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Efficacy and safety of DBPR108 (prusogliptin) as an add-on to metformin therapy in patients with type 2 diabetes: A 24-week, multi-centre, randomized, double-blind, placebo-controlled, superiority, phase III clinical trial

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Abstract

Aim: To evaluate the efficacy and safety of DBPR108 (prusogliptin), a novel dipeptidyl peptidase-4 (DPP-4) inhibitor, as an add-on therapy in patients with type 2 diabetes (T2D) that is inadequately controlled with metformin.

Materials and Methods: In this 24-week, multi-centre, randomized, double-blind, placebo-controlled, superiority, phase III study, adult T2D patients with HbA1c levels ranging from 7.0% to 9.5% on stable metformin were enrolled and randomized (2:1) into the DBPR108 + metformin and placebo + metformin groups. The primary endpoint was the change from baseline in HbA1c at week 24 of DBPR108 versus placebo as an add-on therapy to metformin.

Results: At week 24, the least-square mean (standard error) change from baseline in HbA1c was significantly greater in the DBPR108 group (−0.70% [0.09%]) than in the placebo group (−0.07% [0.11%]) ($P < .001$), with a treatment difference of −0.63% (95% confidence interval: −0.87%, −0.39%) on the full analysis set. A higher proportion of patients achieved an HbA1c of 6.5% or less (19.7% vs. 8.5%) and an HbA1c of 7.0% or less (50.0% vs. 21.1%) at week 24 in the DBPR108 + metformin group. Furthermore, add-on DBPR108 produced greater reductions from baseline in fasting plasma glucose and 2-hour postprandial plasma glucose without causing weight gain. The overall frequency of adverse events was similar between the two groups.

Conclusions: DBPR108 as add-on therapy to metformin offered a significant improvement in glycaemic control, was superior to metformin monotherapy (placebo) and was safe and well-tolerated in patients with T2D that is inadequately controlled with metformin.

KEYWORDS
DBPR108, DPP-4 inhibitor, metformin, type 2 diabetes

1 | INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are significant antidiabetic agents that stimulate insulin secretion and inhibit glucagon secretion by elevating endogenous glucagon-like peptide-1 concentration, resulting in body weight neutrality and a low incidence of hypoglycaemia.[1] Commercially available DPP-4 inhibitors have been shown to reduce HbA1c levels by 0.4%-0.9% (eliminate placebo effect) in Chinese patients with type 2 diabetes (T2D).[2] However, saxagliptin was also reported to increase the hospitalization rate for heart failure.[3,4] As such, dose adjustments in saxagliptin, sitagliptin, alogliptin or vildagliptin therapies have been recommended in T2D patients with renal insufficiency.[2]

DBPR108 (prusogliptin, (2S, 4S)-1-[2-[[1,1-dimethyl-3-oxo-3-(1-pyrrolidinyl) propyl] amino] acetyl]-4-fluoro-2-pyrrolidinecarbonitrile), which is designed and developed by the Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes in Taiwan, is a novel peptidomimetic DPP-4 inhibitor that displays selectivity towards DPP-4 over DPP-2, DPP-8, DPP-9 and FAP.[5,6] In the previous phase II study, DBPR108 (100 mg once daily) monotherapy significantly decreased the baseline HbA1c at week 12 (−0.75%) to a similar extent as with sitagliptin (−0.44%), vildagliptin (−0.53%) and saxagliptin (−0.90%).[1,7-9] Moreover, no cardiovascular or renal events were observed in the administration of DBPR108 in patients with T2D.[1]

The addition of DPP-4 inhibitors to metformin therapy has been recommended by the American Diabetes Association (ADA) and Chinese Diabetes Society (CDS) in patients with inadequately controlled T2D.[2,10] Co-administration of commercial DPP-4 inhibitors with metformin has a limited clinically relevant effect on the pharmacokinetics of commonly prescribed medications for patients with T2D.[11,12] Our preliminary drug–drug interaction study (unpublished results) revealed that the co-administration of DBPR108 and metformin had a moderate effect on the exposure of DBPR108 in the plasma, and the clinically relevant consequences caused by moderately decreased DBPR108 exposure need to be further determined. Conversely, only minor changes in metformin exposure were observed, which was unlikely to be clinically relevant. Similar to sitagliptin[13] and vildagliptin,[14] DBPR108 also had little impact on the inhibition or activation of human cytochrome P450 (CYP) enzymes and a low potential for CYP enzyme-related drug interactions. Therefore, the objective of this study was to evaluate the efficacy and safety of DBPR108 (100 mg once daily) as an add-on therapy to metformin in patients with inadequately controlled T2D.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a 24-week, multi-centre, randomized, double-blind, placebo-controlled, superiority, phase III clinical trial conducted in 30 centres in China from January 2020 to June 2021. Specifically, the study comprised a 2-week screening period, a 2-week dietary and exercise lead-in period, a 1-week baseline period, a 24-week treatment period and a 2-week follow-up period. Eligible patients were randomized into either the DBPR108 + metformin or placebo + metformin group in a 2:1 ratio (Figure 1). The study had a total of six hospital visits (at the end of the screening period and baseline period, and at 4, 8, 12 and 24 weeks of treatment) and three telephone visits (at the end of week 16 and week 20 of treatment, and at the follow-up period). In addition to HbA1c measurement at visit 1 (screening period), fasting plasma glucose (FPG) and 2-hour postprandial plasma glucose (PPG) were measured at visit 2 (baseline period, at weeks −1 to 0), visit 5 (week 12 ± 3 days) and visit 6 (week 24 ± 7 days). Similarly, electrocardiography (ECG) was measured at visits 1, 2, 5 and 6. Clinical tests and diagnostics, including vital signs, physical examination, weight, blood routine, blood chemistry and urinalysis, were scheduled from visits 1-6 approximately once every 4 weeks. Furthermore, adverse events (AEs) were recorded from the moment informed consent was signed until the last follow-up (week 26 ± 3 days).

The protocol and informed consent form were approved by the clinical trials ethics committee of Peking Union Medical College Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki, quality management specifications for drug clinical trials, and Good Clinical Practice. All patients provided written informed consent prior to inclusion in the study. The trial was registered at ClinicalTrials.gov (NCT04218734).

2.2 | Patients

The inclusion criteria were: T2D diagnosis according to the World Health Organization diagnostic criteria for diabetes (1999), age 18-75 years, body mass index ranging from 19 to 35 kg/m^2, inadequate glycaemic control (HbA1c 7.0%-9.5%) and administration of stable metformin (≥1000 mg/day) for at least 8 weeks prior to screening. Additional information on the exclusion criteria can be found in the supporting information.

2.3 | Randomization and masking

Randomization numbers were generated centrally by an independent statistician using SAS software (SAS Institute Inc., Cary, NC, USA; version 9.4). As previously mentioned, eligible patients were randomized in a 2:1 ratio through an Interactive Web Response System. Medical staff and patients were also masked to treatment allocation.

2.4 | Interventions

From the lead-in period to the end of the 24-week treatment period, patients received an uninterrupted and stable dose of metformin (Glucophage, metformin hydrochloride tablets, 500 mg/tablet, Sino-American Shanghai Squibb Pharmaceuticals Co., Ltd.) equal to the

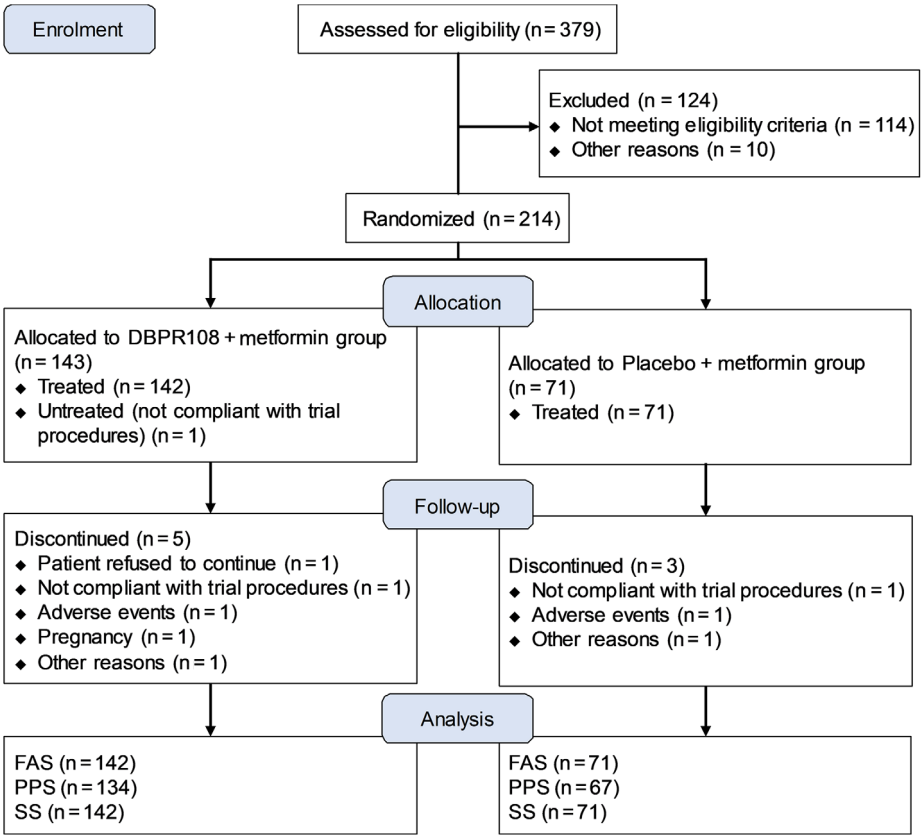

FIGURE 1 Patient disposition. FAS, full analysis set; PPS, per-protocol set; SS, safety set

daily dose used within the 8 weeks prior to the screening period. During the 24-week treatment period, patients received 100 mg of DBPR108 (100 mg/tablet, CSCP ZhongQi Pharmaceutical Technology [Shijiazhuang] Co., Ltd.), which was based on the previous phase II study results,[1] or placebo once daily at least 30 min before breakfast, in addition to the ongoing metformin regimen. Rescue therapy was permitted if FPG remained at less than 13.9 mmol/L after 2 weeks of treatment.

2.5 | Outcomes

The primary efficacy outcome was the change from baseline in HbA1c at week 24 of DBPR108 versus placebo as an add-on therapy to metformin. Secondary efficacy outcomes included the percentages of patients with an HbA1c of 6.5% or less and an HbA1c of 7.0% or less at week 24; change from baseline in HbA1c at week 12; and change from baseline in FPG, 2-hour PPG and body weight at weeks 12 and 24.

Safety outcomes were assessed based on the frequency and severity of AEs, serious AEs (SAEs) and treatment-emergent adverse events (TEAEs). Other safety outcomes, such as clinical symptoms, vital signs, 12-lead ECG and clinical laboratory tests, including haematology, urinalysis and blood chemistry, were also conducted.

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, v. 22.1) and summarized by preferred terms. If an event was reported more than once with the same preferred term, the AE was counted only once with the greatest severity. The severity of AEs was classified as follows: (a) mild, if slightly interfering with everyday activities; (b) moderate, if significantly interfering with everyday activities; and (c) severe, if the functional impairment prevents everyday activities. A hypoglycaemic event was defined when plasma glucose values were less than 3.9 mmol/L for patients receiving drug treatment.[2]

2.6 | Statistical analyses

Power analysis suggested that, considering a 20% drop-out rate, 210 randomized patients (a ratio of 2:1, 140 in the DBPR108 + metformin group and 70 in the placebo + metformin group) were required to provide power (1 – β) of 80% or higher, and a one-sided α at .025 to detect a difference of 0.6% in the HbA1c mean change from baseline to week 24 between the two groups with a standard deviation (SD) of 1.3. Following the intent-to-treat principle, all randomized patients who had received at least one dose of the study drugs and had undergone at least one post-treatment efficacy evaluation were included in the full analysis set (FAS). All patients in the FAS who at least completed the 24-week treatment, had primary efficacy measurement, had medical compliance of 80%-120%, and did not commit any major protocol deviations (e.g. violation of key eligibility criteria), were included in the per-protocol set (PPS). Moreover, all randomized patients who had at least one dose of the study drugs were included in the safety analysis set (SS). For all analyses, patients

were grouped according to the actual treatment received. Baseline characteristics, efficacy analyses and sensitivity analyses were performed using the FAS. The robustness of the primary efficacy result was assessed in the FAS and PPS, whereas safety analyses were performed in the SS.

Primary efficacy analysis was performed using an analysis of covariance (ANCOVA) model, with baseline HbA1c values as the covariate and the groups and centres as fixed effects. The last observation carried forward (LOCF) method was used to impute missing HbA1c values at week 24. The superiority test was based on the primary efficacy outcome, and the hypotheses were as follows: null hypothesis (H_0: $\mu_T - \mu_C \geq 0$), alternative hypothesis (H1: $\mu_T - \mu_C < 0$), one-sided $\alpha = .025$, where μ_T and μ_C denoted the mean change from baseline in HbA1c at week 24 in the DBPR108 + metformin and placebo + metformin groups, respectively. Therefore, if the upper limit of the two-sided 95% confidence interval (CI) for the difference in least-square (LS) mean change from baseline in HbA1c at week 24 for both groups in the ANCOVA model was below the prespecified superiority margin of 0% ($P < .025$), superiority could be concluded. Sensitivity analyses were performed similarly to the primary efficacy outcome analysis. The subset disposition of the sensitivity analyses was as follows: (a) subset 1 consisted of patients who did not receive rescue therapy in the FAS, wherein missing HbA1c values at week 24 were imputed using LOCF; and (b) subset 2 consisted of all patients in the FAS, wherein the HbA1c at week 24 was imputed using LOCF prior to rescue therapy initiation in patients who received rescue therapy, whereas missing HbA1c values at week 24 were imputed using LOCF in patients who did not receive rescue therapy. Additionally, secondary efficacy outcomes (HbA1c, FPG, 2-hour PPG and body weight) were analysed using ANCOVA, with baseline value as the covariate and groups as fixed effects. For comparisons of two groups of continuous variables, the *T*-test (if the normality and homogeneity of variance assumptions were met) or the Wilcoxon rank sum test (if the normality or homogeneity of variance assumptions were not met) was used. The Chi-square test (if all expected counts were greater than or equal to 5) or Fisher's exact test (if at least one expected count was less than 5) was used for categorical variables.

All statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA; version 9.4), and a *P* value of less than .05 was considered statistically significant in all two-tailed tests. Categorical variables were described using counts and percentages, and continuous variables were described using means, SDs or standard errors (SEs), as appropriate.

3 | RESULTS

3.1 | Patient disposition and characteristics

A total of 214 patients were randomized into the DBPR108 + metformin (n = 143) or placebo + metformin groups (n = 71), of whom

TABLE 1 Patient demographics and baseline characteristics (FAS)

Variable	DBPR108 + metformin group (n = 142)	Placebo + metformin group (n = 71)	*P*
Sex			.923[a]
Male	71 (50.0)	36 (50.7)	
Female	71 (50.0)	35 (49.3)	
Age (y)	57.9 (8.73)	57.3 (9.14)	.705[b]
Race			.429[c]
Han	136 (95.8)	70 (98.6)	
Others	6 (4.2)	1 (1.4)	
Weight (kg)	68.40 (11.948)	68.60 (11.819)	.907[d]
BMI (kg/m^2)	25.58 (2.992)	25.38 (3.506)	.662[d]
Time since diagnosis (mo)	21.255 (30.6196)	33.202 (58.8141)	.448[b]
HbA1c (%)	7.783 (0.5419)	7.875 (0.5801)	.287[b]
FPG (mmol/L)	9.028 (1.6069)	9.215 (1.6924)	.413[b]
2-hour PPG (mmol/L)	15.363 (3.0213)	14.897 (3.0156)	.289[d]
SBP (mmHg)	126.2 (12.68)	126.8 (13.04)	.734[d]
DBP (mmHg)	80.2 (7.99)	80.7 (10.02)	.715[d]

Note: Data are expressed as n (%) or mean (SD) unless otherwise noted.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FAS, full analysis set; FPG, fasting plasma glucose; PPG, postprandial plasma glucose, SBP, systolic blood pressure.
[a]Chi-square test.
[b]Wilcoxon rank sum test.
[c]Fisher's exact test.
[d]*T*-test.

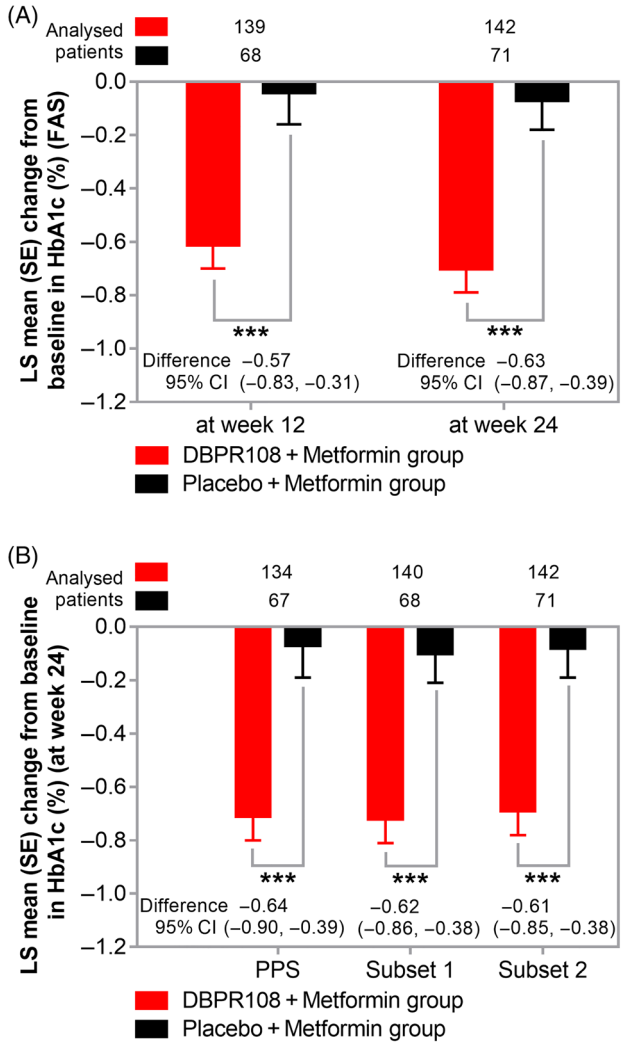

FIGURE 2 HbA1c change from baseline: A, At weeks 12 and 24 in the FAS, and B, At week 24 in the PPS, subset 1 (patients who did not receive rescue therapy in the FAS) and subset 2 (all patients in the FAS). For patients in the FAS, subset 1 and subset 2 (who did not receive rescue therapy), missing HbA1c values at week 24 were imputed using the LOCF method, and in subset 2 (those who received rescue therapy), HbA1c values were imputed using the LOCF method prior to rescue therapy initiation. Data are presented in LS means with SEs. FAS, full analysis set; LOCF, last observation carried forward; LS, least-square; PPS, per-protocol set; SE, standard error. ***$P < .001$

206 (DBPR108 + metformin: 96.5%, 138/143; placebo + metformin: 95.8%, 68/71) completed the study. Details of patient disposition are shown in Figure 1.

Patient demographics and baseline characteristics were generally balanced across the treatment groups (Tables 1 and S1). The mean HbA1c at baseline and the mean dose intensity of metformin were 7.78% and 1345.5 mg/day, respectively, in the DBPR108 + metformin group, which were similar to those in the placebo + metformin group (7.85% and 1387.0 mg/day).

3.2 | Primary efficacy outcomes

In the FAS, the addition of DBPR108 to metformin therapy produced a more significant reduction from baseline in HbA1c at week 24 (LS mean ± SE: −0.70% ± 0.09%), as compared with that with placebo (−0.07% ± 0.11%) ($P < .001$) (Figure 2A and Table S1). The upper limit of the 95% CI for the between-group difference was −0.39, which was less than the superiority margin of 0% ($P < .001$). Therefore, the primary superiority endpoint in this study was met.

In the PPS, the LS mean (SE) change from baseline in HbA1c at week 24 was −0.71% (0.09%) for DBPR108 and −0.07% (0.12%) for placebo ($P < .001$) (Figure 2B). Results in the PPS were consistent with the FAS analysis, supporting the robustness of the primary endpoint.

Results in subset 1 for sensitivity analysis showed that the LS mean (SE) change from baseline in HbA1c at week 24 was −0.72% (0.09%) for DBPR108 and −0.10% (0.11%) for placebo ($P < .001$) (Figure 2B). In subset 2, the LS mean (SE) change from baseline in HbA1c at week 24 was −0.69% (0.09%) for DBPR108 and −0.08% (0.11%) for placebo ($P < .001$) (Figure 2B). Sensitivity analyses were also consistent with the FAS analysis, supporting the superiority conclusion of the primary endpoint.

3.3 | Secondary efficacy outcomes

The addition of DBPR108 to metformin therapy significantly reduced the change from baseline in HbA1c at week 12 compared with that in placebo (Table S1). The LS mean (SE) change from baseline in HbA1c at week 12 was −0.61% (0.09%) for DBPR108 and −0.04% (0.12%) for placebo ($P < .001$) (Figure 2A).

Significantly higher percentages of patients in the DBPR108 + metformin group (19.7% and 50.0%, respectively) reached HbA1c levels of 6.5% or less and of 7.0% or less at week 24 than those of the placebo + metformin group (8.5% [$P = .037$] and 21.1% [$P < .001$], respectively) (Figure 3A).

Similarly, the reduction from baseline in FPG was significantly greater in the DBPR108 + metformin group than that of the placebo + metformin group (Table S1). The LS mean (SE) change from baseline in FPG at week 12 was −0.76 (0.20) mmol/L for DBPR108 and 0.49 (0.25) mmol/L for placebo ($P < .001$) (Figure 3B). Furthermore, the LS mean (SE) change from baseline in FPG at week 24 was −0.63 (0.22) mmol/L for DBPR108 and 0.07 (0.28) mmol/L for placebo ($P = .025$) (Figure 3B).

Add-on treatment with DBPR108 resulted in a significant reduction from baseline in 2-hour PPG than that with placebo (Table S1). The LS mean (SE) change from baseline in 2-hour PPG at week 12 was −2.33 (0.33) mmol/L for DBPR108 and −0.15 (0.41) mmol/L for placebo ($P < .001$) (Figure 3C). Moreover, the LS mean (SE) change from baseline in 2-hour PPG at week 24 was −2.43 (0.33) mmol/L for DBPR108 and −0.70 (0.43) mmol/L for placebo ($P < .001$) (Figure 3C).

Lastly, there was a smaller reduction from baseline in body weight with DBPR108, as compared with that with placebo (Table S1). The

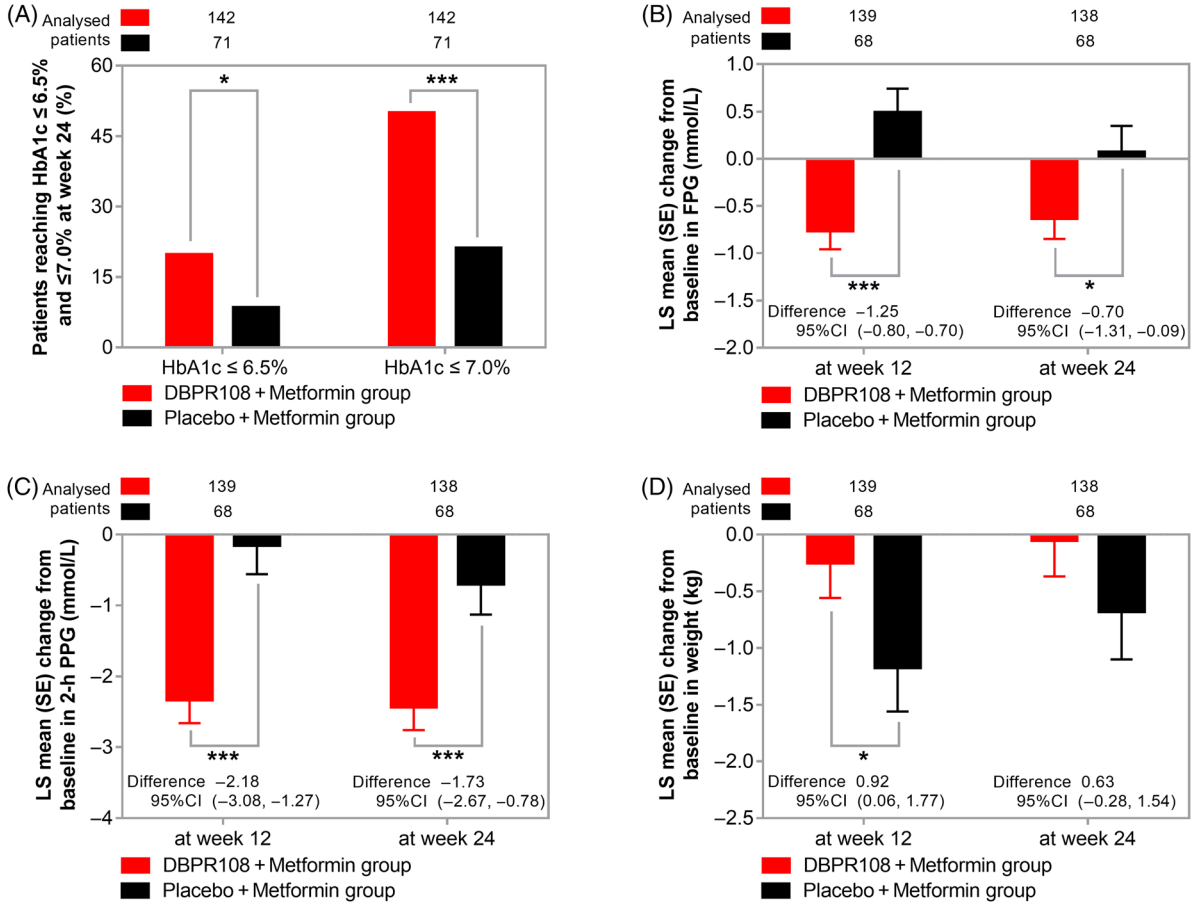

FIGURE 3 A, Percentages of patients reaching HbA1c ≤ 6.5% and ≤7.0% at week 24 (FAS). Changes from baseline in B, FPG, C, 2-hour PPG, and D, Weight at weeks 12 and 24 (FAS). Data in panels (B)-(D) are presented as LS means with SEs. FAS, full analysis set; FPG, fasting plasma glucose; LS, least-square; PPG, postprandial plasma glucose; SE, standard error; *$P < .05$; ***$P < .001$

LS mean (SE) change from baseline in body weight at week 12 was −0.25 (0.31) kg for DBPR108 and −1.17 (0.39) kg for placebo ($P < .05$) (Figure 3D). Similar findings were observed at week 24, wherein the LS mean (SE) change was −0.05 (0.32) kg for DBPR108 and −0.68 (0.42) kg for placebo ($P = .171$) (Figure 3D).

3.4 | Safety

Overall AEs and TEAEs are summarized in Table 2. The proportion of patients who reported any AEs was similar across both groups. The incidence of AEs, TEAEs and treatment-emergent SAEs was 83.8% (119/142), 59.2% (84/142) and 4.2% (6/142) in the DBPR108 + metformin group and 81.7% (58/71), 64.8% (46/71) and 5.6% (4/71) in the placebo + metformin group, respectively. No deaths occurred in either group during the study period. Furthermore, the proportion of patients who discontinued because of TEAEs (1.4%) was similar for both groups. Drug-related TEAEs were reported by 8.5% of patients (12/142) in the DBPR108 + metformin group and by 11.3% of patients (8/71) in the placebo + metformin group. All drug-related TEAEs were mild or moderate in severity, and the most common (n > 1 in either group) drug-related TEAEs were abnormal hepatic function (DBPR108, 1.4% [2/142]; placebo, 1.4% [1/71]), urinary tract infection (placebo, 2.8% [2/71]) and insomnia (DBPR108, 1.4% [2/142]). No drug-related hypoglycaemia was reported in either group.

In addition, no clinically significant abnormalities in clinical laboratory tests, vital signs or physical examinations were observed in patients of either group.

4 | DISCUSSION

The ADA and CDS guidelines indicate the necessity of adding DPP-4 inhibitors to metformin to achieve glycaemic goals in T2D patients whose HbA1c target has not been achieved after approximately 3 months of metformin therapy.[2,10] In this phase III, randomized clinical trial, patients with T2D who were taking stable metformin (≥1000 mg/day) and failed to meet the HbA1c target (7.0%-9.5%) for more than 8 weeks prior to screening were enrolled and received 100 mg of DBPR108 as add-on therapy for 24 weeks.

Our study showed that adding 100 mg of DBPR108 to metformin was more effective in improving HbA1c and significantly reducing FPG and 2-hour PPG than placebo. These results were similar to

TABLE 2 Summary of AEs (SS)

Events	DBPR108 + metformin group (n = 142)			Placebo + metformin group (n = 71)		
AEs	119 (83.8)			58 (81.7)		
Death	0 (0.0)			0 (0.0)		
TEAEs	84 (59.2)			46 (64.8)		
Treatment-emergent SAEs	6 (4.2)			4 (5.6)		
Discontinuation because of TEAEs	2 (1.4)			1 (1.4)		
Drug-related TEAEs	12 (8.5)			8 (11.3)		
Drug-related TEAEs	Mild	Moderate	Severe	Mild	Moderate	Severe
Insomnia	1 (0.7)	1 (0.7)	0	0	0	0
Hepatic function abnormal	2 (1.4)	0	0	1 (1.4)	0	0
Hyperuricaemia	1 (0.7)	0	0	1 (1.4)	0	0
Hypocalcaemia	1 (0.7)	0	0	0	0	0
WBC count increased	1 (0.7)	0	0	0	0	0
Blood uric acid increased	1 (0.7)	0	0	0	0	0
Pancreatic enzymes increased	1 (0.7)	0	0	0	0	0
Constipation	1 (0.7)	0	0	0	0	0
Nausea	1 (0.7)	0	0	0	0	0
Diarrhoea	1 (0.7)	0	0	0	0	0
Vomiting	1 (0.7)	0	0	0	0	0
Sinus bradycardia	1 (0.7)	0	0	0	0	0
Anaemia	1 (0.7)	0	0	0	0	0
Rash	1 (0.7)	0	0	0	0	0
Chest discomfort	1 (0.7)	0	0	0	0	0
Asthenia	1 (0.7)	0	0	0	0	0
Urinary tract infection	0	0	0	2 (2.8)	0	0
Abdominal discomfort	0	0	0	1 (1.4)	0	0
Frequent bowel movements	0	0	0	1 (1.4)	0	0
Blood creatinine increased	0	0	0	1 (1.4)	0	0
Amylase increased	0	0	0	1 (1.4)	0	0
Crystals in urine	0	0	0	0	1 (1.4)	0

Note: Data are expressed as n (%) unless otherwise noted.
Abbreviations: AE, adverse event; SAE, serious adverse event; SS, safety set; TEAE, treatment-emergent adverse event; WBC, white blood cell.

sitagliptin or vildagliptin as an add-on to metformin therapy in patients with inadequately controlled T2D.[15,16]

The placebo-subtracted LS mean reduction from baseline in HbA1c at week 24 (−0.63% [95% CI: −0.87%, −0.39%]) was greater than that at week 12 (−0.57% [95% CI: −0.83%, −0.31%]) for the DBPR108 + metformin group, suggesting a long-term efficacy benefit with DBPR108 as an add-on to metformin therapy. Long-term glycaemic control was also observed in studies of other DPP-4 inhibitors, including sitagliptin and vildagliptin.[15-17]

As recommended by the ADA and CDS guidelines, an HbA1c of 7.0% or less is the target level for most non-pregnant adults with T2D, whereas an HbA1c of 6.5% or less is a more stringent target recommended for certain patients with T2D (younger age, shorter disease course, longer erythrocyte lifespan, no complications, and no cardiovascular disease) in the absence of serious hypoglycaemia or other AEs.[2,10] Considering that the enrolled patients were younger than 75 years of age and had no critical concerns over hypoglycaemia, the percentages of patients with an HbA1c of 6.5% or less and of 7.0% or less were chosen as secondary efficacy outcomes. In this study, the proportions of patients who achieved an HbA1c of 6.5% or less and of 7.0% or less at week 24 were significantly greater in the DBPR108 + metformin group (19.7% and 50.0%, respectively) than in the placebo + metformin group (8.5% [$P = .037$] and 21.1% [$P < .001$], respectively). These results were similar to sitagliptin or vildagliptin as an add-on to metformin therapy in patients with inadequately controlled T2D.[15,16] Thus the addition of DBPR108 to metformin should be considered as an alternative regimen in patients with inadequately controlled T2D.

DBPR108 as an add-on to metformin therapy has been revealed to have a neutral effect on body weight, which was consistent with

the results in saxagliptin, sitagliptin, alogliptin and vildagliptin as an add-on to metformin therapy in patients with inadequately controlled T2D.[15,16,18,19]

Over the 24-week period, the addition of DBPR108 to metformin therapy has also been found to be safe and well-tolerated in patients with inadequately controlled T2D. No occurrences of drug-related hypoglycaemia were reported in this trial. Although causality has yet to be established, acute pancreatitis has been associated with DPP-4 inhibitor therapy, including saxagliptin, sitagliptin, alogliptin and vildagliptin.[20-25] In this study, no cases of acute pancreatitis were reported. However, only one case of mildly increased pancreatic enzymes was reported in the DBPR108 + metformin group, which recovered at the end of treatment (serum amylase level raised to 132 U/L at week 12 and decreased to 80 U/L at week 24, normal range: 30-110 U/L). Previous studies have also shown that DPP-4 inhibitors were not associated with the risk of major cardiovascular events in patients with T2D.[26-28] A significant increase in hospitalization rate attributed to heart failure was reported in saxagliptin compared with standard therapy in patients without previous heart failure.[3,4] In our study, no cardiovascular events, such as heart failure, were reported. Overall, our data indicated that DBPR108 as an add-on to metformin therapy was associated with lower safety concerns.

Despite these findings, the favourable efficacy and safety profiles of DBPR108 as an add-on to metformin therapy need to be shown in a long-term study, especially for patients with cardiovascular impairment, renal impairment, or in those who are elderly.

In conclusion, among patients with inadequately controlled T2D, DBPR108 as an add-on to metformin therapy produced a significant reduction from baseline in HbA1c, which fulfilled the superiority endpoint. Greater reductions from baseline in FPG and 2-hour PPG, as well as higher percentages of patients reaching an HbA1c of 6.5% or less and an HbA1c of 7.0% or less, were also shown with add-on DBPR108, as compared with that in placebo. Furthermore, DBPR108 and metformin were safe and well-tolerated, resulting in minimal safety concerns during the study period. Therefore, adding DBPR108 to metformin therapy could be a viable treatment option in patients with inadequately controlled T2D.

AUTHOR CONTRIBUTIONS

XX, JX, HL, JG, other investigators, YH, YX and TZ contributed to the conception and design of the study. XX, JX, HN and JY were involved in the acquisition, analysis and interpretation of the data. XX, JX, HL, JG, other investigators, YH and HZ provided administrative, technical and material support. XX, JX, HL, JG, other investigators, YH, YX, HZ and TZ provided study supervision. Xinhua Xiao, Hongwei Ling, Jianlin Geng, Ya Li, Ping Li, Yujin Ma, Shuguang Peng, Jingqiu Cui, Zhenfeng Shi, Guijun Qin, Weijuan Liu, Weihong Song, Shiwei Cui, Zhaoli Yan, Hongmei Li, Lihui Zhang, Shu Li, Kuanzhi Liu, Jiarui Li, Caibi Peng, Xin Yan, Shuangqing Li, Yushan Guo, Junqing Zhang, Kun Wang, Zhinong Zhang, Chun Xu, Liyong Zhong and Sheng Jiang are investigators. All authors participated in the discussion and approved the manuscript as submitted.

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CONFLICT OF INTEREST

YH, YX, HZ, HN, TZ and JY are employees of CSPC Zhongqi Pharmaceutical Technology (Shijiazhuang) Co., Ltd. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

1. Wang W, Yao J, Guo X, et al. Efficacy and safety of DBPR108 monotherapy in patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled, phase II clinical trial. *Curr Med Res Opin*. 2020;36:1107-1115.
2. Chinese Diabetes Society. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition). *Chin J Diabetes*. 2021;13:315-409.
3. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317-1326.
4. Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation*. 2014;130:1579-1588.
5. Yeh TK, Tsai TY, Hsu T, et al. (2S,4S)-1-[2-(1,1-Dimethyl-3-oxo-3-pyrrolidin-1-yl-propylamino)acetyl]-4-fluoro-pyrrolidine-2-carbonitrile: a potent, selective, and orally bioavailable dipeptide-derived inhibitor of dipeptidyl peptidase IV. *Bioorg Med Chem Lett*. 2010;20:3596-3600.
6. Yeh KC, Yeh TK, Huang CY, et al. DBPR108, a novel dipeptidyl peptidase-4 inhibitor with antihyperglycemic activity. *Life Sci*. 2021;278:119574.
7. Hanefeld M, Herman GA, Wu M, Mickel C, Sanchez M, Stein PP. Once-daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. *Curr Med Res Opin*. 2007;23:1329-1339.
8. Ristic S, Byiers S, Foley J, Holmes D. Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. *Diabetes Obes Metab*. 2005;7:692-698.
9. Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. *Diabetes Obes Metab*. 2008;10:376-386.
10. American Diabetes Association. Standards of medical Care in Diabetes—2021. *Diabetes Care*. 2021;44:S1-S232.
11. Scheen AJ. Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab*. 2010;12:648-658.
12. Tornio A, Niemi M, Neuvonen PJ, Backman JT. Drug interactions with oral antidiabetic agents: pharmacokinetic mechanisms and clinical implications. *Trends Pharmacol Sci*. 2012;33:312-322.
13. Kim D, Wang L, Beconi M, et al. (2R)-4-Oxo-4-[3-(Trifluoromethyl)-5,-6-dihydro[1,2,4]triazolo[4,3-a]pyrazin- 7(8H)-yl]-1-(2,4,5-trifluorophenyl)

butan-2-amine: a potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *J Med Chem*. 2005;48:141-151.
14. He Y-L. Clinical pharmacokinetics and pharmacodynamics of Vildagliptin. *Clin Pharmacokinet*. 2012;51:147-162.
15. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl Peptidase-4 inhibitor Sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care*. 2006;29:2638-2643.
16. Pan C, Xing X, Han P, et al. Efficacy and tolerability of vildagliptin as add-on therapy to metformin in Chinese patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2012;14:737-744.
17. Katzeff HL, Williams-Herman D, Xu L, et al. Long-term efficacy of sitagliptin as either monotherapy or add-on therapy to metformin: improvement in glycemic control over 2 years in patients with type 2 diabetes. *Curr Med Res Opin*. 2015;31:1071-1077.
18. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care*. 2009;32:1649-1655.
19. Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q, for the Alogliptin study 008 group. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. *Int J Clin Pract*. 2009;63:46-55.
20. Pinto LC, Rados DV, Barkan SS, Leitão CB, Gross JL. Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: a meta-analysis with trial sequential analysis. *Sci Rep*. 2018;8:782.
21. Lee CF, Sun MS, Tai YK. Saxagliptin-induced recurrent acute pancreatitis. *Intern Med*. 2014;53:1351-1354.
22. Engel SS, Williams-Herman DE, Golm GT, et al. Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis. *Int J Clin Pract*. 2010;64:984-990.
23. Girgis CM, Champion BL. Vildagliptin-induced acute pancreatitis. *Endocr Pract*. 2011;17:e48-e50.
24. Tkáč I, Raz I. Combined analysis of three large interventional trials with gliptins indicates increased incidence of acute pancreatitis in patients with type 2 diabetes. *Diabetes Care*. 2017;40:284-286.
25. Rehman MB, Tudrej BV, Soustre J, et al. Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: meta-analysis of placebo-controlled randomized clinical trials. *Diabetes Metab*. 2017;43:48-58.
26. Mannucci E, Mosenzon O, Avogaro A. Analyses of results from cardiovascular safety trials with DPP-4 inhibitors: cardiovascular outcomes, predefined safety outcomes, and pooled analysis and meta-analysis. *Diabetes Care*. 2016;39:S196-S204.
27. Gallwitz B. Clinical use of DPP-4 inhibitors. *Front Endocrinol*. 2019;10:389.
28. Liu D, Jin B, Chen W, Yun P. Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM): a systematic review and meta-analysis. *BMC Pharmacol Toxicol*. 2019;20:15.

SUPPORTING INFORMATION

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

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