally consistent with these previous findings. One significant strength of the present study is the addition of dapagliflozin in the form of dapagliflozin/linagliptin FDC, which has not been previously investigated in patients under metformin and linagliptin dual therapy. In India, Jain et al. reported the efficacy of simultaneous adding of dapagliflozin/linagliptin FDC to metformin,[16] showing a − 1.28% reduction in HbA1c over 16 weeks, which is greater than the −0.77% reduction observed in the present study over 24 weeks. These differences could be attributed to variations in baseline HbA1c (8.7% in their study vs. 7.9% in the present study), study design (background metformin monotherapy vs. linagliptin–metformin dual therapy in the present study), and possible ethnic differences. The findings from these studies suggest that adding dapagliflozin to linagliptin, either simultaneously or sequentially, effectively lowers HbA1c.

Beyond their glucose-lowering effects, SGLT2 inhibitors offer additional distinctive benefits, including weight loss, body composition alterations, lipid accumulation reductions, and decreased urinary protein excretion.[29] This study demonstrated significant reductions in most metabolic parameters, including BMI, body weight, and waist circumference, after adding an SGLT2 inhibitor. HOMA-IR and QUICKI improvements indicate enhanced insulin sensitivity with SGLT2 inhibitors, which aligns with earlier findings.[30,31] Despite some evidence suggesting that SGLT2 inhibitors indirectly improve beta-cell function, the increase in HOMA-β levels, an index of insulin secretion function of pancreatic beta cells, was not statistically significant in the AJU-A51 group.[18,32] A previous Japanese study on ipragliflozin found similar findings, with no changes in HOMA-β levels but an increased C-peptide index after ipragliflozin treatment.[33] SGLT2 inhibitors lower plasma insulin levels by increasing hepatic insulin clearance, which might contribute to insufficient improvements in HOMA-β levels.[33] Regarding lipid metabolism, AJU-A51 significantly reduced TG and increased HDL-C levels compared with the placebo. By contrast, neither treatment group showed significant differences in TC and LDL-C levels. This finding aligns with previous studies that found a lack of correlation between LDL-C levels and the use of SGLT2 inhibitors.[29,34] Although our study was limited by not measuring urine albumin excretion, dapagliflozin add-on treatment might exhibit renal protective effects with long-term follow-up.[35]

The addition of dapagliflozin to dual therapy was generally well tolerated, with similar rates of overall and severe adverse events across treatment groups. No cases of hypoglycaemia were observed, which corresponds to preclinical findings and mechanisms of action of SGLT2 inhibitors.[36] Indeed, clinical studies have consistently shown that DPP-4 inhibitor and SGLT2 inhibitor combinations do not increase the hypoglycaemia incidence compared to when each component was administered alone,[37–40] unless simultaneously combined with insulin or insulin secretagogues.[41] Given this background, earlier combination therapy of linagliptin and dapagliflozin may be a preferable choice for T2D with uncontrolled hyperglycaemia compared with sulphonylureas[42] and insulin[43] as a third agent. Although there are special concerns about the association of euglycaemic ketoacidosis and urinary tract infection with SGLT2 inhibitors,[44,45] the present study found no cases of metabolic acidosis/ketosis or urogenital infections, except for one case of vulvovaginal pruritus in the AJU-A51 group (Supporting Information, Table S4). The relatively low incidence of urogenital infections observed with dapagliflozin in our study may be attributed to several factors, including the concurrent use of DPP-4 inhibitors,[46] the Asian population studied,[47] and hygiene education provided during the study period.[48]

The present study has some limitations. First, all participants were Korean patients with T2D, limiting the generalizability of the findings to other populations or ethnicities. Second, the relatively small sample size might result in underestimation of the incidence of adverse events. Third, the efficacy of dapagliflozin could not be compared with that of other antidiabetic agents as placebo was used as the comparator in this study. Fourth, the absence of measures of postprandial glucose and C-peptide levels inhibits a more thorough comprehension of the impacts of dapagliflozin. Fifth, excluding patients with eGFR < 60 mL/min/1.73 m^2 might limit the generalizability of our findings. Given that metformin, linagliptin and dapagliflozin can be safely used in patients with lower eGFR, our results need validation in patients with eGFR < 60 mL/min/1.73 m^2. Despite these limitations, this study has the strength that it is the first to investigate the effects of adding dapagliflozin to metformin and linagliptin in the form of dapagliflozin/linagliptin FDC.

In conclusion, the addition of dapagliflozin and linagliptin FDC (AJU-A51) to metformin was efficacious and well tolerated in the

treatment of patients with T2D and demonstrated superiority to linagliptin treatment plus metformin. Dapagliflozin as a third-line agent, especially in the form of a FDC with linagliptin, may provide a valuable treatment option as add-on therapy for patients who have inadequate glycaemic control with linagliptin and metformin. Its additional metabolic benefits and low risk of adverse events might be especially beneficial for patients who are at high risk of hypoglycaemia or are obese.

AUTHOR CONTRIBUTIONS

W.J.L. and J.Y.P. designed the study. J.H.H. and M.J.K. contributed equally to this study as first authors. All authors contributed to the recruitment of participants and data acquisition. J.H.H. and M.J.K. contributed to data analysis. J.H.H., M.J.K. and W.J.L. interpreted the data and drafted the initial manuscript. All the authors critically reviewed and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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