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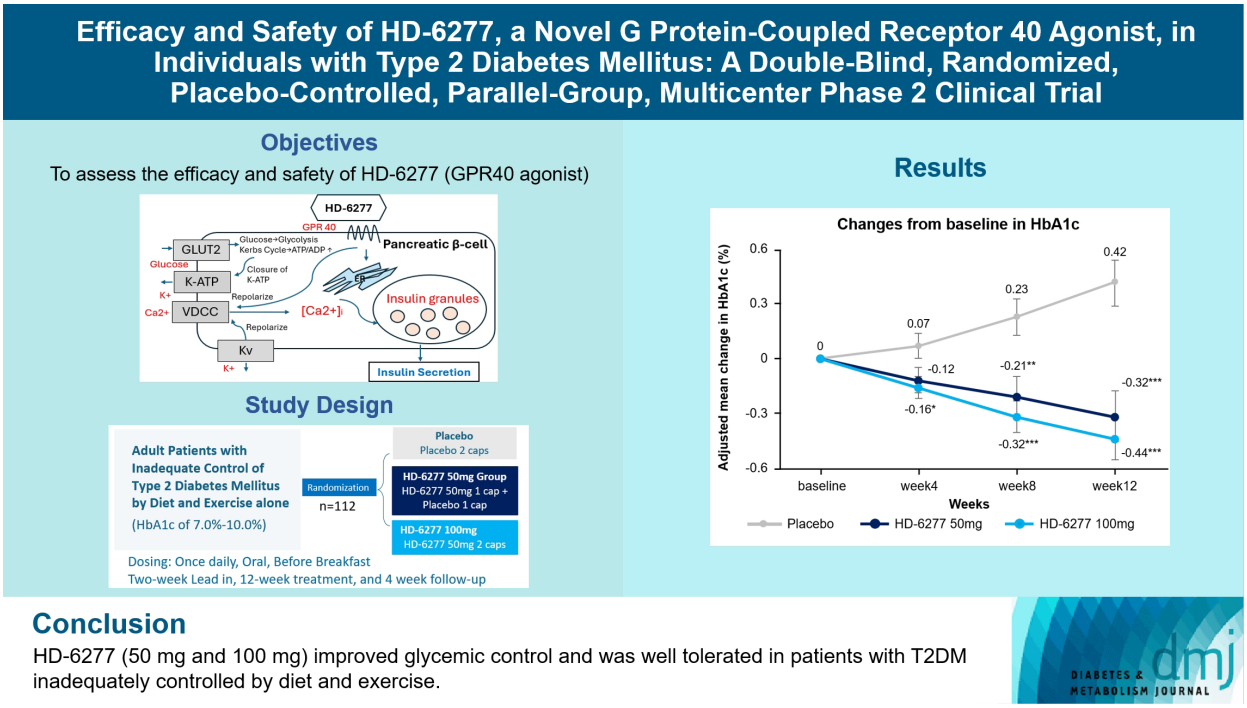

Highlights

- **This study evaluated the efficacy and safety of HD-6277 in patients with T2DM.**
- **HD-6277 significantly reduced HbA1c and fasting glucose levels.**
- **No clinically meaningful treatment-related adverse effects were observed.**
- **HD-6277 represents a potential new therapeutic option for T2DM.**

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Efficacy and Safety of HD-6277, a Novel G Protein-Coupled Receptor 40 Agonist, in Individuals with Type 2 Diabetes Mellitus: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Phase 2 Clinical Trial

Yong-ho Lee[1,2,3], Kyung Wan Min[4], Jun Hwa Hong[5], Soo Lim[6], Jae Myung Yu[7], Choon Hee Chung[8], Jun Sung Moon[9], Jong Chul Won[10], Chul Woo Ahn[11], Jie-Eun Lee[12], Tae Nyun Kim[13], Byung-Wan Lee[1,2]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[2]Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, Korea
[3]Institute for Innovation in Digital Healthcare (IIDH), Yonsei University College of Medicine, Seoul, Korea
[4]Department of Endocrinology and Metabolism, Nowon Eulji Medical Center, Eulji University, Seoul, Korea
[5]Department of Internal Medicine, Daejeon Eulji Medical Center, Eulji University, Daejeon, Korea
[6]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[7]Division of Endocrinology and Metabolism, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, College of Medicine, Hallym University, Seoul, Korea
[8]Department of Internal Medicine and Research Institute of Metabolism and Inflammation, Yonsei University Wonju College of Medicine, Wonju, Korea
[9]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea
[10]Division of Endocrinology and Metabolism, Department of Internal Medicine, Gimpo Woori Hospital, Gimpo, Korea
[11]Division of Endocrinology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[12]Division of Endocrinology and Metabolism, Department of Internal Medicine, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Korea
[13]Division of Endocrinology and Metabolism, Department of Internal Medicine, Inje University College of Medicine, Busan, Korea

Background: This study assessed the efficacy and safety of HD-6277, a novel oral G protein-coupled receptor 40 (GPR40) agonist in adults with inadequate control of type 2 diabetes mellitus (T2DM).
Methods: This double-blind, randomized, placebo-controlled phase 2 trial recruited 112 individuals aged 18–75 years with T2DM and glycosylated hemoglobin (HbA1c) levels between 7.0% and 10.0% while on diet and exercise alone for at least 8 weeks before screening. Parallel-group randomized trials of HD-6277 (50 and 100 mg groups vs. placebo) were conducted for 12 weeks. The primary outcome was the change in HbA1c levels from baseline to week 12. Secondary outcomes included changes in HbA1c, fasting plasma glucose (FPG), postprandial glucose, insulin, glycoalbumin, and C-peptide at weeks 4, 8, and 12.
Results: At week 12, HD-6277 at 50 and 100 mg demonstrated statistically significant reductions in HbA1c compared to placebo, with least square (LS) mean differences of –0.73% (95% confidence interval [CI], –1.11 to –0.35; $P=0.0002$) and –0.85% (95% CI, –1.21 to –0.50; $P<0.0001$), respectively. Both doses also produced clinically meaningful reductions in FPG. Additionally, HD-6277 at 100 mg significantly increased the insulinogenic index compared to placebo, with an LS mean difference of 1.91 (95% CI, 0.34 to 3.48; $P=0.0175$). No clinically relevant treatment-related adverse events were observed.
Conclusion: HD-6277 at 50 and 100 mg improved glycemic control and was well-tolerated in adults with T2DM inadequately managed with diet and exercise. GPR40 agonists may offer a promising new therapeutic option for T2DM.

Keywords: Clinical trial; Clinical trial, phase II; Diabetes mellitus; Diabetes mellitus, type 2; Glycated serum albumin; Randomized controlled trial; Receptors, G-protein-coupled; Treatment outcome

Corresponding author: Byung-Wan Lee https://orcid.org/0000-0002-9899-4992
Department of Internal Medicine, Institute of Endocrine Research, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
E-mail: bwanlee@yuhs.ac

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INTRODUCTION

As type 2 diabetes mellitus (T2DM) progresses, β-cells gradually deteriorate, resulting in an absolute insulin deficiency in the later stages [1,2]. Epidemiological studies have demonstrated that hyperglycemia doubles the risk of macrovascular diseases and microvascular complications [3,4]. Therefore, lifestyle modifications and pharmacological interventions are both necessary to reduce the risk of complications [5].

Despite the availability of various therapeutic options with different mechanisms of action, some individuals fail to achieve targeted glycemic control with existing medications [6-8]. In Korea, approximately 24.5% to 32.4% of individuals aged 30 years or older with T2DM achieve glycosylated hemoglobin (HbA1c) target of <6.5% [9], indicating that a substantial proportion of individuals with T2DM are not well-controlled. Furthermore, several of these agents are associated with adverse effects such as hypoglycemia, thereby highlighting the need for the development of safer and more effective treatments.

The G protein-coupled receptor 40 (GPR40) is expressed in pancreatic β-cells [10] and is a promising therapeutic target for T2DM, as it enhances glucose-dependent insulin secretion, potentially delaying pancreatic β-cell dysfunction [11]. GPR40 is activated by medium and long chain fatty acids, which stimulate phospholipase C and triggering intracellular Ca^{2+} release via the Inositol 1,4,5 trisphosphate (IP_3) signaling pathway [12]. This mechanism allows for effective glucose reduction without the risk of hypoglycemia [11]. GPR40 agonists effectively reduced blood glucose levels in rodent models of T2DM by increasing insulin secretion [11,13]. Phase 1 and 2 clinical trials of the GPR40 agonist TAK-875 demonstrated notable reductions in fasting and postprandial glucose as well as HbA1c, showing efficacy comparable to that of the sulfonylurea glimepiride in patients with T2DM [14,15]. However, serious adverse effects on hepatic function were observed in phase 3 clinical trials, leading to withdrawal from clinical development [16]. The early discontinuation of TAK-875, despite its robust glycemic efficacy, has underscored the need for novel GPR40 agonists with improved safety profiles, particularly with respect to hepatic tolerance. Given their potential to enhance insulin secretion in a glucose-dependent manner, GPR40 agonists remain a mechanistically compelling class of therapeutics for T2DM, especially for patients at risk of hypoglycemia or with limited β-cell function. Nevertheless, the progress in developing novel GPR40 agonists has been limited, with only a few compounds advancing to later stages of clinical investigation.

HD-6277, one novel GPR40 agonist, is a distinct GPR40-targeted agent with structural refinements that enhance metabolic stability and reduce hepatotoxic risk, without compromising receptor affinity or selectivity. HD-6277 exhibited superior efficacy compared to that of reference drugs and control compounds in a nonclinical study. While glucagon like peptide-1 (GLP-1) receptor agonists and sodium glucose cotransporter 2 (SGLT2) inhibitors have been associated with reductions in lean body mass in elderly patients [17,18], nonclinical data show that HD-6277 attenuates muscle atrophy and preserves muscle strength, suggesting it may serve as a complementary therapeutic option to mitigate this limitation [19]. A phase 1 clinical trial conducted in Germany also demonstrated that HD-6277 exhibited favorable tolerability when administered as a single dose up to 300 mg and orally once daily at doses up to 200 mg for 14 days in healthy adults [20]. Therefore, the objective of the present phase 2 clinical trial was to evaluate the safety and efficacy of the novel GPR40 agonist, HD-6277 (50 and 100 mg monotherapy), in individuals with T2DM inadequately controlled by diet and exercise.

METHODS

Study design

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, phase 2 clinical trial to assess the efficacy and safety of HD-6277 in adults with inadequate control of T2DM through diet and exercise for 12 weeks. The main objective of this trial was to assess whether HD-6277 could safely reduce HbA1c in individuals with inadequate control of T2DM by diet and exercise compared to the effects of a placebo and to assess changes in glycemic parameters and safety. Participants were individuals diagnosed with T2DM with HbA1c levels between 7.0% and 10.0% while on a diet and exercise regimen for at least 8 weeks prior to screening. After informed consent was obtained, the individuals entered a 2-week placebo run-in phase for confirmation. Participants were then randomized to receive a placebo, HD-6277 at 50 mg, or HD-6277 at 100 mg for 12 weeks. The efficacy and safety endpoints were assessed at the last hospital visit. This study was conducted in compliance with the consolidated standards of trial (CONSORT) reporting guidelines.

Participants

The enrollment criteria for the study were as follows: 18–75 years of age; diagnosis of T2DM with HbA1c between 7.0% and 10.0% (inclusive); diet and exercise for at least 8 weeks prior to screening. Those who experienced severe hypoglycemia during the previous 3 months and/or a positive pregnancy test in female individuals with child-bearing potential, diagnosis of type 1 diabetes mellitus or other immune-mediated diabetes syndromes, or severe complications of a diabetes episode were excluded. Individuals from 11 Korean institutions were enrolled.

Intervention and baseline evaluation

After the screening procedure, eligible individuals underwent a placebo run-in period of 2 weeks. Individuals were randomized to the HD-6277 50, 100 mg, or placebo groups. HbA1c levels at screening (≤8.5% or >8.5%) were used as stratification factors for randomization. The randomized treatment was orally administered in a capsule form once daily for 12 weeks, with visits scheduled at 4-week intervals.

Outcome measures

Efficacy

The primary outcome of the study was changes in HbA1c levels from baseline at week 12. The secondary outcomes included the changes in HbA1c at weeks 4 and 8 from baseline, percentage of individuals achieving HbA1c levels <7.0%, and changes in fasting plasma glucose (FPG) and postprandial glucose, insulin, glycoalbumin, and C-peptide at weeks 4, 8, and 12 from baseline. The oral glucose tolerance test, with measurements of blood glucose and insulin, was conducted at weeks 4, 8, and 12. Additionally, body weight, glycoalbumin/HbA1c ratio, 60 minutes insulinogenic index (IGI_{60}), homeostasis model assessment of β-cell function (HOMA-β), homeostasis model assessment of insulin resistance (HOMA-IR), and cluster determinant 36 at weeks 4, 8, and 12 from baseline were evaluated as exploratory endpoints.

Safety

The study safety endpoints were treatment-emergent adverse events (TEAEs), laboratory tests, physical examination, vital signs, and 12-lead electrocardiogram (ECG). TEAEs that occurred from the treatment period to the end of the study were collected and analyzed.

Statistical analysis

The intervention was considered effective if the HD-6277 (50 or 100 mg) use was superior to the placebo use based on a statistical significance of $\alpha=0.05$ and the model specified below (i.e., $P<0.05$). The null hypothesis was that there would be no difference in the change in mean HbA1c from baseline at 12-week post randomization period (i.e., the treatment effect) between HD-6277 (50 or 100 mg) and placebo. Sample size was computed as the primary outcome. Based on a previous clinical trial of another GPR40 agonist, the estimated effect size for the primary outcome derived from these data using baseline treatment changes in the HD-6277 (50 or 100 mg) versus placebo groups was $d=0.83$ (mean 1.0%, standard deviation 1.2%). We also assumed two-sided $\alpha=0.05$ and power=80%. The primary outcome (changes in HbA1c levels at week 12) required a total sample size of 85. Anticipating a 25% dropout rate, 115 participants were recruited for each group.

Continuous variables are presented with descriptive statistics at each time point, and the significance of the change from baseline within a group was tested using paired *t*-test. Between-group differences in continuous variables were tested using standard analysis of variance (ANOVA) independently at each time point. Categorical variables were summarized as the number of participants or events and percentages and tested for between-group differences using the chi-squared test. The main analysis for efficacy and exploratory evaluation was ANOVA. A point estimate, 95% confidence interval (CI), and two-sided *P* values were reported for the treatment effect and the difference between the treatment effects. Sensitivity and subgroup analyses were performed to test the robustness of the results. The subgroup analyses by sex were prespecified in the protocol. Additional subgroup analyses, including those by age (<60 or ≥60 years), BMI (<25 or ≥25 kg/m²), and HOMA-β (below or above the median), were conducted *post hoc* and considered exploratory. No formal adjustments for multiplicity were applied. While the main analysis set for the efficacy and exploratory evaluation was conducted using the full analysis set, the efficacy and exploratory analyses were evaluated using the per-protocol set. All drug-administered participants of the study were included in the safety analysis, and their safety event information was collected. Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 (https://www.meddra.org). All statistical tests were two-sided at a significance level of $P<0.05$ (with no multiplicity adjustments). Statistical Analysis Software

(SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Ethics statement

The present study protocol was reviewed and approved by the Ministry of Food and Drug Safety and the Institutional Review Board of Yonsei University Severance Hospital (IRB No. 4-2022-024) and was conducted in accordance with the ethical principles of the Declaration of Helsinki as well as with the International Conference on Harmonization Note for Guidance on Good Clinical Practice. The study was registered at ClinicalTrials.gov (identifier NCT05666128). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

Baseline characteristics

A total of 142 individuals were enrolled in the study from June 17, 2022 to June 28, 2023. Thirty individuals were excluded from randomization. The reasons for ineligibility were withdrawal of consent in five cases, failure to meet the inclusion/exclusion criteria in 24 cases, and the occurrence of an AE in one case. Hence, 112 enrolled individuals were randomized, 37 of whom were allocated to the placebo group and 31 and 44 to the HD-6277 50 and 100 mg groups, respectively (Fig. 1). The overall demographics and baseline characteristics of the participants were comparable across the three groups (Table 1).

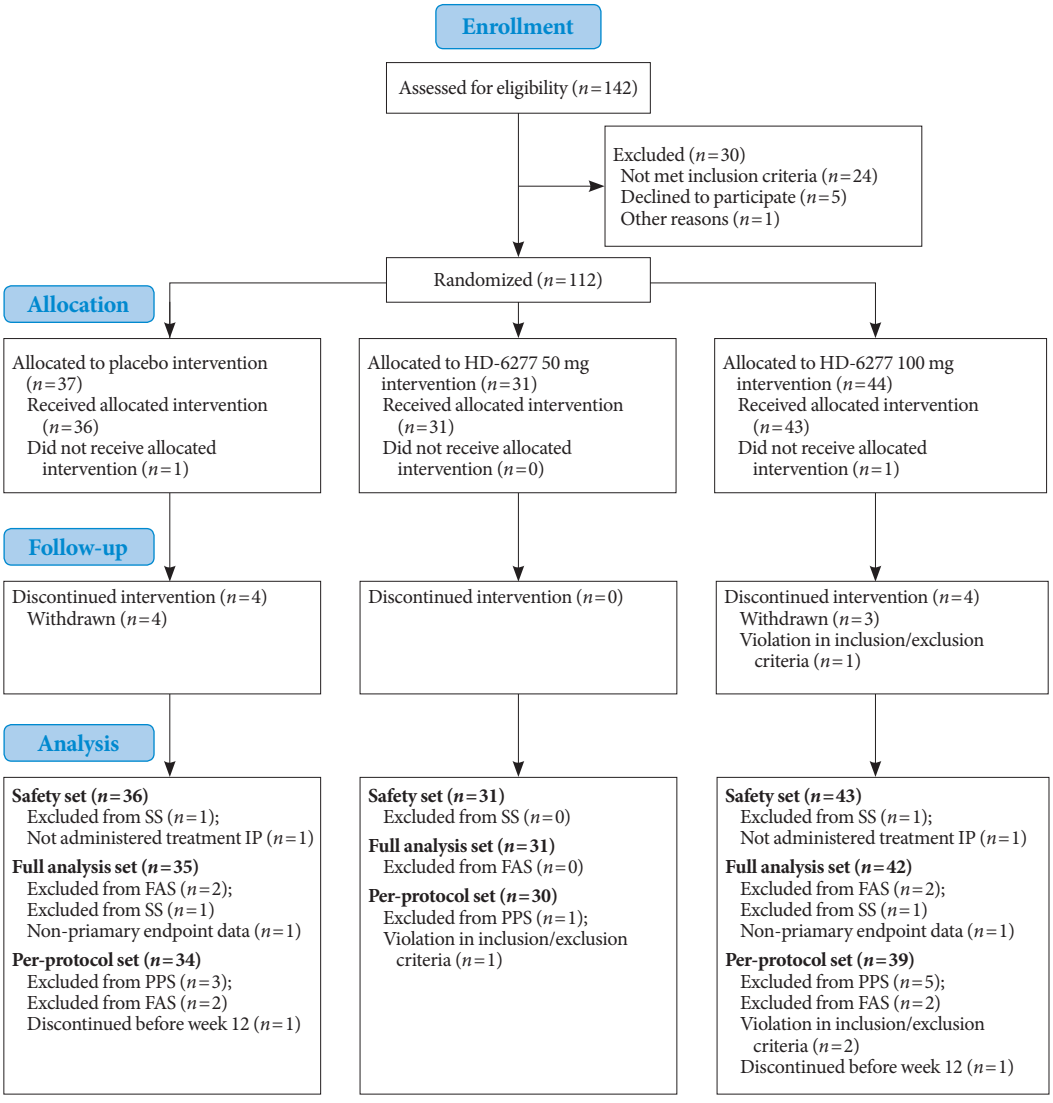

Fig. 1. Subject dispositions. SS, safety set; FAS, full analysis set; PPS, per-protocol set.

Table 1. Demographics and baseline characteristics

Characteristic	Placebo (n=35)	HD-6277 (50 mg) (n=31)	HD-6277 (100 mg) (n=42)	P value
Age, yr	56.7±12.0	60.0±11.0	61.7±7.7	0.1049
Sex				0.1207
Male	24 (68.57)	14 (45.16)	21(50.00)	
Female	11 (31.43)	17 (54.84)	21 (50.00)	
Weight, kg	72.8±12.2	69.2±14.7	65.1±11.9	0.0328
BMI, kg/m^2	26.5±3.4	26.4±4.1	24.9±3.0	0.1010
Duration of diabetes, yr	6.42±7.51	6.56±5.46	7.54±5.28	0.6824
HbA1c, %	7.68±0.92	7.38±0.58	7.64±0.86	0.2846
HbA1c, mmol/mol[a]	60.5±10.1	57.2±6.4	59.9±9.4	0.2846
FPG, mg/dL	148.2±43.3	134.2±20.7	142.5±38.7	0.2987
HOMA-IR	4.23±3.04	4.09±2.74	3.29±2.38	0.2632
HOMA-β[b]	48.7±38.9	52.1±25.4	48.0±34.3	0.8806
SBP, mm Hg	128.7±12.9	126.7±13.0	128.0±12.8	0.8227
DBP, mm Hg	77.3±9.7	75.0±9.6	74.9±7.7	0.4321
Prior medication[c]	10 (28.57)	5 (16.13)	12 (28.57)	0.4015
Concomitant medication[d]	34 (97.14)	29 (93.55)	37 (88.10)	0.3109
GA, %	19.3±3.5	18.3±2.8	19.3±3.5	0.3713
GA/HbA1c	2.50±0.31	2.47±0.30	2.51±0.28	0.8088

Values are presented as mean±standard deviation or number of patients (%). P values are based on analysis of variance (ANOVA) tests for continuous variables and Pearson chi-squared tests for categorical variables.
BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment β-cell function; SBP, systolic blood pressure; DBP, diastolic blood pressure; GA, glycoalbumin.
[a](HbA1c [%]–2.152)/0.09148. The presented data are based on the data collected at baseline (day 0), [b]Analyses were conducted after removing outlier values in week 12, [c]Medications that were administered and completed before the initiation of the investigational product (IP), [d]Concomitant medications: administered before or after IP initiation and completed or continued during treatment (excluding medications started during the follow-up period).

The mean age ranged from 56.7 to 61.7 years, the mean BMI ranged from 24.9 to 26.5 kg/m^2. The mean duration since the diagnosis of T2DM and average HbA1c were 6.56 years and 7.38% in the HD-6277 50 mg group, 7.54 years and 7.64% in the HD-6277 100 mg group, and 6.42 years and 7.68% in the placebo group. In the placebo group, four individuals withdrew their consent after randomization. In the HD-6277 100 mg group, three individuals withdrew consent, and one individual discontinued after randomization.

Efficacy outcomes

The primary endpoint showed a statistically significant reduction in HbA1c levels at week 12 in the HD-6277 50 and 100 mg groups compared to the placebo group, by –0.73% (95% CI, –1.11 to –0.35; P=0.0002) and –0.85% (95% CI, –1.21 to –0.50; P<0.0001), respectively (Table 2). Similarly, significant reductions were also seen at week 8 in HbA1c in the HD-6277 50 mg and HD-6277 100 mg groups over placebo one, by –0.44% and –0.55% (Supplementary Table 1). Additionally, the least square (LS) mean change in HbA1c compared to placebo at week 4 was –0.23% (95% CI, –0.41 to –0.05; P=0.0113) in the 100 mg group. The HbA1c level was also decreased by 0.19% in the 50 mg group, but this was not statically significant (95% CI, –0.38 to 0.00; P=0.0517). These results suggest that the adjusted mean change in HbA1c appeared more pronounced in the HD-6277 100 mg group compared to the 50 mg group after baseline of HbA1c was considered (Fig. 2). The proportion of individuals achieving HbA1c levels <7.0% (53 mmol/mol) at week 12 was significantly higher in the HD-6277 50 mg group (n=19 of 31 individuals; 61.29%, P=0.0075) and the HD-6277

Table 2. Primary and secondary endpoints of the 12-week

Variable	Mean±SD				LSM (95% CI)	*P* value
	Treatment	Baseline	Week 12	Change	Difference from placebo	
Primary endpoint						
HbA1c, %	Placebo	7.68±0.92	8.10±1.63	0.42±1.13		
	50 mg	7.38±0.58	7.07±0.67	−0.32±0.42	−0.73 (−1.11 to −0.35)	0.0002
	100 mg	7.64±0.86	7.20±0.80	−0.44±0.60	−0.85 (−1.21 to −0.50)	<0.0001
Secondary endpoint						
FPG, mg/dL	Placebo	148.2±43.3	160.9±75.5	12.7±42.3		
	50 mg	134.2±20.7	124.4±20.4	−9.8±12.5	−22.6 (−37.9 to −7.3)	0.0042
	100 mg	142.5±38.7	127.5±22.3	−15.0±30.2	−27.7 (−41.9 to −13.5)	0.0002
Post-meal glucose (1 hr), mg/dL	Placebo	299.9±68.1	302.7±88.7	5.6±44.2		
	50 mg	274.3±49.0	255.0±43.0	−19.3±40.4	−24.9 (−46.8 to −2.9)	0.0268
	100 mg	279.5±53.9	262.6±54.0	−15.3±47.7	−20.9 (−41.4 to −0.4)	0.0457
Post-meal glucose (2 hr), mg/dL	Placebo	300.9±68.4	310.5±98.9	11.8±57.7		
	50 mg	266.2±76.4	250.6±60.6	−15.5±54.1	−27.3 (−54.3 to −0.4)	0.0472
	100 mg	271.8±79.2	245.0±70.4	−24.3±52.7	−36.1 (−61.2 to −10.9)	0.0054
Glycoalbumin, %	Placebo	19.3±3.5	20.8±6.3	1.6±3.7		
	50 mg	18.3±2.8	17.3±2.8	−1.0±1.3	−2.6 (−3.8 to −1.4)	<0.0001
	100 mg	19.3±3.5	18.4±3.1	−0.9±1.7	−2.5 (−3.6 to −1.4)	<0.0001
Insulin (fasting), μU/mL	Placebo	11.6±8.2	10.4±7.3	−1.2±4.9		
	50 mg	12.5±9.6	13.4±9.7	0.9±4.3	2.1 (−0.2 to 4.3)	0.0763
	100 mg	9.3±5.5	8.7±4.7	−0.6±4.7	0.6 (−1.5 to 2.7)	0.5691
Insulin (1 hr), μU/mL	Placebo	46.0±39.0	44.2±47.4	−2.3±26.8		
	50 mg	57.8±62.0	65.9±83.3	8.1±32.5	10.3 (−3.2 to 23.9)	0.1334
	100 mg	38.9±23.7	49.4±28.9	10.6±23.7	12.8 (0.2 to 25.5)	0.0467
Insulin (2 hr), μU/mL	Placebo	52.5±44.9	51.8±47.4	−1.6±21.7		
	50 mg	59.7±51.0	71.2±68.8	11.6±32.5	13.1 (0.6 to 25.7)	0.0401
	100 mg	48.0±26.9	53.7±32.3	6.1±22.0	7.7 (−4.1 to 19.4)	0.1976
C-peptide, ng/mL	Placebo	2.40±1.01	2.26±0.92	−0.14±0.58		
	50 mg	2.64±0.89	2.75±0.94	0.11±0.55	0.24 (−0.05 to 0.53)	0.0975
	100 mg	2.18±0.74	2.17±0.68	−0.01±0.63	0.13 (−0.14 to 0.40)	0.3473

Least square means and confidence intervals are based on analysis of variance. Missing values were imputed by last observation carried forward (LOCF) method. The *P* values are based on Fisher's least significant difference (LSD) method for multiple comparisons.
SD, standard deviation; LSM, least square mean; CI, confidence interval; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; C-peptide, connecting peptide.

100 mg group (n=20 of 42 individuals; 47.62%, P=0.0879) than it was in the placebo group (n=10 of 35 individuals, 28.57%) (Fig. 3).

Along with the reduction in HbA1c levels, FPG and postprandial glucose (1- and 2-hour) levels at week 12 were significantly decreased by 22.6 mg/dL in the 50 mg group and 27.7 mg/dL in the 100 mg group (all P<0.05) (Table 2). Also, the level of glycoalbumin was decreased by 2.6% and 2.5%, respectively, in both groups (all P<0.0001) (Table 2). Moreover, FPG and glycoalbumin levels were significantly decreased in both groups at week 4 (all P<0.05) (Supplementary Table 2).

Regarding insulin secretory function and sensitivity homeo-

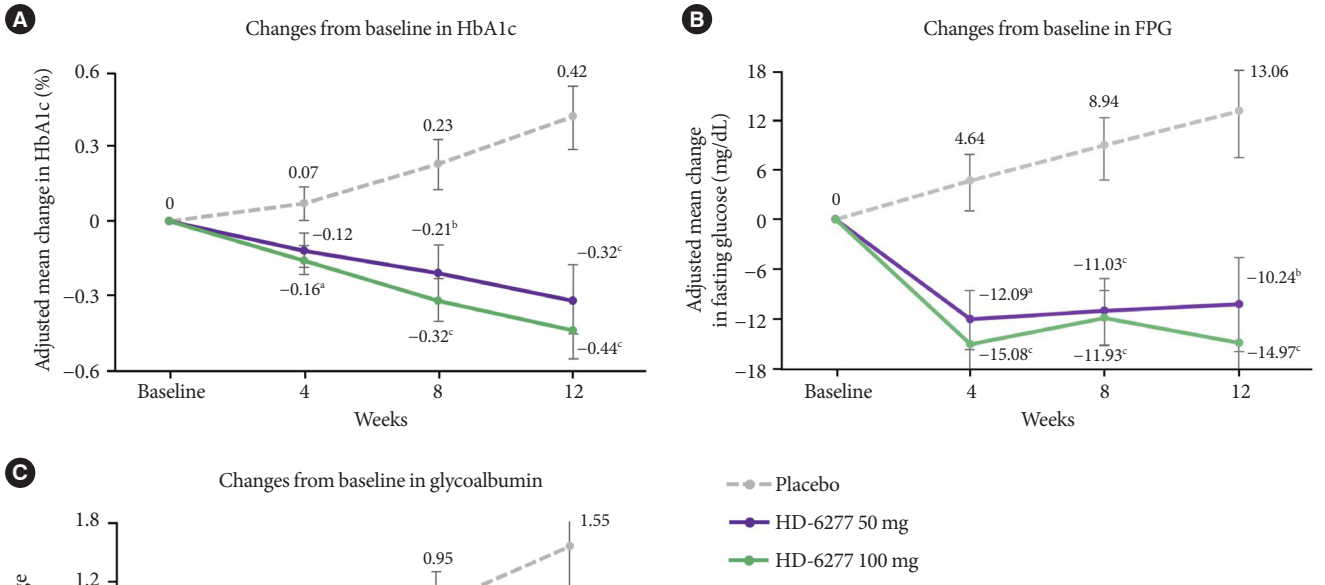

Fig. 2. Least square mean changes from baseline in major efficacy endpoint through 12 weeks. (A) Glycosylated hemoglobin (HbA1c). (B) Fasting plasma glucose (FPG). (C) Glycoalbumin. Analysis of covariance with baseline HbA1c values. [a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$ for HD-6277 vs. placebo at weeks 4, 8, and 12.

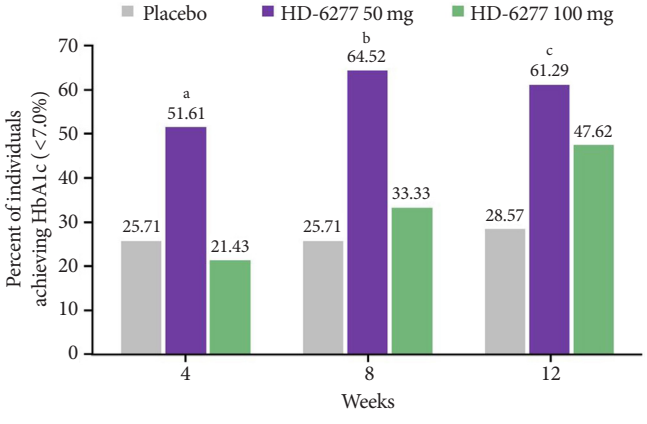

Fig. 3. Proportions of subjects achieving glycosylated hemoglobin (HbA1c) (<7.0%). [a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$ for HD-6277 vs. placebo at weeks 4, 8, and 12.

stasis, the levels of HOMA-β were significantly increased from baseline both in the 50 and 100 mg groups at week 12 (Supplementary Table 3), while there was no statistical difference in fasting insulin, C-peptide, and HOMA-IR (Table 2, Supplementary Table 3). The level of IGI_{60} was significantly increased at week 8 and 12 relative to placebo in the 100 mg (1.77 μU/mL per mg/dL, $P=0.0162$ and 1.91 μU/mL per mg/dL, $P=0.0175$, respectively) but did not exhibit a statistically significant difference in the 50 mg group. Additionally, the insulin levels (1 hour) increased relative to placebo (12.8 μU/mL; 95% CI, 0.2 to 25.5; $P=0.0467$) in the 100 mg group, and insulin levels at 2 hours increased relative to placebo (13.1 μU/mL; 95% CI, 0.6 to 25.7; $P=0.0401$).

In the subgroup analysis for HbA1c and glycoalbumin at week 12, no significant interaction was observed between treatment groups and sex, age, or HOMA-β. A potential interaction was observed only for BMI in relation to HbA1c ($P=0.0635$), whereas no significant interaction was noted for glycoalbumin across any subgroup (Supplementary Table 4).

Safety outcomes

No serious adverse drug reactions (SADRs) or deaths occurred. While one serious AE was reported in both the 50 and 100 mg groups, neither event was classified as a SADR (Table 3). Fol-

Table 3. The major adverse events that occurred during the treatment period

Variable	Placebo (n=36)	HD-6277 50 mg (n=31)	HD-6277 100 mg (n=43)
TEAEs	7 (19.4) [13]	7 (22.6) [10]	8 (18.6) [12]
Serious AEs	0 (0.0) [0]	1 (3.2) [1]	1 (2.3) [1]
ADRs	1 (2.8) [1]	0 (0.0) [0]	1 (2.3) [1]
Hypoglycemia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
LFT			
AST, IU/L			
Baseline	24.8±6.9	23.8±6.0	26.8±9.7
Week 12	25.5±11.1	23.2±6.0	25.8±8.1
Change	0.2±10.0	−0.6±4.8	−1.2±8.4
ALT, IU/L			
Baseline	29.4±13.9	25.8±14.1	30.7±19.9
Week 12	30.5±13.3	25.0±13.6	27.9±13.2
Change	0.5±11.5	−0.7±12.2	−3.3±16.3
Bilirubin, mg/dL			
Baseline	0.92±0.39	0.82±0.33	0.92±0.38
Week 12	0.97±0.42	0.77±0.28	0.91±0.35
Change	0.05±0.33	−0.05±0.21	−0.02±0.30

Values are presented as number of patients (%) [number of events] or mean±standard deviation.
TEAE, treatment-emergent adverse event; AE, adverse event; ADR, adverse drug reaction; LFT, liver function test; AST, aspartate aminotransferase; ALT, alanine transaminase.

lowing HD-6277 50, 100 mg, and placebo treatment in individuals with T2DM, 35 TEAEs in 22 (20.0%) individuals were reported (Table 3). In total, 20.0% of the individuals in the HD-6277 50 mg group experienced 10 TEAEs (mild, 9; moderate, 0; severe, 1), 18.6% of the individuals in the HD-6277 100 mg group experienced 12 TEAEs (mild, 8; moderate, 4; severe, 0), and 19.4% of the individuals in the placebo group experienced 13 TEAEs (mild, 11; moderate, 2; severe, 0). In total, 9.7% of individuals in the HD-6277 50 mg group reported six adverse events of special interest (AESIs), 4.7% in the HD-6277 100 mg group reported two AESIs, and 2.8% in the placebo group reported one AESI. Among patients who experienced AESIs, there were no cases of hypoglycemia. Clinically significant changes or findings were not observed in clinical laboratory evaluations, including liver function tests, vital sign assessments, 12-lead ECGs, and physical examinations. Consistent with the findings detailed in Supplementary Tables 5 and 6, liver and renal function test parameters demonstrated no statistically significant changes from baseline at weeks 4, 8, or 12 in either the HD-6277 50 or 100 mg group, relative to placebo.

DISCUSSION

The present study investigated the efficacy and safety of HD-6277, the first in a new class of oral GPR40 agonists. In this phase 2a clinical trial, we found that once-daily oral administration of HD-6277 at 50 or 100 mg doses for 12 weeks significantly improved glycemic control in individuals with T2DM. HD-6277 at 50 or 100 mg doses resulted in mean reductions in HbA1c from baseline to −0.73% and −0.85%, respectively, in week 12, compared to that of the placebo group. The safety and tolerability profiles of HD-6277 were comparable to those of the placebo group. Our findings regarding FPG and glycoalbumin demonstrated that the glucose-lowering efficacy was observed at week 4, suggesting a rapid and potent glucose-lowering action of HD-6277. The results of HD-6277 coincide with prior phase 2 clinical trial of TAK-875, showing a decrease in HbA1c from baseline of −1.12% with 50 mg and −0.65% with a 6.25 mg dose [15]. TAK-875, a free fatty acid receptor 1 (FFAR1) modulator, has proven to effectively lower glucose levels in both diabetic animals and humans [21]. Specifically, it achieved a significant reduction in HbA1c levels of 1.18% at a dose of 50 mg and 1.20% at a 100 mg dose in Japanese individuals [22]. Despite these promising glucose-lowering results, liver toxicity emerged during clinical trials, leading to discontinuation of the study [16,22]. HD-6277 showed that indicators of liver function such as aspartate aminotransferase and alanine aminotransferase activities did not reveal any discernible trends that would suggest hepatotoxicity or increased liver enzyme levels. This clinical data was congruent with the previous liver toxicity test of HD-6277 conducted in a nonclinical trial, as well as liver-specific adverse effects observed in the liver histopathology of the 2-week repeated toxicity test in Beagle dogs [23]. Moreover, renal function markers such as blood urea nitrogen, uric acid, creatinine, and N-acetyl-β-D-glucosaminidase (NAG) did not exhibit any trend.

With respect to other oral glycemic agents, SGLT2 inhibitor dapagliflozin decreased HbA1c by 0.86% from a baseline of 8.08% to 7.22% at 24 weeks after drug administration, with a confirmed difference in LS mean −0.69% (95% CI, −0.59 to −0.79) compared to placebo [24]. In the case of the DPP-4 inhibitor sitagliptin, HbA1c decreased by 0.70% from a baseline

of 7.96%–7.26% at 24 weeks after drug administration, with a confirmed difference in LS mean –0.65% (95% CI, –0.87 to –0.42) compared to placebo [25]. These findings imply that the glucose-lowering efficacy of HD-6277 is comparable to that of existing antidiabetic medications.

Regarding enhancement of insulin secretion function and sensitivity, we observed significant improvements in IGI_{60} following 12 weeks of treatment with HD-6277 100 mg, compared to the placebo group. This reflects the mechanism of HD-6277 as an insulin secretagogue. An increase in IGI_{60} indicates increased insulin secretion in β-cells, making IGI_{60} a more accurate index for β-cell function than is HOMA-β [26,27]. Unlike HOMA-β, which reflects β-cell function in the fasting state, IGI_{60} captures early-phase insulin secretion in response to glucose load and thus presents a more accurate reflection of pharmacodynamic effect of GPR40 agonists. While both IGI_{60} and HOMA-β provide complementary insights into β-cell secretory function, insulin resistance represents another critical factor influencing glycemic control. In this study, HOMA-IR, a surrogate marker of insulin resistance, evaluated a different aspect of glucose metabolism. However, it exhibited inconsistent results in individuals treated with HD-6277, suggesting that the glucose-lowering effect of HD-6277 is primarily mediated through enhanced insulin secretion rather than substantial changes in insulin sensitivity. With respect to dose-response relationship, a greater mean reduction in HbA1c was observed in the 100 mg group; however, a smaller proportion of participants achieved the target HbA1c (<7.0%) compared to the 50 mg group. The additional modest HbA1c reduction could be explained by the significant enhancement of insulin secretory function demonstrated by IGI_{60}. However, obvious discrepancy between HbA1c and meeting the target HbA1c could stem from differences in baseline HbA1c values between groups. Participants in the 100 mg group tended to have slightly higher baseline HbA1c values compared to those in the 50 mg group, requiring a larger absolute reduction to reach the target. Although not statistically significant as per ANOVA (P=0.2846), this baseline difference could potentially influence the proportion of patients achieving the target HbA1c. The results underscore that improvements in mean HbA1c and the proportion of participants achieving glycemic targets do not always align, particularly in studies with relatively small sample sizes and variation in baseline glycemic control. These findings further necessitate critical examination of market dose selection, whether the effect of β-cell function might warrant prioritizing the 100 mg dose.

With respect to safety, an important aspect of HD-6277 is the absence of hypoglycemic events during the 12 weeks of the trial, although GPR40 agonists are known to potentiate β-cell function and insulin secretion. This outcome may be attributed to the enhancement of glucose-dependent insulin secretion.

However, this study possessed several limitations. As the clinical trial was conducted with only Korean individuals, the current findings may not be extrapolated to other ethnicities without considering the different pathophysiological aspects of Caucasian and East Asian population [28]. For example, β-cell dysfunction plays a crucial role in the onset of T2DM within East Asian populations [29,30]. To further evaluate treatment consistency, subgroup analyses were conducted for sex, age, BMI, and HOMA-β. Among these, only the analyses by sex were prespecified in the protocol, while the others were *post hoc* and exploratory in nature. In the formal interaction analysis using ANOVA models including treatment group, subgroup category, and their interaction term, no significant interactions were observed between treatment and sex, age, or HOMA-β in relation to either HbA1c or glycoalbumin. A potential interaction was noted only between treatment and BMI for HbA1c outcomes (P=0.0635), suggesting that BMI may modulate the treatment response. However, glycoalbumin outcomes did not exhibit interaction effects across any subgroup, indicating consistency of treatment effect regardless of baseline characteristics. As no formal multiplicity adjustments for analyses of secondary and exploratory endpoints, which were assessed at multiple time points, the risk of type I error is increased. Thus, these findings are considered hypothesis-generating rather than confirmatory and nominally significant findings for these endpoints warrant cautious interpretation. Therefore, further pivotal studies, specifically designed and adequately powered to evaluate these endpoints, will be necessary to substantiate our findings.

In conclusion, considering the glucose-lowering efficacy and safety profiles observed in this phase 2 clinical trial, HD-6277 is a novel and promising oral agent for the treatment of individuals with T2DM, as evidenced by significant changes in the mean reduction in HbA1c. Further phase 3 clinical trials utilizing a larger number of participants are necessary to confirm the efficacy and safety of the novel GPR40 agonist as a therapeutic for T2DM.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2025.0528.

CONFLICTS OF INTEREST

Jun Sung Moon has been associate editor of the *Diabetes & Metabolism Journal* since 2022. He was not involved in the review process of this article. Otherwise, there was no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception or design: Y.L.
Acquisition, analysis, or interpretation of data: Y.L., K.W.M., J.H.H., S.L., J.M.Y., C.H.C., J.S.M., J.C.W., C.W.A., J.E.L., T.N.K.
Drafting the work or revising: Y.L., B.W.L.
Final approval of the manuscript: B.W.L.

ORCID

Yong-ho Lee *https://orcid.org/0000-0002-6219-4942*
Byung-Wan Lee *https://orcid.org/0000-0002-9899-4992*

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Supplementary Table 1. Secondary and exploratory endpoints of the 8-week

Variable	Mean±SD				LSM (95% CI)	*P* value
	Treatment	Baseline	Week 8	Change	Difference from placebo	
Secondary endpoint						
HbA1c, %	Placebo	7.68±0.92	7.91±1.37	0.23±0.76		
	50 mg	7.38±0.58	7.18±0.83	−0.21±0.47	−0.44 (−0.74 to −0.14)	0.0049
	100 mg	7.64±0.86	7.31±0.78	−0.32±0.58	−0.55 (−0.83 to −0.27)	0.0002
FPG, mg/dL	Placebo	148.2±43.3	155.7±51.5	7.5±24.7		
	50 mg	134.2±20.7	124.9±20.8	−9.3±15.6	−16.8 (−28.5 to −5.2)	0.0051
	100 mg	142.5±38.7	130.4±28.2	−12.0±27.9	−19.6 (−30.4 to −8.8)	0.0005
Post-meal glucose (1 hr), mg/dL	Placebo	299.9±68.1	297.5±78.6	0.5±40.6		
	50 mg	274.3±49.0	264.1±47.9	−12.9±37.3	−13.4 (−32.2 to 5.4)	0.1600
	100 mg	279.5±53.9	267.2±56.9	−10.7±35.7	−11.2 (−28.7 to 6.3)	0.2071
Post-meal glucose (2 hr), mg/dL	Placebo	300.9±68.4	304.6±82.6	5.9±40.2		
	50 mg	266.2±76.4	247.1±65.6	−22.3±51.7	−28.2 (−53.1 to −3.2)	0.0272
	100 mg	271.8±79.2	239.7±83.3	−29.2±56.3	−35.1 (−58.3 to −11.9)	0.0034
Glycoalbumin	Placebo	19.3±3.5	20.2±5.5	1.0±2.8		
	50 mg	18.3±2.8	17.3±3.1	−1.0±1.5	−1.9 (−3.0 to −0.9)	0.0003
	100 mg	19.3±3.5	18.2±3.1	−1.1±1.7	−2.0 (−3.0 to −1.1)	<0.0001
Insulin (fasting), μU/mL	Placebo	11.6±8.2	10.8±8.1	−0.8±5.5		
	50 mg	12.5±9.6	12.4±9.0	−0.1±4.2	0.7 (−1.9 to 3.2)	0.6009
	100 mg	9.3±5.5	9.0±5.0	−0.3±5.5	0.5 (−1.9 to 2.8)	0.7015
Insulin (1 hr), μU/mL	Placebo	46.0±39.0	42.1±35.9	−4.4±23.6		
	50 mg	57.8±62.0	65.2±51.3	6.3±32.3	10.7 (−2.5 to 23.9)	0.1100
	100 mg	38.9±23.7	48.4±29.4	9.4±23.9	13.8 (1.6 to 26.1)	0.0275
Insulin (2 hr), μU/mL	Placebo	52.5±44.9	48.2±37.1	−5.1±31.2		
	50 mg	59.7±51.0	65.4±52.9	5.3±17.7	10.4 (−1.6 to 22.5)	0.0884
	100 mg	48.0±26.9	53.0±35.9	5.3±21.5	10.4 (−0.8 to 21.6)	0.0679
C-peptide, ng/mL	Placebo	2.40±1.01	2.36±0.95	−0.04±0.57		
	50 mg	2.64±0.89	2.72±0.86	0.08±0.41	0.12 (−0.18 to 0.42)	0.4431
	100 mg	2.18±0.74	2.21±0.73	0.03±0.77	0.07 (−0.21 to 0.35)	0.6054
Exploratory endpoint						
HOMA-IR	Placebo	4.23±3.04	4.29±3.86	0.06±2.47		
	50 mg	4.09±2.74	3.79±2.66	−0.30±1.56	−0.36 (−1.53 to 0.81)	0.5401
	100 mg	3.29±2.38	2.96±2.19	−0.33±2.79	−0.39 (−1.48 to 0.69)	0.4765
HOMA-β[a]	Placebo	48.7±38.9	45.9±35.3	−2.8±21.1		
	50 mg	52.1±25.4	62.2±33.0	10.1±22.3	12.9 (1.8 to 23.9)	0.0234
	100 mg	48.0±34.3	53.1±31.6	5.1±21.0	7.8 (−2.1 to 17.8)	0.1216
IGI_{60}, μU/mL per mg/dL[b]	Placebo	4.44±4.63	4.13±3.94	−0.38±2.95		
	50 mg	5.82±5.25	6.57±4.21	0.71±3.18	1.10 (−0.45 to 2.64)	0.1617
	100 mg	4.25±3.20	5.66±4.33	1.39±3.19	1.77 (0.33 to 3.21)	0.0162
GA/HbA1c	Placebo	2.50±0.31	2.53±0.36	0.03±0.17		
	50 mg	2.47±0.30	2.40±0.29	−0.07±0.13	−0.10 (−0.17 to −0.03)	0.0070
	100 mg	2.51±0.28	2.48±0.26	−0.04±0.13	−0.07 (−0.13 to −0.00)	0.0448

(*Continued to the next page*)

Supplementary Table 1. Continued

Variable	Mean±SD				LSM (95% CI)	*P* value
	Treatment	Baseline	Week 8	Change	Difference from placebo	
CD36, ng/mL	Placebo	44.5±81.4	46.8±94.1	2.3±18.4		
	50 mg	54.8±124.1	54.2±112.7	−0.5±20.4	−2.8 (−22.0 to 16.4)	0.7742
	100 mg	59.8±198.9	53.5±146.4	−6.3±58.0	−8.5 (−26.4 to 9.3)	0.3443
Weight, kg	Placebo	72.8±12.2	72.4±13.0	−0.4±2.5		
	50 mg	69.2±14.7	69.2±14.7	−0.0±1.3	0.4 (−0.5 to 1.3)	0.4108
	100 mg	65.1±11.9	65.1±11.7	−0.0±1.4	0.4 (−0.4 to 1.2)	0.3376

LSMs and CIs are based on analysis of variance. Missing values were imputed by last observation carried forward (LOCF) method. The *P* values are based on Fisher's least significant difference (LSD) method for multiple comparisons.
SD, standard deviation; LSM, least square mean; CI, confidence interval; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; C-peptide, connecting peptide; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; IGI, insulinogenic index; GA, glycoalbumin; CD36, cluster of differentiation 36.
[a]Analyses were conducted after removing outlier values in week 12, [b](Insulin [1 hr]−insulin [fasting])/(glucose [1 hr]−glucose [fasting])×18.

Supplementary Table 2. Secondary and exploratory endpoints of the 4-week

Variable	Mean±SD			LSM (95% CI)	*P* value
	Treatment	Baseline	Week 4	Change	Difference from placebo
Secondary endpoint					
HbA1c, %	Placebo	7.68±0.92	7.75±1.13	0.07±0.43	
	50 mg	7.38±0.58	7.27±0.81	−0.12±0.37	−0.19 (−0.38 to 0.00)	0.0517
	100 mg	7.64±0.86	7.48±0.78	−0.16±0.36	−0.23 (−0.41 to −0.05)	0.0113
FPG, mg/dL	Placebo	148.2±43.3	151.0±44.4	2.8±21.6	
	50 mg	134.2±20.7	124.4±20.5	−9.8±12.0	−12.6 (−23.8 to −1.4)	0.0276
	100 mg	142.5±38.7	127.2±27.9	−15.2±29.1	−18.0 (−28.4 to −7.7)	0.0008
Post-meal glucose (1 hr), mg/dL	Placebo	299.9±68.1	305.3±80.2	4.4±38.5	
	50 mg	274.3±49.0	268.0±51.3	−9.3±36.4	−13.8 (−33.6 to 6.1)	0.1716
	100 mg	279.5±53.9	259.6±50.6	−18.2±38.1	−22.7 (−41.7 to −3.7)	0.0200
Post-meal glucose (2 hr), mg/dL	Placebo	300.9±68.4	310.4±84.0	11.0±44.0	
	50 mg	266.2±76.4	250.4±79.3	−18.4±51.6	−29.4 (−53.1 to −5.7)	0.0156
	100 mg	271.8±79.2	256.8±77.1	−7.3±39.6	−18.3 (−41.0 to 4.3)	0.1118
Glycoalbumin, %	Placebo	19.3±3.5	19.7±4.3	0.5±1.6	
	50 mg	18.3±2.8	17.7±2.9	−0.6±1.2	−1.1 (−1.8 to −0.4)	0.0029
	100 mg	19.3±3.5	18.8±3.4	−0.5±1.4	−0.9 (−1.6 to −0.3)	0.0044
Insulin (fasting) μU/mL	Placebo	11.6±8.2	11.4±8.8	−0.2±4.6	
	50 mg	12.5±9.6	13.6±12.3	1.1±5.5	1.3 (−1.2 to 3.7)	0.3068
	100 mg	9.3±5.5	8.7±5.1	−0.6±4.9	−0.4 (−2.7 to 1.8)	0.6970
Insulin (1 hr), μU/mL	Placebo	46.0±39.0	45.7±34.4	−3.2±25.6	
	50 mg	57.8±62.0	65.8±66.1	7.1±15.7	10.2 (−0.7 to 21.1)	0.0651
	100 mg	38.9±23.7	40.6±24.2	0.4±19.9	3.6 (−6.8 to 14.0)	0.4965
Insulin (2 hr), μU/mL	Placebo	52.5±44.9	59.5±51.7	2.6±36.3	
	50 mg	59.7±51.0	69.1±80.5	9.0±37.7	6.4 (−9.7 to 22.4)	0.4313
	100 mg	48.0±26.9	51.5±30.2	3.7±14.6	1.2 (−14.2 to 16.5)	0.8820
C-peptide, ng/mL	Placebo	2.40±1.01	2.43±1.02	0.03±0.54	
	50 mg	2.64±0.89	2.78±1.07	0.14±0.57	0.10 (−0.20 to 0.40)	0.5042
	100 mg	2.18±0.74	2.15±0.74	−0.03±0.69	−0.06 (−0.34 to 0.22)	0.6669
Exploratory endpoint					
HOMA-IR	Placebo	4.23±3.04	4.58±4.59	0.35±2.56	
	50 mg	4.09±2.74	4.11±3.17	0.01±1.71	−0.34 (−1.52 to 0.85)	0.5738
	100 mg	3.29±2.38	2.81±2.26	−0.48±2.71	−0.83 (−1.93 to 0.26)	0.1341
HOMA-β[a]	Placebo	48.7±38.9	44.7±28.3	−4.0±19.6	
	50 mg	52.1±25.4	64.8±33.9	12.7±25.8	16.7 (5.6 to 27.8)	0.0035
	100 mg	48.0±34.3	54.1±34.6	6.1±19.5	10.1 (0.2 to 20.1)	0.0465
IGI_{60}, μU/mL per mg/dL[b]	Placebo	4.44±4.63	4.15±3.43	−0.49±3.69	
	50 mg	5.82±5.25	6.45±5.12	0.60±2.14	1.09 (−1.65 to 3.83)	0.4312
	100 mg	4.25±3.20	5.72±8.12	1.27±7.51	1.77 (−0.86 to 4.39)	0.1845
GA/HbA1c	Placebo	2.50±0.31	2.53±0.33	0.03±0.14	
	50 mg	2.47±0.30	2.43±0.26	−0.04±0.11	−0.07 (−0.14 to −0.01)	0.0300
	100 mg	2.51±0.28	2.50±0.31	−0.01±0.15	−0.04 (−0.10 to 0.02)	0.1887

(*Continued to the next page*)

Supplementary Table 2. Continued

Variable	Mean±SD				LSM (95% CI)	*P* value
	Treatment	Baseline	Week 4	Change	Difference from placebo	
CD36, ng/mL	Placebo	44.5±81.4	48.9±96.6	4.3±18.3		
	50 mg	54.8±124.1	55.8±112.3	1.1±26.2	−3.3 (−23.6 to 17.1)	0.7503
	100 mg	59.8±198.9	51.8±142.6	−7.9±60.5	−12.3 (−31.2 to 6.6)	0.2003
Weight, kg	Placebo	72.8±12.2	72.5±13.0	−0.4±2.1		
	50 mg	69.2±14.7	69.4±14.6	0.1±1.1	0.5 (−0.2 to 1.3)	0.1806
	100 mg	65.1±11.9	64.9±11.9	−0.1±1.1	0.3 (−0.4 to 0.9)	0.4759

LSMs and CIs are based on analysis of variance. Missing values were imputed by last observation carried forward (LOCF) method. The *P* values are based on Fisher's least significant difference (LSD) method for multiple comparisons.
SD, standard deviation; LSM, least square mean; CI, confidence interval; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; C-peptide, connecting peptide; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; IGI, insulinogenic index; GA, glycoalbumin; CD36, cluster of differentiation 36.
[a]Analyses were conducted after removing outlier values in week 12, [b](Insulin [1 hr]−insulin [fasting])/(glucose [1 hr]−glucose [fasting])×18.

Supplementary Table 3. Exploratory endpoints of the 12-week

Exploratory endpoint	Mean±SD				LSM (95% CI)	*P* value
	Treatment	Baseline	Week 12	Change	Difference from placebo	
HOMA-IR	Placebo	4.23±3.04	4.28±4.42	0.05±3.40		
	50 mg	4.09±2.74	4.05±2.65	−0.04±1.49	−0.09 (−1.37 to 1.19)	0.8875
	100 mg	3.29±2.38	2.82±2.11	−0.47±2.53	−0.52 (−1.71 to 0.67)	0.3910
HOMA-β[a]	Placebo	48.7±38.9	42.2±32.0	−6.5±25.1		
	50 mg	52.1±25.4	63.5±27.5	11.5±19.0	17.9 (6.8 to 29.1)	0.0019
	100 mg	48.0±34.3	52.2±28.5	4.2±20.0	10.7 (0.7 to 20.7)	0.0368
IGI_{60}, μU/mL per mg/dL[b]	Placebo	4.44±4.63	4.38±4.83	−0.14±3.28		
	50 mg	5.82±5.25	6.59±6.70	0.77±3.40	0.91 (−0.77 to 2.59)	0.2867
	100 mg	4.25±3.20	6.05±4.06	1.77±3.52	1.91 (0.34 to 3.48)	0.0175
GA/HbA1c	Placebo	2.50±0.31	2.54±0.34	0.04±0.18		
	50 mg	2.47±0.30	2.44±0.30	−0.03±0.14	−0.07 (−0.15 to 0.01)	0.0856
	100 mg	2.51±0.28	2.55±0.27	0.03±0.16	−0.01 (−0.08 to 0.06)	0.7966
CD36, ng/mL	Placebo	44.5±81.4	41.9±84.2	−2.7±30.9		
	50 mg	54.8±124.1	60.3±120.0	5.5±65.4	8.2 (−24.4 to 40.8)	0.6190
	100 mg	59.8±198.9	49.1±122.5	−10.7±86.3	−8.0 (−38.3 to 22.2)	0.6007
Weight, kg	Placebo	72.8±12.2	72.1±13.0	−0.7±2.8		
	50 mg	69.2±14.7	68.9±14.7	−0.3±2.0	0.4 (−0.7 to 1.5)	0.4809
	100 mg	65.1±11.9	65.0±11.9	−0.1±1.8	0.6 (−0.4 to 1.6)	0.2046

LSMs and CIs are based on analysis of variance. Missing values were imputed by last observation carried forward (LOCF) method. The *P* values are based on Fisher's least significant difference (LSD) method for multiple comparisons.

SD, standard deviation; LSM, least square mean; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; IGI, insulinogenic index; GA, glycoalbumin; HbA1c, glycosylated hemoglobin; CD36, cluster of differentiation 36.

[a]Analyses were conducted after removing outlier values in week 12, [b](Insulin [1 hr]−insulin [fasting])/(glucose [1 hr]−glucose [fasting])×18.

Supplementary Table 4. Summary of subgroup analysis for HbA1c and glycoalbumin at week 12

Variable	Subgroup	Treatment	Mean±SD			LSM (95% CI)	*P* value
			No.	Baseline	Week 12	Change	Difference from placebo	
HbA1c, %								
Sex	Male	Placebo	24	7.58±0.82	8.13±1.46	0.55±1.15		
		50 mg	14	7.42±0.55	7.17±0.78	−0.25±0.46	−0.81 (−1.32 to −0.29)	0.0026
		100 mg	21	7.93±1.05	7.36±1.04	−0.56±0.81	−1.12 (−1.58 to −0.66)	<0.0001
	Female	Placebo	11	7.92±1.13	8.04±2.03	0.12±1.08		
		50 mg	17	7.36±0.62	6.99±0.57	−0.37±0.38	−0.49 (−1.08 to 0.11)	0.1076
		100 mg	21	7.35±0.47	7.04±0.43	−0.31±0.22	−0.43 (−1.00 to 0.14)	0.1395
Age	<60 years	Placebo	18	7.90±1.01	8.36±1.96	0.47±1.40		
		50 mg	14	7.37±0.44	7.12±0.59	−0.25±0.40	−0.72 (−1.26 to −0.17)	0.0105
		100 mg	15	8.15±1.11	7.38±1.04	−0.77±0.80	−1.24 (−1.77 to −0.70)	<0.0001
	≥60 years	Placebo	17	7.46±0.79	7.82±1.18	0.37±0.79		
		50 mg	17	7.39±0.70	7.03±0.74	−0.37±0.44	−0.73 (−1.26 to −0.21)	0.0066
		100 mg	27	7.35±0.50	7.10±0.63	−0.25±0.36	−0.62 (−1.09 to −0.14)	0.0113
BMI	<25 kg/m^2	Placebo	13	7.81±0.94	8.81±1.86	0.99±1.30		
		50 mg	13	7.18±0.37	6.91±0.48	−0.27±0.38	−1.26 (−1.84 to −0.69)	<0.0001
		100 mg	25	7.65±0.89	7.33±0.89	−0.32±0.40	−1.32 (−1.82 to −0.81)	<0.0001
	≥25 kg/m^2	Placebo	22	7.61±0.93	7.68±1.36	0.08±0.88		
		50 mg	18	7.53±0.67	7.18±0.77	−0.35±0.45	−0.42 (−0.90 to 0.04)	0.0736
		100 mg	17	7.61±0.83	7.01±0.61	−0.61±0.79	−0.68 (−1.15 to −0.21)	0.0052
HOMA-β[a]	<42.41	Placebo	18	7.94±0.93	8.60±1.90	0.66±1.48		
		50 mg	12	7.57±0.74	7.52±0.86	−0.05±0.29	−0.71 (−1.26 to −0.14)	0.0146
		100 mg	24	7.72±0.92	7.39±0.89	−0.33±0.43	−0.99 (−1.46 to −0.52)	<0.0001
	≥42.41	Placebo	17	7.41±0.86	7.57±1.11	0.16±0.52		
		50 mg	19	7.27±0.45	6.79±0.28	−0.48±0.40	−0.65 (−1.15 to −0.14)	0.0127
		100 mg	18	7.52±0.78	6.95±0.59	−0.57±0.77	−0.74 (−1.25 to −0.22)	0.0052
Glycoalbumin, %								
Sex	Male	Placebo	24	19.2±3.6	21.3±6.8	2.1±4.1		
		50 mg	14	18.4±3.2	17.4±3.0	−1.0±1.2	−3.1 (−4.7 to −1.4)	0.0003
		100 mg	21	19.6±4.3	18.8±3.9	−0.8±2.1	−2.9 (−4.3 to −1.4)	0.0001
	Female	Placebo	11	19.5±3.6	19.9±5.4	0.4±2.2		
		50 mg	17	18.2±2.6	17.1±2.6	−1.0±1.4	−1.5 (−3.3 to 0.4)	0.1239
		100 mg	21	18.9±2.3	17.9±2.1	−1.0±1.2	−1.4 (−3.2 to 0.4)	0.1147
Age	<60 years	Placebo	18	19.6±3.9	21.2±7.0	1.7±4.0		
		50 mg	14	17.1±3.1	16.3±3.2	−0.9±1.2	−2.5 (−4.2 to −0.8)	0.0042
		100 mg	15	20.4±4.6	18.4±4.3	−2.0±2.1	−3.6 (−5.3 to −2.0)	<0.0001
	≥60 years	Placebo	17	19.0±3.2	20.4±5.7	1.5±3.5		
		50 mg	17	19.2±2.2	18.1±2.1	−1.1±1.4	−2.6 (−4.2 to −0.9)	0.0024
		100 mg	27	18.6±2.5	18.3±2.4	−0.3±1.1	−1.8 (−3.3 to −0.3)	0.0203
BMI	<25 kg/m^2	Placebo	13	20.9±3.5	23.6±6.6	2.7±4.3		
		50 mg	13	18.1±2.1	17.5±2.1	−0.7±1.2	−3.4 (−5.3 to −1.5)	0.0005
		100 mg	25	19.6±3.8	19.0±3.3	−0.6±1.4	−3.3 (−4.9 to −1.7)	0.0001

(*Continued to the next page*)

Supplementary Table 4. Continued

Variable	Subgroup	Treatment	Mean±SD			LSM (95% CI)	*P* value
			No.	Baseline	Week 12	Change	Difference from placebo	
	≥25 kg/m^2	Placebo	22	18.3±3.3	19.2±5.7	0.9±3.2		
		50 mg	18	18.4±3.3	17.1±3.2	−1.3±1.3	−2.1 (−3.7 to −0.6)	0.0062
		100 mg	17	18.8±3.0	17.4±2.6	−1.4±2.0	−2.3 (−3.8 to −0.7)	0.0046
HOMA-β[a]	<42.41	Placebo	18	20.8±3.6	23.3±7.2	2.5±4.7		
		50 mg	12	19.8±3.0	19.1±2.9	−0.7±1.1	−3.2 (−5.0 to −1.4)	0.0006
		100 mg	24	20.3±3.9	19.4±3.4	−0.9±1.7	−3.4 (−4.9 to −1.9)	<0.0001
	≥42.41	Placebo	17	17.7±2.8	18.3±4.0	0.6±1.8		
		50 mg	19	17.3±2.3	16.1±1.9	−1.2±1.4	−1.8 (−3.4 to −0.2)	0.0275
		100 mg	18	17.9±2.0	17.0±2.2	−0.9±1.8	−1.5 (−3.1 to −0.1)	0.0695

Missing values were imputed by last observation carried forward (LOCF) method. LSMs and CIs are based on analysis of variance (ANOVA) models including fixed effects for treatment, subgroup (e.g., sex, age, BMI, or HOMA-β), and their interaction. *P* values are derived using Fisher's least significant difference (LSD) method for multiple comparisons. *P* values for the interaction between subgroup and treatment were >0.10, except for BMI in HbA1c (*P*=0.0635). Baseline characteristics are based on the data collected at baseline (day 0).

HbA1c, glycosylated hemoglobin; SD, standard deviation; LSM, least square mean; CI, confidence interval; BMI, body mass index; HOMA-β, homeostatic model assessment of β cell function.

[a]Analyses were conducted after removing outlier values in week 12.

Supplementary Table 5. Liver function test of the 4, 8, and 12-week

Variable	Placebo (*n*=36)	HD-6277 50 mg (*n*=31)	HD-6277 100 mg (*n*=43)	*P* value
AST, IU/L				
Baseline	24.8±6.9	23.8±6.0	26.8±9.7	
Week 4	23.9±7.0	23.4±6.1	26.4±12.7	
Week 8	25.1±7.5	23.1±5.4	28.0±18.3	
Week 12	25.5±11.1	23.2±6.0	25.8±8.1	
Change at week 4	−1.3±6.1	−0.5±5.1	−0.6±13.9	0.9341
Change at week 8	−0.3±6.9	−0.7±5.1	0.8±16.4	0.8516
Change at week 12	0.2±10.0	−0.6±4.8	−1.2±8.4	0.7436
ALT, IU/L				
Baseline	29.4±13.9	25.8±14.1	30.7±19.9	
Week 4	31.0±14.8	25.9±15.6	32.0±27.8	
Week 8	31.1±14.7	24.2±12.3	28.6±13.8	
Week 12	30.5±13.3	25.0±13.6	27.9±13.2	
Change at week 4	1.3±10.3	0.1±6.7	0.9±25.5	0.9632
Change at week 8	1.1±11.3	−1.5±10.2	−2.9±17.8	0.4508
Change at week 12	0.5±11.5	−0.7±12.2	−3.3±16.3	0.4716
Bilirubin, mg/dL				
Baseline	0.92±0.39	0.82±0.33	0.92±0.38	
Week 4	0.94±0.53	0.70±0.24	0.92±0.38	
Week 8	0.98±0.57	0.76±0.29	0.91±0.38	
Week 12	0.97±0.42	0.77±0.28	0.91±0.35	
Change at week 4	0.01±0.31	−0.11±0.21	−0.01±0.26	0.1157
Change at week 8	0.05±0.36	−0.06±0.24	−0.03±0.22	0.2609
Change at week 12	0.05±0.33	−0.05±0.21	−0.02±0.30	0.3801

Values are presented as mean±standard deviation. *P* values are based on analysis of variance (ANOVA) tests.
AST, aspartate aminotransferase; ALT, alanine transaminase.

Supplementary Table 6. Renal function test of the 4, 8, and 12-week

Variable	Placebo (n=36)	HD-6277 50 mg (n=31)	HD-6277 100 mg (n=43)	P value
BUN, mg/dL				
Baseline	14.6±3.0	14.2±3.8	14.0±3.6	
Week 4	14.7±3.4	14.5±3.5	14.5±4.0	
Week 8	15.0±3.6	15.0±3.5	14.9±3.6	
Week 12	14.2±3.3	15.0±3.5	14.2±4.3	
Change at week 4	0.2±3.0	0.3±3.9	0.4±3.5	0.9791
Change at week 8	0.5±3.1	0.9±3.5	0.8±4.0	0.8856
Change at week 12	−0.3±2.9	0.9±3.1	0.2±3.5	0.3653
Uric acid, mg/dL				
Baseline	4.85±1.16	5.00±1.09	4.60±1.14	
Week 4	4.84±1.09	5.06±1.14	4.60±1.13	
Week 8	4.88±1.10	5.12±1.21	4.64±1.04	
Week 12	4.70±1.12	5.14±1.28	4.65±1.23	
Change at week 4	0.02±0.58	0.05±0.61	−0.01±0.70	0.9127
Change at week 8	0.03±0.82	0.11±0.74	0.03±0.60	0.8631
Change at week 12	−0.14±0.81	0.14±0.84	0.08±0.69	0.2946
Creatinine, mg/dL				
Baseline	0.85±0.17	0.80±0.16	0.81±0.18	
Week 4	0.83±0.14	0.82±0.17	0.80±0.16	
Week 8	0.84±0.16	0.81±0.17	0.79±0.14	
Week 12	0.83±0.15	0.79±0.16	0.79±0.15	
Change at week 4	−0.01±0.07	0.02±0.08	−0.00±0.07	0.1980
Change at week 8	−0.01±0.08	0.01±0.07	−0.02±0.09	0.2611
Change at week 12	−0.02±0.06	−0.01±0.07	−0.01±0.08	0.8640
eGFR, mL/min/1.73 m^2				
Baseline	92.5±14.9	89.5±14.9	88.7±11.5	
Week 4	93.3±13.0	88.2±15.1	89.1±11.7	
Week 8	93.3±14.5	88.2±15.0	90.1±11.0	
Week 12	93.9±13.7	90.3±14.9	89.9±10.6	
Change at week 4	1.3±6.2	−1.3±7.5	0.2±6.6	0.2934
Change at week 8	0.7±6.9	−1.2±6.4	1.5±8.2	0.2789
Change at week 12	1.4±5.6	0.8±6.1	1.2±7.6	0.9417
NAG, U/L				
Baseline	14.47±16.98	10.30±6.00	11.30±11.48	
Week 4	13.56±13.03	9.73±6.03	12.65±9.70	
Week 8	9.64±7.75	9.74±5.51	11.16±8.96	
Week 12	12.59±17.79	9.20±6.82	12.43±10.15	
Change at week 4	−1.23±17.75	−0.94±5.75	1.63±10.06	0.5429
Change at week 8	−5.31±16.21	−0.34±5.82	0.06±10.52	0.1118
Change at week 12	−2.36±22.01	−1.11±5.57	0.89±13.84	0.5304

Values are presented as mean±standard deviation. P values are based on analysis of variance (ANOVA) tests.
BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; NAG, N-acetyl-β-D-glucosaminidase.