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ORIGINAL ARTICLE

Efficacy and safety of initial combination therapy with gemigliptin and metformin compared with monotherapy with either drug in patients with type 2 diabetes: A double-blind randomized controlled trial (INICOM study)

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Background: Gemigliptin is a new dipeptidyl peptidase-IV inhibitor. We investigated the efficacy and safety of initial combination therapy with gemigliptin and metformin compared with monotherapy with either drug in patients with type 2 diabetes (T2D).

Methods: A total of 433 T2D patients with a glycosylated haemoglobin (HbA1c) level of 7.5% to 11.0% and a fasting plasma glucose (FPG) concentration <270 mg/dL were randomly assigned to 3 groups: (1) gemigliptin 50 mg qd + metformin 1000 to 2000 mg qd (titrated individually), (2) gemigliptin 50 mg qd, or (3) metformin 1000 to 2000 mg qd. The primary end-point was the change in HbA1c level after 24 weeks. Secondary end-points were the changes in FPG, insulin, proinsulin and C-peptide levels. The percentages of responders who achieved an HbA1c level <7% (or <6.5%) were compared between treatment groups.

Results: Baseline HbA1c levels were 8.7% in all groups. The mean changes in HbA1c level from baseline to week 24 were −2.06%, −1.24% and −1.47% in the combination, gemigliptin monotherapy and metformin monotherapy groups, respectively. The 95% confidence intervals for between-group differences in HbA1c changes were −1.02 to −0.63 in the combination group vs the gemigliptin group and −0.82 to −0.41 vs the metformin group, which confirmed the superiority of combination therapy. A significantly higher percentage of patients in the combination therapy group reached the target HbA1c level <7% (or <6.5%) compared with the monotherapy groups. No severe side effects were observed.

Conclusions: In T2D patients, the initial combination of gemigliptin and metformin had superior efficacy without safety concerns compared with monotherapy with either drug.

KEYWORDS

DPP-IV inhibitor, phase III study, type 2 diabetes

[†]See Appendix S1.

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1 | INTRODUCTION

In 2015, the International Diabetes Federation estimated that approximately 415 million people have diabetes mellitus worldwide and that 36% of them live in the Western Pacific region.[1] Approximately 193 million people with diabetes have not been diagnosed, and 1 in 10 adults are expected to have diabetes in 2040.[1] Type 2 diabetes (T2D) is a complex disease involving mechanisms such as β-cell dysfunction, peripheral insulin resistance, abnormal liver glucose metabolism and impaired incretin effects.

The role of incretin is emphasized in the pathogenesis and treatment of T2D. An incretin, glucagon-like peptide-1 (GLP-1) plays an important role in glucose metabolism and other physiological functions.[2] GLP-1 is degraded rapidly by dipeptidyl peptidase-IV (DPP-IV), and GLP-1 reactions can be enhanced after meals by inhibiting DPP-IV and the degradation of GLP-1. DPP-IV inhibitors are insulin dependent and their use rarely leads to hypoglycaemia.[3–5] DPP-IV inhibitors can be administered orally, unlike GLP1-1 agonists which must be injected.

Gemigliptin is a powerful selective DPP-IV inhibitor. In a phase I clinical trial targeting healthy men, gemigliptin was well tolerated, with no serious side effects from repeated administrations. The half-life in the whole-dose groups (25-600 mg) was 17 to 21 hours, and the pharmacokinetics of gemigliptin were not affected by food. When given at a single dose of >25 mg, DPP-IV inhibition occurred after 24 hours, postprandial GLP-1 level increased and postprandial glucose level decreased.[6,7] A phase II clinical trial found significant reduction in HbA1c level at all gemigliptin doses (50, 100 and 200 mg), and 50 mg was selected as the appropriate dose.[8] A phase III clinical trial to determine the efficacy and safety of monotherapy with gemigliptin performed in multiple nations reported significant reductions in HbA1c and fasting plasma glucose (FPG) levels with 50 mg gemigliptin compared with placebo.[9] A superior rate of achievement of the target of an HbA1c level <7% or 6.5% was found without clinically significant adverse events (AEs). A 52-week drug-tolerance study confirmed the long-term safety of gemigliptin 50 mg monotherapy (results in preparation for submission).

Previously, single anti-diabetic agents, particularly metformin, were given to new T2D patients, and the dose was increased at 2 to 3-month intervals to reach the HbA1c target level. Recent recommendations include early combination therapy with 2 drugs with different mechanisms to provide faster and better glucose control in patients with an HbA1c level ≥7.5%.[10,11] The objective of this initial combination (INICOM) study was to evaluate the efficacy and safety of combined gemigliptin 50 mg plus metformin compared with monotherapy with either drug in T2D patients.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multinational, multicentre, randomized, parallel group, double-blind, phase III trial to evaluate the efficacy and safety of initial combination therapy with gemigliptin 50 mg once daily and metformin once daily compared with monotherapy with either drug in T2D patients (ClinicalTrials.gov registration number: NCT01787396). The study was conducted at 31 sites in Korea and 9 sites in Thailand between April 2013 and December 2014. The independent ethics committee or institutional review board of each participating hospital approved the study protocol.

The study included an 8-week wash-out period for patients who had been treated with only one oral anti-diabetic medication. This was followed by a 2-week single-blind placebo run-in period for all patients. Thereafter, patients received 24 weeks of double-blind treatment in 1 of 3 groups: (1) gemigliptin 50 mg qd + metformin 1000 to 2000 mg qd with dose titration for each patient or the respective monotherapies, (2) gemigliptin 50 mg qd, or (3) metformin 1000 to 2000 mg qd with a matching placebo.

The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. All patients gave written, informed consent before inclusion in the study.

2.2 | Study subjects

The study included men and women with T2D, aged 20 years and older, who had not received any anti-diabetic medication. We also included those who, at the time of recruitment, were taking a single oral anti-diabetic drug, and they were asked to stop their medication during the 8-week wash-out period. T2D patients who had provided consent and who had an HbA1c level of 7.5% to 11.0% and an FPG <270 mg/dL were eligible for the run-in period. After completion of the run-in period, patients with treatment compliance ≥70% were randomized into 1 of the 3 groups.

Patients were excluded if they had any of the following exclusion criteria: had type 1 diabetes; had received insulin or a GLP-1 analogue in the previous 6 months; had a body mass index (BMI) of <20 or >40 kg/m^2; had an elevated serum creatinine concentration (>1.5 mg/dL) or aspartate/alanine aminotransferase (AST/ALT) ratio (>2.5 times the upper normal value); had experienced a myocardial infarction, stroke or transient ischaemic attack in the previous 6 months; or had unstable congestive heart failure or arrhythmia. Patients were also excluded if they were judged by the investigator to be inappropriate for this trial. Full inclusion and exclusion criteria are presented in Table S1 of Appendix S1.

2.3 | Study interventions

Patients were randomized (1:1:1) to receive gemigliptin 50 mg qd + metformin 1000 to 2000 mg qd (titrated individually) initial combination therapy, gemigliptin 50 mg qd monotherapy, or metformin 1000 to 2000 mg qd monotherapy for 24 weeks. Stratified block randomization was performed according to each patient's baseline HbA1c level and the presence or absence of prior history of oral anti-diabetic medications. After randomization, patients underwent a forced 6-week titration phase. During the first 2 weeks of this phase, all patients received metformin 500 mg qd (or a matching placebo). The dose of metformin was increased to 1000 mg qd at week 2, after which it was maintained for a further 2 weeks. At week 4, if the patient did not achieve the predefined FPG level of ≤110 mg/dL, the dose was increased to 1500 mg qd. Finally, the dosage of metformin was titrated to between 1000 and 2000 mg qd based on the FPG level at week 6, and the individually fixed dose was maintained until the end of the study.

Other anti-diabetic drugs or drugs affecting blood glucose level were prohibited during the study. Patients whose glycaemia was not adequately controlled during the study received an oral anti-diabetic agent (sulfonylurea) as rescue therapy.

2.4 | Measurement of anthropometric and biochemical parameters

Each subject's height, body weight, waist circumference and blood pressure were measured using standard methods. BMI was calculated by dividing the body weight (in kilograms) by the square of the height (metres squared).

The samples for each efficacy parameter analysis were measured at the central laboratory (SCL, Seoul, South Korea). To monitor safety, clinical laboratory examinations were performed at each hospital. The levels of FPG and postprandial glucose at 2 hours (PP2) were measured using the hexokinase method in blinded fashion at the central laboratory. HbA1c level was measured using a Cobas Integra Tina-Quant G2 instrument (Roche, Rotkreuz, Switzerland) and a National Glycohemoglobin Standardization Program-certified process. The concentrations of insulin, proinsulin, C-peptide and lipids (total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol) were measured in de-identified samples at the central laboratory. Serum insulin and C-peptide concentrations were measured using radioimmunoassays (Immunotech, Radiova, Czech Republic and Diasource, Louvain, Belgium, respectively). Serum proinsulin level was measured using an ELISA (EMD Millipore Co, St. Charles, Missouri).

A 75 g standard oral glucose tolerance test (OGTT) was performed at week 0 and again at week 24 to investigate dynamic glucose metabolism status. For the OGTT, the patient was given 75 g of an oral glucose solution at 0 minutes, and blood samples were taken at 0, 30, 60 and 120 minutes. The areas under the curve during the 2-hour OGTT ($AUC_{0\text{-}2h}$) for glucose and insulin were calculated using the trapezoidal method. The ratio of $AUC_{0\text{-}2h}$ insulin (or C-peptide) to $AUC_{0\text{-}2h}$ glucose was used to measure insulin secretory capacity. The homoeostasis model assessment (HOMA) for insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were calculated using fasting plasma insulin and glucose concentrations.[12] Insulin sensitivity was measured using the Matsuda index.[13] The insulinogenic index was calculated at 30 minutes (IGI_{30}) and 60 minutes (IGI_{60}) using the following equation: [30 or 60-minutes insulin − fasting insulin]/[30 or 60-minutes glucose − fasting glucose].[14] The disposition index, which reflects β-cell function adjusted for insulin sensitivity, was calculated as IGI × Matsuda index.[15,16]

- HOMA-IR = fasting plasma insulin (μU/mL) × FPG (mg/dL)/405
- HOMA-β = 360 × fasting plasma insulin (μU/mL)/[FPG (mg/dL) − 63]
- Matsuda Index = 10^4/(FPG [mg/dL] × fasting insulin [μU/mL] × mean glucose $_{OGTT}$[mg/dL] × mean insulin $_{OGTT}$[μU/mL]]$^{0.5}$
- Disposition index$_{30}$ or Disposition index$_{60}$ = IGI_{30} or IGI_{60} × Matsuda index

Other blood parameters, such as blood urea nitrogen, creatinine, AST/ALT, amylase and lipase, were analysed at each hospital and evaluated according to each hospital's reference range.

2.5 | Study end-points and safety assessments

The primary efficacy end-point was the mean change in HbA1c level from baseline to week 24. Subgroup analysis according to stratification factors was conducted. The secondary efficacy end-points were the responder rate at week 24, percentage of patients with an HbA1c level <7% or <6.5%, and the mean changes in the levels of FPG, fasting insulin, fasting proinsulin, fasting C-peptide, HOMA-β and HOMA-IR from baseline to week 24. The mean changes in body weight, waist circumference, OGTT parameters, insulinogenic index, proinsulin/insulin ratio and lipid parameters from baseline to week 24 were also compared.

To assess safety, any AEs, vital signs, clinical laboratory parameters and 12-lead electrocardiography (ECG) results were recorded at the initial screening and throughout the study. The investigator at the site evaluated any possible causal relationships between the

study medication and AEs. Hypoglycaemic episodes were recorded from the reported AEs (symptomatic) and laboratory test results (asymptomatic) and were predefined according to a plasma glucose level <70 mg/dL in accordance with the American Diabetes Association Standards of Medical Care in Diabetes.[17]

2.6 | Statistical analyses

The sample size in each treatment group (143 patients per arm) afforded 80% power at a significance level $\alpha = .025$, considering a standard deviation (SD) of 1.21, true mean difference of −0.45 and 20% of drop-out rate. A last-observation-carried-forward approach was used to replace missing data for the efficacy assessment.

Descriptive statistics (mean, SD, median, maximum and minimum) are used to describe continuous variables of baseline demographic and biochemical parameters. Categorical variables are expressed as counts and percentages. The primary efficacy analysis was conducted using analysis of covariance. The mean changes in HbA1c level from baseline to week 24 in each treatment group were adjusted for baseline HbA1c level, patient's nationality (Korean or Thai) and presence/absence of prior history of oral anti-diabetic medications.

To evaluate the superiority of the initial combination treatment compared with monotherapy with either drug, two-sided 95% confidence intervals (CIs) for the treatment difference were used to compare with mean change in HbA1c level in the initial combination group relative to those in gemigliptin monotherapy and metformin monotherapy groups. Superiority was demonstrated if the upper limit of the two-sided 95% CIs in both groups was <0.

Among the other efficacy end-points, the mean change in FPG level was determined using analysis of covariance adjusted for baseline HbA1c level, patient's nationality (Korean or Thai) and presence/absence of prior history of anti-diabetic medications. As for the results of other secondary efficacy analyses, the number of patients and percentages are presented for categorical data and descriptive statics including the mean and SD are presented for continuous data. The intergroup differences were tested using chi-square analysis (or Fisher's exact test) or two-sample *t* test (or Wilcoxon's rank-sum test).

3 | RESULTS

3.1 | Patient disposition, demographics and clinical characteristics

A total of 433 (357 Korean and 76 Thai) T2D patients were randomized. Of the randomized patients, 389 (316 Korean and 73 Thai) patients (89.8%) completed the 24-week study (Figure 1). The number of patients who were assigned to each treatment group and the number of dropouts before completion of the study were similar. Consent withdrawal was the most common reason for discontinuation.

The efficacy results focus on the full analysis set (FAS). The baseline demographics and clinical characteristics of the study population were similar between treatment groups in the FAS (Table 1). The mean age was 53.9 years, and 17.7% of the entire population was classified as elderly (≥65 years). Koreans comprised 82.1% and Thais 17.9% of the entire study population. The mean duration from diagnosis of T2DM was 3.92 years. The mean HbA1c and FPG level at the screening visit were 8.68% and 175.32 mg/dL, respectively.

3.2 | Efficacy

After the 6-week forced-titration phase, the fixed dose of metformin was lower in the initial combination group than in either monotherapy group, and the fixed dose for each patient was maintained for the 24 weeks in most patients (Table S2 of Appendix S1).

The mean changes in HbA1c level from baseline to week 24 were −2.06% in the initial combination group, −1.24% in the gemigliptin monotherapy group, and −1.47% in the metformin monotherapy group (Figure 2A). The adjusted mean treatment differences for the initial combination group vs the gemigliptin and metformin monotherapy groups were −0.82% with 95% CI (−1.02, −0.63) ($P < .001$) and −0.62% with 95% CI (−0.82, −0.41) ($P < .001$), respectively. These results show the superiority of the initial combination therapy over monotherapy with either drug.

Subgroup analysis according to the baseline HbA1c level (≥8.5% vs <8.5%) and the presence or absence of prior history of oral anti-diabetic medication showed that patients with a higher baseline HbA1c level (≥8.5%) and patients who never used anti-diabetic agents within 6 months had a greater reduction in HbA1c level from baseline to week 24.

For the responder rates, 82.4% of patients reached the target HbA1c level <7% at week 24 in the initial combination group; this was higher than the percentages of 40.7% in the gemigliptin monotherapy group and 50.0% in the metformin monotherapy group ($P < .01$ for both comparisons of the combination group vs either monotherapy group). The percentage of patients with an HbA1c level <6.5% at week 24 was also significantly higher in the initial combination group than in either monotherapy group (Figure 2B).

After 24 weeks, FPG concentration was significantly lower than the baseline level in all treatment groups. In the initial combination group, the mean change in FPG level from baseline to week 24 was −57.0 mg/dL ($P < .001$). The combination group had a significantly greater reduction in FPG level compared with both monotherapy groups. The adjusted mean treatment differences for the initial combination group vs the gemigliptin and metformin monotherapy groups were −26.6 mg/dL (95% CI, −33.7, −19.5) and −13.3 mg/dL (95% CI, −19.9, −6.7), respectively (Table 2).

The plasma insulin response during the OGTT increased progressively from 30 to 60 minutes. The $AUC_{0\text{-}2h}$ of glucose decreased significantly from baseline to week 24 in the initial combination group, and this decrease was greater than that in each monotherapy group. By contrast, the $AUC_{0\text{-}2h}$ values for insulin and C-peptide increased significantly from baseline in the initial combination group, and this increase was greater than that in each monotherapy group. HOMA-β and the proinsulin to insulin ratio also improved significantly from baseline to week 24 in the initial combination group, and this increase was significantly greater than that in each monotherapy group. Similarly, the IGI and disposition index increased significantly in the initial combination group compared to the gemigliptin or metformin

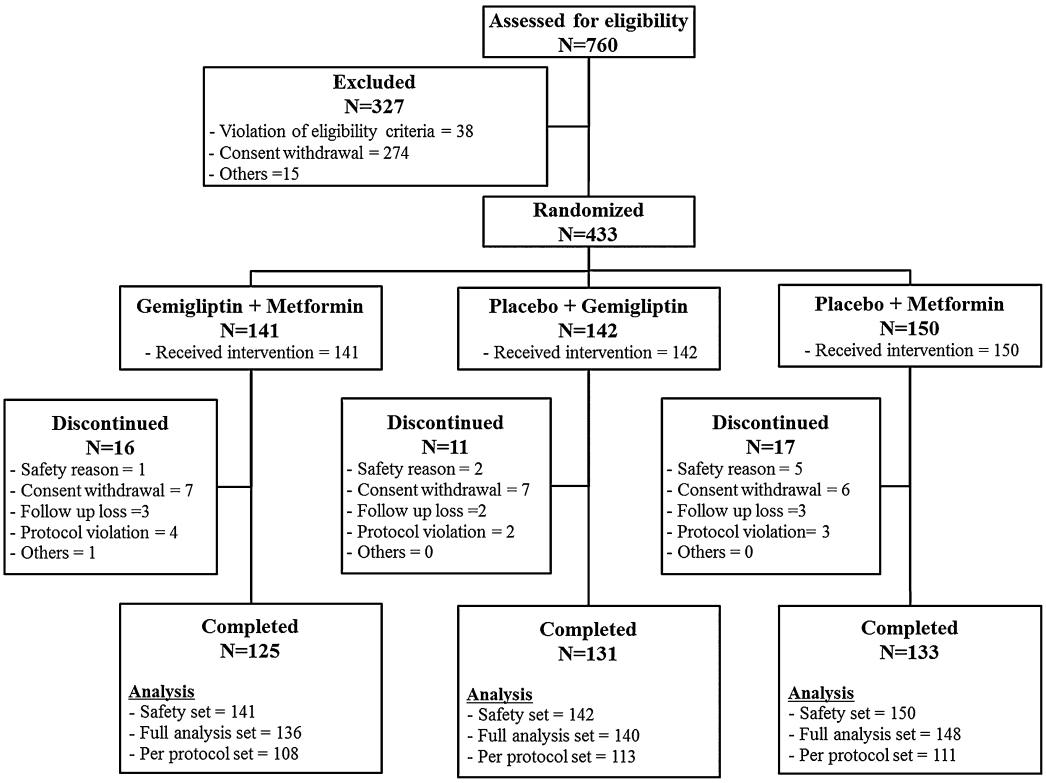

FIGURE 1 Flow diagram of the study participants.

monotherapy group. By contrast, the HOMA-IR decreased significantly from baseline in the initial combination group, and this decrease was greater than that in the gemigliptin monotherapy group.

For the lipid metabolism end-points, the concentrations of total cholesterol and LDL-cholesterol decreased significantly from baseline in all 3 groups, and the reduction was greater in the initial combination group than in the monotherapy groups. At week 24, the mean change in total cholesterol level was −16.9 mg/dL in the initial combination group, −10.7 mg/dL in the gemigliptin monotherapy group, and −12.6 mg/dL in the metformin monotherapy. The mean changes in LDL-cholesterol level were −19.5 mg/dL in the initial combination group, −14.2 mg/dL in the gemigliptin monotherapy group, and −16.1 mg/dL in the metformin monotherapy group. The levels of HDL-cholesterol and triglycerides did not change significantly in any group.

Between baseline and week 24, body weight decreased significantly by 0.8 kg in the metformin group and slightly, by 0.4 kg, in the initial combination group but not in the gemigliptin group (Table 2).

3.3 | Rescue therapy

The percentage of patients needing rescue therapy during the 24 weeks was lower in the initial combination group than in the other 2 groups. Rescue therapy was needed by 2 patients (1.47%) in the initial combination group, 6 patients (4.29%) in the gemigliptin monotherapy group and 9 patients (6.08%) in the metformin monotherapy group.

3.4 | Safety and tolerability

The percentage of patients with treatment-emergent adverse events (TEAEs) was similar among treatment groups (Table 3). No deaths occurred during the study. Nasopharyngitis was the most frequently reported TEAE (8.51%, 13.38% and 12.00% in the initial combination, gemigliptin monotherapy and metformin monotherapy groups, respectively). The incidence of serious AEs (SAEs) was lower and was similar among treatment groups. No SAE was found to be treatment related.

The percentages of patients with treatment-related AEs were 17.02%, 7.04% and 14.67% in the initial combination, gemigliptin monotherapy and metformin monotherapy groups, respectively. Most treatment-related AEs were gastrointestinal disorders (dyspepsia, diarrhoea, nausea or constipation). The incidence of treatment-related gastrointestinal disorders was not higher in the initial combination group than in the metformin monotherapy group. These findings show that combination therapy had no deleterious effects on safety.

The overall frequency of hypoglycaemic events was low. No hypoglycaemia was reported in the gemigliptin monotherapy group; 2.13% of patients in the initial combination group and 1.33% in the metformin monotherapy group exhibited hypoglycaemia. No episodes required medical assistance.

There were no clinically meaningful effects of the treatments on any laboratory safety parameter. The number of patients with an amylase or lipase level ≥3 times the upper normal limit at any visit was similar among treatment groups: 2 patients (1.42%) in the initial combination group, 1 patient (0.70%) in the gemigliptin monotherapy group and 4 patients (2.67%) in the metformin monotherapy group. One instance of increased lipase level in the initial combination group was judged to be related to the treatment, but no pancreatitis was reported during the entire study period.

TABLE 1 Baseline demographics and clinical characteristics

	Gemigliptin + metformin (n = 136)	Gemigliptin (n = 140)	Metformin (n = 148)
Age, years	54.4 ± 10.4	53.4 ± 11.0	54.0 ± 11.3
Body mass index, kg/m^2	25.8 ± 3.5	26.1 ± 3.5	25.8 ± 3.5
Nationality, n (%)			
Korean	111 (81.6)	117 (83.6)	120 (81.1)
Thai	25 (18.4)	23 (16.4)	28 (18.9)
Male/female, n (%)	78 (57.4)/58 (42.7)	80 (57.1)/60 (42.9)	89 (60.1)/59 (39.9)
Body weight, kg	69.3 ± 11.7	69.5 ± 12.2	69.1 ± 10.8
Duration of diabetes, years	4.2 ± 4.3	3.5 ± 4.6	4.1 ± 5.2
Anti-diabetic medications, n (%)			
Used within 6 mo	48 (35.3)	51 (36.4)	60 (40.5)
Used monotherapy	15 (11.0)	10 (7.1)	13 (8.8)
Washed out	33 (24.3)	41 (29.3)	47 (31.8)
Never used within 6 mo	88 (64.7)	89 (63.6)	88 (59.5)
HbA1c, %	8.65 ± 0.88	8.66 ± 0.90	8.73 ± 0.91
FPG, mg/dL	172.7 ± 47.7	169.7 ± 42.5	178.6 ± 49.7
Fasting serum insulin, μIU/mL	10.5 ± 5.4	10.5 ± 6.6	10.2 ± 5.2
Fasting serum proinsulin, pM	22.7 ± 18.6	24.5 ± 25.1	22.2 ± 16.3
Fasting serum C-peptide, ng/mL	2.7 ± 1.1	2.6 ± 1.2	2.6 ± 1.0
Fasting proinsulin to insulin ratio	0.32 ± 0.21	0.32 ± 0.19	0.33 ± 0.21
OGTT parameters			
PP1, mg/dL	333.9 ± 53.0	351.6 ± 57.3	359.2 ± 75.9
PP2, mg/dl	349.6 ± 71.4	360.4 ± 71.2	359.9 ± 87.8
Postprandial (2 h) insulin, μIU/mL	24.9 ± 16.6	32.8 ± 28.8	25.7 ± 20.2
Postprandial (2 h) proinsulin, pM	46.5 ± 22.2	66.1 ± 53.5	46.2 ± 30.1
Postprandial (2 h) C-peptide, ng/mL	6.0 ± 2.0	6.4 ± 2.8	6.0 ± 2.9
$AUC_{0\text{-}2h}$ glucose, mg × h/dL	597.1 ± 102.3	629.7 ± 104.1	643.5 ± 142.1
$AUC_{0\text{-}2h}$ insulin, μIU × h/mL	42.4 ± 23.2	52.1 ± 41.9	44.5 ± 35.2
$AUC_{0\text{-}2h}$ proinsulin, pM × h	69.7 ± 40.5	102.3 ± 89.9	72.3 ± 49.3
$AUC_{0\text{-}2h}$ C-peptide, ng × h/mL	9.1 ± 2.8	9.9 ± 4.4	9.0 ± 3.6
HOMA-β	42.0 ± 31.6	40.4 ± 30.6	38.0 ± 25.3
HOMA-IR	4.4 ± 2.2	4.4 ± 2.8	4.5 ± 2.8
IGI_{30}	1.56 ± 1.52	1.65 ± 2.04	1.68 ± 2.98
IGI_{60}	1.66 ± 1.50	2.04 ± 2.49	1.97 ± 3.08
Matsuda index	3.83 ± 1.86	3.41 ± 1.91	3.74 ± 1.83
Disposition $index_{30}$	0.31 ± 0.43	0.21 ± 0.20	0.25 ± 0.35
Disposition $index_{60}$	0.31 ± 0.33	0.25 ± 0.23	0.30 ± 0.36
Total cholesterol, mg/dL	186.1 ± 34.8	192.4 ± 41.6	186.4 ± 37.5
Triglyceride, mg/dL	165.2 ± 99.9	167.5 ± 107.3	159.7 ± 123.7
HDL-cholesterol, mg/dL	47.9 ± 10.7	48.0 ± 11.7	49.9 ± 13.4
LDL-cholesterol, mg/dL	115.7 ± 31.9	121.8 ± 37.0	115.1 ± 35.1
AST, IU/L	24.8 ± 13.8	24.5 ± 13.8	25.7 ± 14.0
ALT, IU/L	28.1 ± 16.3	28.6 ± 17.0	28.8 ± 18.7
Amylase, units	61.8 ± 26.7	64.0 ± 26.7	64.9 ± 30.0
Lipase, units	43.1 ± 42.0	43.8 ± 45.3	44.4 ± 51.8
Blood urea nitrogen, mg/dL	15.0 ± 4.2	14.5 ± 4.1	14.0 ± 3.2
Creatinine, mg/dL	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2

Data are mean ± standard deviation unless otherwise indicated. AST/ALT, aspartate/alanine aminotransferase; AUC, area under the curve; β, beta-cell function; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HbA1c, glycated haemoglobin; HOMA, homeostasis model assessment; IGI, insulinogenic index; IR, insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PP2, postprandial 2 h glucose.

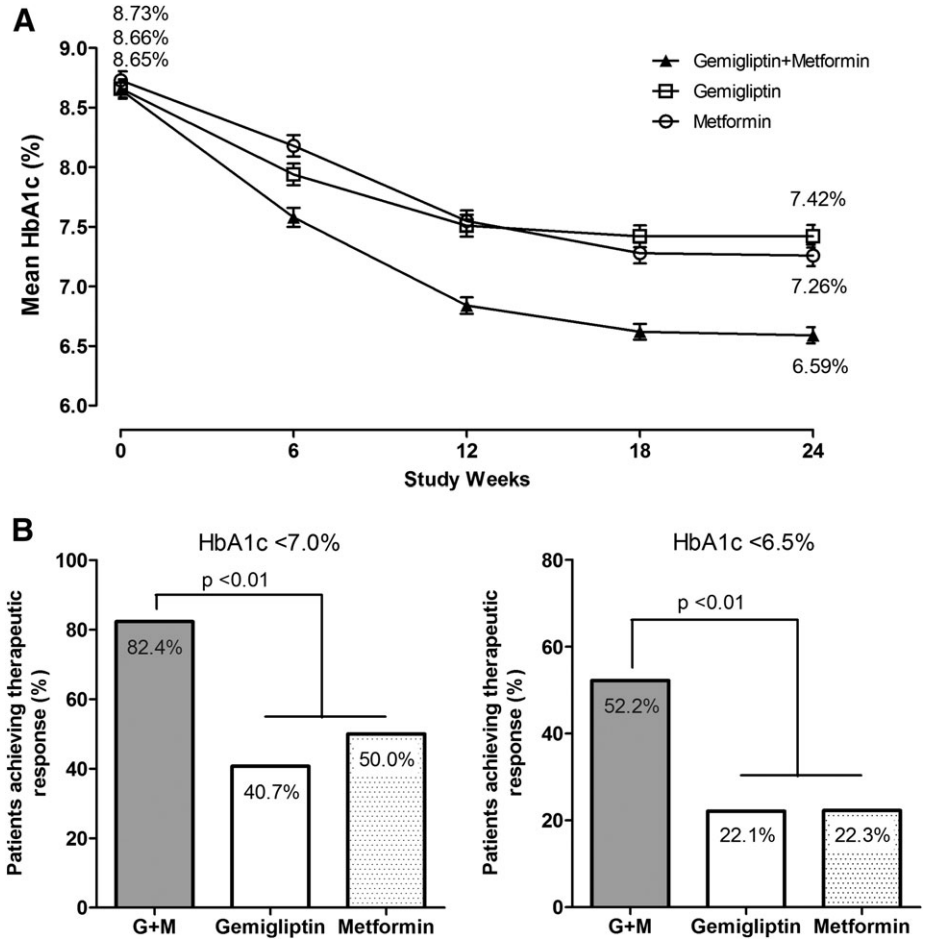

FIGURE 2 A, Changes over time in HbA1c level from baseline to week 24 in groups treated with gemigliptin and metformin combined, gemigliptin alone, and metformin alone. B, Percentages of patients with HbA1c level <7.0% and <6.5%. HbA1c, glycated haemoglobin; G + M, gemigliptin + metformin.

4 | DISCUSSION

The initial combination of gemigliptin and metformin decreased HbA1c levels by 2.06% from baseline to week 24. This decrease was significantly greater than the decreases of 1.24% in the gemigliptin monotherapy group and 1.47% in the metformin monotherapy group. A significantly higher percentage of patients in the initial combination group (82.4%) reached the target HbA1c level of <7% at week 24 compared with 40.7% in the gemigliptin monotherapy group and 50.0% in the metformin monotherapy group.

These results show a superior effect of initial combination therapy with gemigliptin and metformin compared with monotherapy with gemigliptin or metformin alone in T2D patients with baseline HbA1c levels of $8.65 \pm 0.88\%$ to $8.73 \pm 0.91\%$ (no significant difference between groups). The 2.06% reduction in HbA1c level in the initial combination group is similar to that reported for other DPP-IV inhibitors and in metformin combination studies.[18–26] In all 3 groups, the decrease in HbA1c level was greater in patients with a higher baseline HbA1c level (≥8.5%) than in those with a lower HbA1c level (<8.5%), which is also similar to the results of other studies.[18–20,22,24] This may reflect a synergistic effect caused by the mutual complementary interaction of 2 drugs with different mechanisms of action used simultaneously.[27,29] These results support the recent trend for guidelines to recommend initial combination therapy in patients with a high baseline HbA1c level.[29,30]

A significant decrease in FPG level from baseline to week 24 was observed in the combination group, and the decrease was greater than that in each monotherapy group. Consistent with this result, the fasting serum insulin and C-peptide levels also decreased significantly. As for the HbA1c level, FPG concentration decreased more in the groups with a higher baseline level (≥165.5 mg/dL).

The results of the OGTT were similar. PP2 concentration and the $AUC_{0\text{-}2h}$ for glucose decreased more in the combination therapy group than in both monotherapy groups. The $AUC_{0\text{-}2h}$ values for insulin and C-peptide increased significantly in the combination therapy group compared with both monotherapy groups.

In terms of insulin secretory function, HOMA-β and the proinsulin/insulin ratio also improved in the combination therapy group compared with both monotherapy groups. The IGI_{60}, which reflects early phase insulin secretion, and the disposition $index_{60}$, which indicates β-cell function adjusted for insulin sensitivity, increased significantly in the combination therapy group compared with the metformin or gemigliptin monotherapy group. By contrast, the HOMA-IR decreased significantly in the combination group compared with each monotherapy group. The initial combination of these 2 drugs seemed to improve glucose control in both fasting and postprandial states, and to improve insulin resistance and β-cell function more than that achieved with monotherapy with either drug. These data are similar to those reported for different DPP-IV inhibitors.[18–23] Both improvement in β-cell function and alleviation of insulin resistance lend

TABLE 2 Summary of changes from baseline in efficacy endpoints at week 24

	G + M (n = 136)	G (n = 140)	M (n = 148)	Δ comparison between groups	Mean difference (mean ± SE)	95% CI[1]
FPG, mg/dL						
Baseline	172.7 ± 47.7	169.7 ± 42.5	178.6 ± 49.7	**G + M vs G**	−26.6 ± 3.6	(−33.7, −19.5)**
Week 24	115.7 ± 28.9	141.1 ± 40.8	131.0 ± 35.5	**G + M vs M**	−13.3 ± 3.4	(−19.9, −6.7)**
Δ Mean[2]	−57.0 ± 42.0**	−28.6 ± 37.8**	−47.6 ± 43.9**			
PP1, mg/dL						
Baseline	333.9 ± 53.0	351.6 ± 57.3	359.2 ± 75.9	**G + M vs G**	−49.2 ± 13.1	(−75.2, −23.3)**
Week 24	217.2 ± 60.4	281.7 ± 53.1	255.2 ± 42.6	**G + M vs M**	−22.81 ± 13.9	(−50.5, 4.9)*
Δ Mean	−114.4 ± 67.6**	−65.1 ± 59.6**	−91.6 ± 65.9**			
PP2, mg/dL						
Baseline	349.6 ± 71.4	360.4 ± 71.2	359.9 ± 87.8	**G + M vs G**	−64.8 ± 16.5	(−97.6, −32.1)**
Week 24	211.4 ± 62.7	285.1 ± 72.3	251.6 ± 55.4	**G + M vs M**	−41.7 ± 17.0	(−75.4, −7.9)**
Δ Mean	−137.9 ± 85.3**	−73.0 ± 75.0**	−96.2 ± 76.8**			
$AUC_{0\text{-}2h}$ glucose, mg × h/dL						
Baseline	597.1 ± 102.3	629.7 ± 104.1	643.5 ± 142.1	**G + M vs G**	−86.5 ± 24.3	(−134.8, −38.2)**
Week 24	390.2 ± 96.5	510.6 ± 100.1	450.6 ± 73.2	**G + M vs M**	−35.5 ± 25.1	(−85.4, 14.5)
Δ Mean	−203.5 ± 121.5**	−117.0 ± 112.5**	−168.0 ± 119.5**			
$AUC_{0\text{-}2h}$ insulin, μIU × h/mL						
Baseline	42.4 ± 23.2	52.1 ± 41.9	44.5 ± 35.2	**G + M vs G**	8.2 ± 8.2	(−8.2, 24.6)*
Week 24	69.7 ± 46.5	68.1 ± 57.8	52.3 ± 35.1	**G + M vs M**	16.8 ± 8.0	(0.9, 32.6)**
Δ Mean	26.2 ± 40.4**	18.0 ± 39.1**	9.4 ± 35.6*			
$AUC_{0\text{-}2h}$ C-peptide, ng × h/mL						
Baseline	9.1 ± 2.8	9.9 ± 4.4	9.0 ± 3.6	**G + M vs G**	1.0 ± 0.6	(−0.1, 2.1)*
Week 24	12.1 ± 3.8	11.7 ± 4.2	9.9 ± 3.6	**G + M vs M**	2.1 ± 0.6	(0.8, 3.4)**
Δ Mean	2.9 ± 2.6**	1.9 ± 3.0**	0.8 ± 3.5			
$AUC_{0\text{-}2h}$ insulin/$AUC_{0\text{-}2h}$ glucose						
Baseline	0.07 ± 0.04	0.09 ± 0.09	0.08 ± 0.08	**G + M vs G**	0.05 ± 0.02	(0, 0.1)**
Week 24	0.19 ± 0.14	0.15 ± 0.15	0.12 ± 0.09	**G + M vs M**	0.07 ± 0.02	(0.02, 0.12)**
Δ Mean	0.11 ± 0.13**	0.06 ± 0.11**	0.05 ± 0.09**			
IGI_{30}						
Baseline	1.56 ± 1.52	1.65 ± 2.04	1.68 ± 2.98	**G + M vs G**	1.53 ± 0.85	(-0.16, 3.22)
Week 24	5.22 ± 5.22	3.8 ± 4.63	2.79 ± 2.29	**G + M vs M**	2.17 ± 0.81	(0.57, 3.77)
Δ Mean	3.58 ± 4.70**	2.05 ± 3.44**	1.41 ± 2.49**			
IGI_{60}						
Baseline	1.66 ± 1.50	2.04 ± 2.49	1.97 ± 3.08	**G + M vs G**	3.59 ± 1.50	(0.62, 6.57)**
Week 24	7.61 ± 9.22	4.35 ± 5.66	2.97 ± 3.16	**G + M vs M**	4.79 ± 1.53	(1.74, 7.84)**
Δ Mean	5.87 ± 9.28**	2.28 ± 4.06**	1.09 ± 3.92**			
Matsuda index						
Baseline	3.83 ± 1.86	3.41 ± 1.91	3.74 ± 1.83	**G + M vs G**	0.95 ± 0.45	(0.05, 1.85)*
Week 24	4.87 ± 2.95	3.45 ± 1.80	4.83 ± 1.89	**G + M vs M**	0.36 ± 0.53	(0.69, 1.41)
Δ Mean	1.09 ± 2.78**	0.14 ± 1.34	0.73 ± 2.18**			
Disposition $index_{30}$						
Baseline	0.31 ± 0.43	0.21 ± 0.2	0.25 ± 0.35	**G + M vs G**	0.46 ± 0.15	(0.15, 0.76)*
Week 24	1.05 ± 0.92	0.49 ± 0.43	0.63 ± 0.52	**G + M vs M**	0.35 ± 0.17	(0.01, 0.68)
Δ Mean	0.73 ± 0.96**	0.27 ± 0.4**	0.38 ± 0.59**			
Disposition $index_{60}$						
Baseline	0.31 ± 0.33	0.25 ± 0.23	0.3 ± 0.36	**G + M vs G**	0.89 ± 0.26	(0.36, 1.41)**
Week 24	1.53 ± 1.67	0.58 ± 0.53	0.63 ± 0.60	**G + M vs M**	0.90 ± 0.28	(0.34, 1.46)**
Δ Mean	1.21 ± 1.71**	0.32 ± 0.45**	0.31 ± 0.70**			
HOMA-β						
Baseline	42.0 ± 31.6	40.4 ± 30.6	38.0 ± 25.3	**G + M vs G**	23.5 ± 6.0	(11.7, 35.2)**

TABLE 2 Continued

	G + M (n = 136)	G (n = 140)	M (n = 148)	Δ comparison between groups	Mean difference (mean ± SE)	95% CI[1]
Week 24	80.8 ± 69.7	57.7 ± 39.2	60.6 ± 38.9	**G + M vs M**	17.0 ± 6.1	(5.0, 28.9)**
Δ Mean	39.1 ± 61.8**	15.7 ± 27.5**	22.2 ± 30.0**			
HOMA-IR						
Baseline	4.4 ± 2.2	4.4 ± 2.8	4.5 ± 2.8	**G + M vs G**	−0.8 ± 0.3	(−1.3, −0.2)**
Week 24	2.8 ± 1.8	3.6 ± 2.3	2.8 ± 1.5	**G + M vs M**	−0.0 ± 0.3	(−0.6, 0.5)
Δ Mean	−1.5 ± 2.2**	−0.8 ± 2.1**	−1.5 ± 2.3**			
Proinsulin to insulin ratio						
Baseline	0.32 ± 0.21	0.32 ± 0.19	0.33 ± 0.21	**G + M vs G**	−0.09 ± 0.02	(−0.13, −0.04)**
Week 24	0.19 ± 0.14	0.27 ± 0.19	0.22 ± 0.16	**G + M vs M**	−0.03 ± 0.02	(−0.08, 0.01)*
Δ Mean	−0.14 ± 0.20**	−0.05 ± 0.16**	−0.10 ± 0.17**			
Total cholesterol, mg/dL						
Baseline	186.1 ± 34.8	192.4 ± 41.6	186.4 ± 37.5	**G + M vs G**	−6.2 ± 3.9	(−14.0, 1.5)
Week 24	168.5 ± 31.9	179.6 ± 39.4	174.7 ± 33.6	**G + M vs M**	−4.4 ± 4.0	(−12.2, 3.4)
Δ Mean	−16.9 ± 32.1**	−10.7 ± 30.6**	−12.6 ± 31.3**			
Triglyceride, mg/dL						
Baseline	165.2 ± 99.9	167.5 ± 107.3	159.7 ± 123.7	**G + M vs G**	0.5 ± 13.6	(−26.3, 27.3)
Week 24	174.4 ± 135.4	163.4 ± 115.0	158.5 ± 80.4	**G + M vs M**	−2.8 ± 13.8	(−30.0, 24.3)
Δ Mean	6.5 ± 125.0	6.0 ± 89.8	9.3 ± 92.5			
HDL-cholesterol, mg/dL						
Baseline	47.9 ± 10.7	48.0 ± 11.7	49.9 ± 13.4	**G + M vs G**	−1.2 ± 1.0	(−3.2, 0.8)
Week 24	46.7 ± 10.4	48.8 ± 12.8	49.8 ± 12.3	**G + M vs M**	−0.5 ± 1.0	(−2.5, 1.5)
Δ Mean	−0.9 ± 8.3	0.3 ± 7.8	−0.4 ± 7.8			
LDL-cholesterol, mg/dL						
Baseline	115.7 ± 31.9	121.8 ± 37.0	115.1 ± 35.1	**G + M vs G**	−5.3 ± 3.5	(−12.2, 1.7)
Week 24	95.5 ± 27.5	106.5 ± 34.5	101.2 ± 30.4	**G + M vs M**	−3.5 ± 3.7	(−10.6, 3.7)
Δ Mean	−19.5 ± 30.0**	−14.2 ± 26.3**	−16.1 ± 28.1**			
Body weight, kg						
Baseline	69.3 ± 11.7	69.5 ± 12.2	69.1 ± 10.8	**G + M vs G**	−0.3 ± 0.3	(−0.9, 0.3)
Week 24	68.9 ± 12.1	69.4 ± 12.7	68.2 ± 11.1	**G + M vs M**	0.4 ± 0.3	(−0.2, 1.0)
Δ Mean	−0.4 ± 2.7	−0.1 ± 2.4	−0.8 ± 2.5**			

Data are mean ± standard deviation unless otherwise indicated. AUC, area under the curve; CI, confidence interval; FPG, fasting plasma glucose; G, gemigliptin; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IGI, insulinogenic index; IR, insulin resistance; LDL, low-density lipoprotein; M, metformin; PP1, postprandial 1 hour glucose; PP2, postprandial 2 hour glucose; SE, standard error.

[1]Indicates *P* for comparison of Δ between groups. *$P < .05$, **$P < .01$.

[2]Paired *t* test between baseline and week 24.

credence to the notion of the complementary mechanisms of the gemigliptin and metformin combination.

Furthermore, although GLP-1 level was not measured in this study, changes in active GLP-1 level after combination therapy were reported in the phase I study of gemigliptin, in which co-therapy with gemigliptin and metformin caused a larger increase in active GLP-1 compared with monotherapy.[31] These data suggest that gemigliptin and metformin work through complementary and additive mechanisms to increase active GLP-1 level.[31] In the aforementioned study, glucagon level was lower after combination therapy than after metformin therapy, which is consistent with previously reported results that DPP-IV suppresses plasma glucagon secretion.[32] Thus, it seems clear that the superior glucose-lowering efficacy of gemigliptin and metformin combination therapy compared with monotherapy exists because of the increase in GLP-1 level and decrease in glucagon level.

Interestingly, the titration dose of metformin at week 24 was significantly lower in the combination group than in the 2 monotherapy groups (Table S2 of Appendix S1). This finding suggests that low-dose metformin can be used in the initial combination with gemigliptin and achieve the same degree of glucose reduction. This is consistent with the result of a previous study with a similar design.[26]

The concentrations of total cholesterol and LDL-cholesterol decreased significantly from baseline in all 3 groups, and the reduction was nonsignificantly greater in the initial combination group than in the monotherapy groups. This finding is consistent with a recently reported meta-analysis that showed a possible beneficial effect of DPP-IV inhibitors on lipid metabolism.[33] There were no significant

TABLE 3 Summary of overall safety and selected adverse events (AEs) during the 24 weeks

	Gemigliptin + Metformin (n = 141)		Gemigliptin (n = 142)		Metformin (n = 150)	
	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events
Total TEAEs	86 (61.0)	185	76 (53.5)	158	87 (58.0)	183
Serious AEs	6 (4.3)	6	4 (2.8)	4	7 (4.7)	8
AEs related to study drug[1]	24 (17.0)	33	10 (7.0)	10	22 (14.7)	30
Gastrointestinal AEs related to study drug	16 (11.4)	20	7 (4.9)	7	19 (12.7)	24
AEs reported in ≥ 5.0% of subjects						
Diarrhoea	6 (4.3)	7	0 (0.0)	0	11 (7.3)	11
Dyspepsia	13 (9.2)	14	7 (4.9)	7	10 (6.7)	11
Nasopharyngitis	12 (8.5)	14	19 (13.4)	20	18 (12.0)	23
Back pain	0 (0.0)	0	1 (0.7)	1	8 (5.3)	8
Hypoglycaemia	3 (2.1)	3	0 (0.0)	0	2 (1.3)	7

AE, adverse event; TEAE, treatment-emergent adverse event.

[1]Assessed by investigators.

differences in body weight changes between groups, but waist circumference decreased significantly from baseline in the combination therapy group, with numerically greater decrease compared with the monotherapy groups.

The most frequent adverse drug reactions were gastrointestinal disorders, but the incidence rates of adverse drug reactions did not differ between the combination therapy and metformin groups. SAEs were reported in 6 (4.3%), 4 (2.8%) and 7 (4.7%) patients in the combination therapy, gemigliptin and metformin groups, respectively. In all cases, the relationship between the SAE and the investigational products was assessed as "not related." The incidence rates of diarrhoea and dyspepsia were higher in the 2 groups given metformin than in the gemigliptin monotherapy group, which is similar to the occurrence of AEs reported by other related studies.[20,21,23] These effects seem to result from metformin administration.

Three hypoglycaemic episodes were reported by 3 patients (2.1%) in the combination therapy group; 7 events were reported by 2 patients (1.3%) in the metformin group; and no event was reported in the gemigliptin group. These rates did not differ significantly between groups. This frequency is similar to the incidence rate of hypoglycaemia reported in other studies with a similar design.[22–27] Only a few patients exhibited elevated amylase or lipase levels, and the rate did not differ between groups. There was no case of pancreatitis in this study. Thus, the risk of pancreatitis because of gemigliptin administration was not elevated, which is consistent with recent studies of other DPP-IV inhibitors.[34,35] In addition, no clinically significant changes were observed in vital signs or ECG findings.

5 | CONCLUSION

In this multinational, multicentre, randomized, active-controlled, double-blind, phase III trial with T2D patients, initial combination therapy with gemigliptin and metformin for 24 weeks showed better glucose-lowering efficacy compared with monotherapy with either drug. This combination therapy showed benefits such as improved β-cell function and insulin sensitivity, and had similar safety results in terms of low rates of AEs and hypoglycaemia compared with monotherapy with either drug. These results suggest that gemigliptin, a new DPP-IV inhibitor, combined with metformin is efficacious and safe when used as the initial combination in patients with T2D.

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Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Author contributions

S.L., K.A.H., J.M.Y., P.C., E.S.K., K-H.Y., S.K., M.K.M., K.W.L., D-J.K., M.K. and M.W. contributed to the conduct of the study and the interpretation of data, and drafted, reviewed and approved the manuscript. M-K.L. contributed to the design and conduct of the study and the acquisition, analysis and interpretation of data, and drafted, reviewed and approved the manuscript. E.Y.K. and S-H.K. contributed to the design of the study and analysis and interpretation of data, and reviewed and approved the manuscript.

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SUPPORTING INFORMATION

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