Efficacy and safety of visepegenatide as an add-on therapy to metformin in patients with type 2 diabetes: a randomised, double-blind, parallel, placebo-controlled, phase 3 study

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Summary

Background Visepegenatide, a once-weekly glucagon-like peptide-1 receptor agonist injection, demonstrated effective glycaemic control and good tolerability without the requirement of dose titration in the two completed phase 2 studies. We aimed to evaluate the efficacy and safety of visepegenatide in Chinese patients with type 2 diabetes mellitus (T2DM) inadequately controlled by metformin monotherapy in this phase 3 clinical study.

Methods This multicentre phase 3 clinical study included a 24-week, randomised, placebo-controlled, double-blind period followed by a 28-week open-label extended treatment period. Patients (N = 620) aged ≥18 and ≤75 years with glycated haemoglobin (HbA_{1c}) ≥7.0% and ≤10.5% [≥53.0 and ≤91.27 mmol/mol], were randomized in a 1:1 ratio to receive visepegenatide 150-μg or placebo once-weekly subcutaneous injection during the double-blind period. Subsequently, the patients in the placebo group were switched to visepegenatide treatment (placebo→visepegenatide group), and the patients in the visepegenatide group continued the same treatment during the open-label extended treatment period. The primary endpoint was the change in HbA_{1c} from baseline to week 24.

Findings At week 24, the placebo-adjusted least squares mean (LSM) change of HbA_{1c} was −0.57% (95% CI −0.71 to −0.43) with visepegenatide ($p < 0.001$). The proportion of patients achieving HbA_{1c} < 7.0% and ≤6.5% [<53 and ≤ 48 mmol/mol] was higher in the visepegenatide group versus the placebo group (115 [40.5%] *vs* 50 [17.9%]; $p < 0.001$, and 60 [21.1%] *vs* 17 [6.1%]; $p < 0.001$). Visepegenatide demonstrated a significant reduction in fasting plasma glucose and 2-h postprandial glucose compared with placebo. Trends in the improvement of these variables were maintained during the open-label extended treatment period. No severe gastrointestinal adverse event or severe hypoglycaemia was reported during the 52-week study period.

Interpretation Once-weekly injection of visepegenatide 150 μg as an add-on treatment to metformin therapy significantly improved glycaemic control and was generally well tolerated in Chinese patients with T2DM who were inadequately controlled with metformin monotherapy.

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Keywords: Add-on therapy; Visepegenatide; Metformin; GLP-1 receptor agonist; Type 2 diabetes mellitus

Research in context

Evidence before this study

Visepegenatide (PB-119) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) administered once weekly by subcutaneous (s.c.) injection without the requirement of dose titration. In patients with T2DM, visepegenatide as monotherapy or in combination with metformin has shown its pharmacokinetic characteristics, good glycaemic control, and preliminary safety profile in phase 1 and phase 2 studies. The present study was designed to confirm the efficacy and safety of visepegenatide in the phase 3 study.

Added value of this study

We explored the effect of adding a once-weekly s.c. injection of visepegenatide, a GLP-1 RA, to a stable dose of metformin, in patients with T2DM poorly controlled with metformin monotherapy. This study showed that visepegenatide treatment produced a higher magnitude of reductions in HbA_{1c} with an early onset of treatment response compared with placebo treatment. Visepegenatide improved β-cell function and sustained the effect with prolonged treatment. Subgroup analyses based on age, gender, disease duration, baseline HbA_{1c} levels, and HOMA-β showed similar trends in glycaemic control consistent with the overall population, which indicated that visepegenatide treatment was effective in maintaining glycaemic control in patients with T2DM with heterogeneity. Safety of visepegenatide treatment was also confirmed. In conclusion, the results of this study confirmed both the efficacy and the safety of visepegenatide treatment in patients with T2DM uncontrolled with metformin monotherapy.

Implications of all the available evidence

From the results/evidence of this study, visepegenatide-metformin combination therapy demonstrated a better glycaemic control and better improvement in the impaired β-cell function than metformin monotherapy alone. Visepegenatide treatment elicited an early response and sustained the response for a longer duration without the risk of hypoglycaemia. The subgroup analysis of treatment response and associated factors could provide clarity for patient preference and physician decisions. Visepegenatide provides benefits in weight loss. Incidences of gastrointestinal adverse events (GI AEs) with visepegenatide were lower than with other GLP-1 RAs. Common GI AEs were mild to moderate, which could be well tolerated and mostly resolved with time. With no requirement for dose titration, a once-weekly s.c. injection of visepegenatide combined with metformin could provide a therapeutic option for patients with T2DM.

Introduction

As recommended by the guideline of the American Diabetes Association (ADA), in combination with diet and exercise, metformin monotherapy is the standard of care and first-line medication for patients with T2DM.[1,2] In patients uncontrolled by metformin monotherapy, combination therapy was recommended to achieve treatment goals. In addition, the use of glucagon-like peptide-1 receptor agonist (GLP-1 RA) was strongly recommended by ADA guidelines, as monotherapy or as combination therapy with metformin, to achieve and maintain both glycaemic control and weight management, especially in patients with atherosclerotic cardiovascular disease, indicators of high cardiovascular risk, and established kidney disease.[3–6]

Visepegenatide (PB-119) is a once-weekly, subcutaneous (s.c.), GLP-1 RA injection without the requirement of dose titration. The pharmacokinetic properties of visepegenatide support the rapid and long-term efficacy.[7–9] Like a GLP-1 RA, visepegenatide induces glucose-dependent insulin secretion and delays gastric emptying, thereby lowering glucose excursion.[10] In two prior phase 2 studies, visepegenatide showed encouraging clinical efficacy and limited toxicity in both treatment-naïve patients with T2DM and in patients on metformin monotherapy from China.[11] In treatment-naïve patients with T2DM, all three doses of visepegenatide (75, 150, and 200 μg) reduced HbA_{1c} from baseline to placebo at week 12. In treatment-naïve patients with T2DM, all three doses of visepegenatide (75, 100, 150, and 200 μg) significantly reduced HbA_{1c} (–0.72%, 95% CI –1.01, –0.43; –1.18%, 95% CI –1.47, –0.89; –1.02%, 95% CI –1.30, –0.73) from baseline to placebo at week 12. No treatment emergent adverse events (TEAE), severe hypoglycaemia and death were reported. Phase II dose-finding studies of visepegenatide in combination with metformin in patients with HbA_{1c} > 58 mmol/mol (>7.5%) observed that visepegenatide 150 μg (subcutaneous injection, once weekly) was optimal with the best benefit-risk ratio, thus it was determined as the dosage for phase III trial. However, the long-term efficacy and safety of the optimal dose of visepegenatide have not been established. Hence, the aim of the present 52-week study was to evaluate the efficacy and safety of visepegenatide 150 μg (subcutaneous injection, once weekly) in combination with metformin in Chinese patients with T2DM who had inadequate glycaemic control with metformin monotherapy.

Methods

Study design and participants

This was a multicentre study conducted at 71 centres across China. To assess adherence with treatment, diet,

exercise, and to determine metabolic control parameters, all patients entered a 4-week, placebo, run-in period before being randomised to the treatment. Patients then entered a 24-week, randomised, placebo-controlled, double-blind period, followed by a 28-week open-label extended treatment period. The study design is presented in Fig. S1.

The study protocol and amendments were approved by ethics committees or institutional review boards at each participating centre, and the study was conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients before enrolment in the study. The protocol was registered at ClinicalTrials.gov Identifier: NCT04504396.

This study included adult patients aged between ≥18 and ≤75 years diagnosed with T2DM as defined by the 1999 World Health Organization criteria. Patients were eligible if they had reached ≥1500 mg/day or the maximum tolerated dose (<1500 mg/day but ≥1000 mg/day) with metformin monotherapy treatment for at least 8 weeks at the time of screening, had a glycated haemoglobin (HbA_{1c}) level of ≥7.0% and ≤10.5% [≥53.0 and ≤ 91.27 mmol/mol] before randomisation, had a fasting plasma glucose (FPG) < 15 mmol/L, and had a body mass index (BMI) ≤40.0 kg/m^2 before screening and randomisation. The key exclusion criteria were patients with type 1 diabetes or pancreatic injury; under treatment of other antidiabetic medications other than metformin, under medication of systemic glucocorticoids, or under medication of drugs that may affect their blood glucose metabolism within 8 weeks before screening; estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2; with the continuous use of insulin for >14 days within 6 months before screening; with acute and severe chronic diabetic complications; or with severe hypoglycaemia within 6 months before randomisation.

Randomisation, blinding, and study intervention

After a screening period of no more than 2 weeks, patients entered a 2-week, single-blind, run-in period receiving once-weekly placebo based on metformin treatment. Subsequently, eligible patients were then randomized (1:1) to receive visepegenatide 150-μg or placebo injection once weekly for 24 weeks during the double-blind period. We used computer-generated block randomisation in the PLAN process of SAS9.4 version to randomize patients. This method generates random blinding codes of patients and drugs, ensuring blinding of study participants, investigators, data analyst, and the study sponsor by maintaining identical shape, colour, weight, packing, and labelling of the study drug and placebo until unblinding due to emergency.

At the end of double-blind period, the patients in the placebo group switched to receive once-weekly 150-μg visepegenatide s.c. injection. This group was represented as placebo→visepegenatide during the 28-week open-labelled extended treatment period. The patients initially assigned to the visepegenatide group continued to receive 150-μg visepegenatide in the open-labelled extended treatment period. Throughout the study, patients received a stable dose of background metformin treatment with diet and exercise modification.

The study included a 4-week safety follow-up after the completion of the treatment or discontinuation from the study.

Rescue medication was initiated after confirming the following criteria at the research centre: FPG of >15.0 mmol/L at weeks 1–6, >13.3 mmol/L at weeks 7–12, and ≥11.1 mmol/L at weeks 13–24 during the 24-week double-blind period and FPG >11.1 mmol/L or HbA_{1c} >8% [63.94 mmol/mol] during the 28-week open-label extended period. The rescue medication was glimepiride tablets (Amaryl®).

Endpoints and assessments

The primary efficacy endpoint was change in HbA_{1c} level from baseline to week 24. The key secondary efficacy endpoints during the 24-week double-blind period and the 52-week open-labelled extended treatment period were (i) the proportion of patients achieving HbA_{1c} <7% and ≤6.5% [<53 and ≤ 48 mmol/mol] weeks 24 and 52; (ii) changes in HbA_{1c} at week 52; (iii) changes in FPG, 2-h postprandial plasma glucose (2hPG), fasting and postprandial insulin, C-peptide, and homeostasis model assessment of beta-cell function (HOMA-β) at weeks 24 and 52; (iv) changes in body weight at weeks 24 and 52; and (v) proportion of patients receiving rescue therapy during the double-blind period and the open-label extended treatment period.

Safety was assessed throughout the study based on incidences and severity of adverse events (AEs), including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and hypoglycaemia in various categories. AEs were identified using the Medical Dictionary for Regulatory Activities, Version 22.0. Other safety endpoints included mean changes in calcitonin levels, biochemical parameters, vital signs, 12-lead electrocardiogram, and physical examination.

Statistical analysis

Statistical analysis was performed using SAS9.4 software. The sample size was determined according to the primary endpoint. Assuming a treatment effect of at least 0.4% compared with the placebo group, a standard deviation (SD) of 1.5%, a two-sided α level of 0.05, and a dropout rate of 10%, it was estimated that 600 randomly assigned patients were needed to ensure a power of at least 85% for testing the superiority of visepegenatide to placebo in change of HbA_{1c} levels from baseline to week 24. The block size was 4, stratified according to the commonly used cutoff for disease severity, namely

baseline HbA_{1c} (<8.5% and ≥8.5%). Due to the extended time intervals used for HbA_{1c} measurements and the uncertain relationship between visits influenced by medication, the unstructured (UN) model does not constrain the correlation between visits. Thus, the covariance structure type = UN was employed for subjects in this study. The 'lsmeans command' was used to estimate treatment effects at specific time points and was referred to as 'treatment effects' in the results.

Primary and secondary efficacy endpoints were analysed using the full analysis set, which included all patients in the intent-to-treat population who were randomly assigned to receive at least one treatment dose during the double-blind period and had at least one post-baseline measurement of the primary endpoint. A mixed model for repeated measures (MMRMs) was used to analyse the primary efficacy endpoint of change in HbA_{1c} from baseline between the groups, and missing data were not imputed. The MMRM included the fixed class effects of treatment group, visit, and treatment-by-visit interaction. The baseline HbA_{1c} value was used as a fixed covariate. For other continuous variables, an MMRM was also used to evaluate the treatment effects between the groups during the double-blind period. For binary efficacy variables (proportion of patients reaching an HbA_{1c} of ≤7% or ≤6.5% [<53 or ≤48 mmol/mol]), a chi-square test was used for treatment comparisons. Paired *t* test or signed rank sum was used to compare the within group/intra-group comparison of quantitative changes relative to baseline. During the open-labelled extended treatment period, analyses of change from baseline were implemented using paired *t* test or signed rank sum, and the difference in effect between the groups was not evaluated.

Two estimands were used to assess the treatment efficacy from different perspectives and accounted for intercurrent events differently. For the primary efficacy estimand, we used the treatment policy strategy as per the ICH E9[12] (Statistical Principles for Clinical Trials [E9], addendum on statistical principles related to estimands and sensitivity analysis), representing the average treatment effect of visepegenatide relative to placebo for all patients who had undergone randomisation, regardless of treatment discontinuation and influence of rescue therapy. The secondary efficacy estimand, using the hypothetical strategy as per the ICH E9[12] to consider intercurrent events, was used to compare the efficacy of visepegenatide with placebo and represents the average treatment effect of visepegenatide for all randomly assigned patients, excluding data after the permanent discontinuation of the study drug or the initiation of the rescue medication, which mostly represented the treatment effect in those patients who were able to continue with treatment.

Safety assessments were analysed by comparing the safety of visepegenatide with placebo, irrespective of adherence to the study drug. These analyses were conducted in the safety set, which included all patients who underwent randomisation, received at least one dose of the assigned visepegenatide or placebo and had at least one record of post-baseline safety assessment. A data safety monitoring committee was not involved in this study.

Ethics statement

All the protocols were approved by the ethics committee of Peking University People's Hospital, Beijing, China (Approval number: 2020PHA016).

Prior presentation

Parts of this study were presented as abstract at the EASD conference 2023.

Role of the funding source

The funder was involved in the design of the study, supervision of the study, site monitoring, and collection and analysis of the data. All authors interpreted the data and wrote the report with the support of the funder's medical writing services. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients disposition and baseline characteristics

This phase 3 study of visepegenatide-metformin combination therapy was conducted between November 30, 2020 and April 27, 2023. A total of 1132 patients were screened, and 766 patients were enrolled. Of these, 620 patients were randomly assigned in a 1:1 ratio to receive visepegenatide (n = 310) or placebo (n = 310), with oral metformin as a background medication. During the 24-week double-blind period, 287 (92.6%) participants in the visepegenatide group and 286 (92.2%) participants in the placebo group completed the treatment and entered the extension phase. Overall, 267 (86.1%) from the visepegenatide group and 272 (87.5%) from the placebo→visepegenatide group completed the 52-week treatment period (Fig. 1). Of these, 262 (84.5%) in the visepegenatide group and 268 (86.2%) in the placebo→visepegenatide group completed the safety follow-up.

At baseline, the demographic and clinical characteristics were well balanced between the visepegenatide and placebo groups (Table 1). The mean (SD) age of the patient population was 53.2 years. The proportion of male gender was 63.2% and 57.4% in the visepegenatide and placebo groups, respectively. Further, 43 (13.9%) and 39 (12.6%) patients had mild renal impairment (eGFR ≤60 or <90 mL/min/1.73 m^2) in the visepegenatide and placebo groups, respectively.

Efficacy

The study met its primary endpoint. When using the treatment policy, regardless of treatment

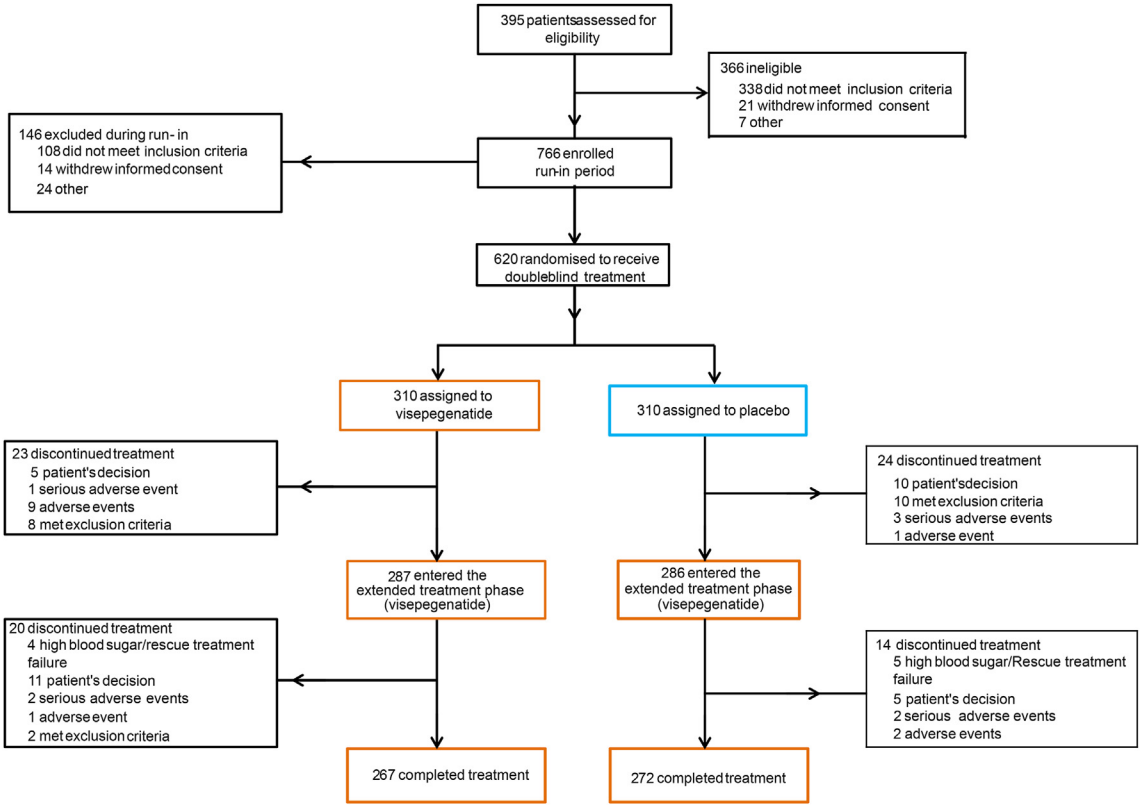

***Fig. 1:* Consort flow chart–trial profile**. Patients received metformin at a stable dose of ≥1500 mg/day or the maximum tolerated dose (<1500 mg/day but ≥1000 mg/day) in both the groups throughout the study period. After the completion of 24-week double-blind period, the patients from placebo group received visepegenatide during extended treatment period.

discontinuation and influence of rescue therapy, at the end of week 24, the mean (SD) HbA_{1c} levels decreased from 8.48% (0.86) to 7.22% (0.88) in the visepegenatide group and from 8.46% (0.79) to 7.73% (0.87) in the placebo group. The least squares mean (LSM) of change in HbA_{1c} from baseline was –1.25% (95% confidence interval (CI), –1.35 to –1.16) in the visepegenatide group and –0.68% (95% CI, –0.78 to –0.59) in the placebo group. Significant difference in HbA_{1c} reduction was found between visepegenatide and placebo (–0.57% (95% CI, –0.71 to –0.43), $p < 0.001$) (Fig. 2a). When assessing primary efficacy as per the hypothetical strategy using data after the exclusion of rescue therapy and treatment discontinuation, visepegenatide treatment resulted in a greater reduction in HbA_{1c} levels at week 24 compared with placebo (–1.27% [95% CI, –1.37 to –1.16] *vs* –0.70% [95% CI, –0.80 to –0.60]). Significant difference in HbA_{1c} reduction was found between these two groups (mean difference [MD] –0.57% (95% CI, –0.71 to –0.42); $p < 0.001$) (Fig. 2b). Changes in HbA_{1c} levels are presented in Fig. 3 and Table 2. Corresponding Mean (95% CI), mmol/mol values for each point are represented in Table 2.

Regarding the early response, visepegenatide had significantly superior HbA_{1c} reduction at week 4 compared to placebo (–0.72% [95% CI, –0.78 to –0.67] *vs* –0.28% [95% CI, –0.34 to –0.23], $p < 0.001$). The treatment response was prolonged during the extended treatment period, with a mean reduction of –1.19% (–1.32 to –1.05) from baseline at week 52 in the visepegenatide group ($p < 0.001$). The placebo→visepegenatide group exhibited a similar treatment response as that of the visepegenatide group (double-blind period), with an HbA_{1c} reduction of –1.29% (–1.40 to –1.18) at week 52. Changes in HbA_{1c} levels are presented in Fig. 3 and Table 2.

Visepegenatide significantly reduced HbA_{1c} levels independent of baseline HOMA-β, age, gender, duration of disease, BMI, body weight, and eGFR levels based on the MMRM model analysis. The changes were significantly higher with visepegenatide compared to placebo from baseline ($p < 0.001$, Fig. S3).

At week 24, a significantly higher proportion of patients achieved the target HbA_{1c} level of <7% [<53 mmol/mol] with visepegenatide treatment compared to placebo (115 [40.5%] *vs* 50 [17.9%]; $p < 0.001$). At week 52, the HbA_{1c} target level of <7% [<53 mmol/mol] was achieved by 99 (37.9%) and 119 (45.2%) patients in the visepegenatide and placebo→visepegenatide groups, respectively.

	Visepegenatide N = 310	Placebo N = 310	Total N = 620
Age, years			
Mean (SD)	52.7 (10.92)	53.7 (10.63)	53.2 (10.78)
Age group, n (%)			
≥18 and <60 years	227 (73.2%)	221 (71.3%)	448 (72.3%)
≥60 and ≤75 years	83 (26.8%)	89 (28.7%)	172 (27.7%)
Gender, n (%)			
Male	196 (63.2%)	178 (57.4%)	374 (60.3%)
Female	114 (36.8%)	132 (42.6%)	246 (39.7%)
Nationality, n (%)			
Han nationality	300 (96.8%)	294 (94.8%)	594 (95.8%)
Other	10 (3.2%)	16 (5.2%)	26 (4.2%)
Weight, (kg)			
Mean (SD)	73.92 (13.39)	72.06 (12.59)	72.99 (13.02)
BMI[a], (kg/m^2)			
Mean (SD)	26.67 (3.70)	26.28 (3.51)	26.47 (3.61)
Duration of diabetes[b] (years)			
Mean (SD)	5.09 (4.65)	5.18 (4.47)	
Diabetes duration group, n (%)			
≤1 year	64 (20.6%)	49 (15.8%)	113 (18.2%)
>1 year and ≤3 years	52 (16.8%)	76 (24.5%)	128 (20.6%)
>3 years and ≤5 years	67 (21.6%)	60 (19.4%)	127 (20.5%)
>5 years	127 (41.0%)	125 (40.3%)	252 (40.6%)
HbA_{1c}, (%)			
Mean (SD)	8.48 (0.86)	8.46 (0.79)	8.47 (0.83)
HbA_{1c} (mmol/mol)	69.23 (9.43)	69.01 (8.64)	69.07 (8.81)
HbA_{1c} group, n (%)			
≤8.5% (≤69.40 mmol/mol)	181 (58.4%)	175 (56.5%)	356 (57.4%)
>8.5% (>69.40 mmol/mol)	129 (41.6%)	135 (43.5%)	264 (42.6%)
FPG, (mmol/L)			
Mean (SD)	9.30 (2.14)	9.28 (2.12)	9.29 (2.13)
eGFR, ($mL/min/1.73m^2$)			
Mean (SD)	104.98 (14.22)	104.99 (13.92)	104.98 (14.06)
≥60–<90 rate, n (%)	43 (13.9%)	39 (12.6%)	82 (13.2%)
≥90 rate, n (%)	267 (86.1%)	271 (87.4%)	538 (86.8%)
Diabetes complications, n (%)			
Have at least one complication	124 (40.0%)	112 (36.1%)	236 (38.1%)
Diabetic retinopathy	65 (21.0%)	56 (18.1%)	121 (19.5%)
Diabetic neuropathy	36 (11.6%)	30 (9.7%)	66 (10.6%)
Diabetic nephropathy	29 (9.4%)	27 (8.7%)	56 (9.0%)
Diabetic Vascular Disease	15 (4.8%)	17 (5.5%)	32 (5.2%)
Diabetic ketosis	7 (2.3%)	19 (6.1%)	26 (4.2%)
Diabetic macroangiopathy	3 (1.0%)	3 (1.0%)	6 (1.0%)
Arteriosclerotic retinopathy	1 (0.3%)	2 (0.6%)	3 (0.5%)
Starvation ketoacidosis	0 (0.0%)	3 (1.0%)	3 (0.5%)
Diabetic ketoacidosis	2 (0.6%)	0 (0.0%)	2 (0.3%)
Peripheral neuropathy	1 (0.3%)	0 (0.0%)	1 (0.2%)
Diabetic eye disease	1 (0.3%)	0 (0.0%)	1 (0.2%)
Ketosis	0 (0.0%)	1 (0.3%)	1 (0.2%)
None	186 (60.0%)	198 (63.9%)	384 (61.9%)

(Table 1 continues on next page)

At week 24, the proportion of patients achieving an $HbA_{1c} \leq 6.5\%$ [≤48 mmol/mol] was significantly higher in the visepegenatide group than placebo (60 [21.1%] *vs* 17 [6.1%]; $p < 0.001$). At week 52, the proportion of patients achieving an $HbA_{1c} \leq 6.5\%$ was 52 (19.9%) and 68 (25.9%) in the visepegenatide group and placebo→visepegenatide groups, respectively (Table 2). In addition, more patients in the visepegenatide group achieved an HbA_{1c} target level (for HbA_{1c} <7%: 47 [15.8%] vs 28 [9.3%]; $p < 0.05$ and for $HbA_{1c} \leq 6.5\%$: 16 [5.4%] vs 0 [0.0%]; $p < 0.001$) at week 4 compared to the placebo group, indicating that visepegenatide could induce early response into treatment.

In the visepegenatide group, mean (SD) FPG was significantly reduced by –1.30 (2.23) mmol/L compared to placebo (–0.68 (2.26) mmol/L); ($p < 0.001$) and remained stable until week 52. Similarly, significant reductions were observed for 2hPG from baseline compared to placebo and remained stable until week 52 ($p < 0.001$) (Table 2). Fasting C-peptide, 2-h postprandial C-peptide, and 2-h postprandial insulin were significantly increased ($p < 0.05$) and fasting insulin considerably decreased ($p > 0.05$) from baseline in the visepegenatide group compared with placebo at week 24 and were maintained till week 52. Similarly, the above-mentioned glycaemic parameters significantly improved in the placebo → visepegenatide group during the extended treatment period (Table 2).

Further, an improvement in HOMA-β was significantly greater in the visepegenatide group at week 24 compared with the placebo group (22.86 [59.83] *vs* 7.19 [37.98]; $p < 0.001$), and the improvement continued till week 52 with a significant increase from baseline (25.72 [93.38]; $p < 0.001$). Similar results were also observed in the placebo → visepegenatide group (14.95 [36.73]; $p < 0.001$; Table 2 and Fig. S2).

Significantly fewer patients in the visepegenatide group than in the placebo group received rescue treatment during the double-blind period (9 [2.9%] *vs* 30 [9.7%]; $p < 0.001$). Further, significant decreases in mean (SD) body weight were observed at week 24 (–0.56 [2.63] kg; $p < 0.05$) and week 52 (–0.62 [2.86] kg; $p < 0.001$) from their baseline value (Table 1). For placebo, during the double-blind treatment, a considerable decrease in mean body weight –0.67 (2.454) kg compared to baseline was observed at week 24. At week 52, the weight reduction in the placebo→visepegenatide was –0.56 (2.575) kg, which was significant compared to the baseline.

Safety

The overall incidences of AEs were similar in both groups during the double-blind period, and most AEs were mild and transient (Table 3). The number of patients with at least one TEAE during the double-blind

period was 221 (71.3%) and 201 (64.8%) in the visepegenatide and placebo groups, respectively and decreasing to 196 (63.2%) in the visepegenatide group during the continuous treatment period. In the placebo→visepegenatide group, 207 (66.8%) patients reported TEAEs during the extended treatment period. Most TEAEs were mild to moderate, and the percentage by the severity of AEs was similar in both groups.

In the visepegenatide and placebo groups, 62 (20.0%) and 41 (13.2%) patients reported gastrointestinal (GI) AEs, respectively, and no severe GI AEs were reported in both groups during the double-blind period. The incidence of GI AEs reduced to 23 (7.4%) in the visepegenatide group during the extended treatment period. The most common GI AEs occurring in the visepegenatide and placebo groups are provided in Table 3. Most GI AEs occurred within the first 4 weeks of treatment and were mostly mild and transient in nature, and resolved after 8 weeks (Table 3).

During the double-blind period, early withdrawal from the treatment due to TEAEs was observed in 6 (1.9%) patients in the visepegenatide group and 1 (0.3%) patient in the placebo group, with GI AEs being the most common reason for withdrawal. Similarly, 2 patients in the placebo→visepegenatide group discontinued treatment due to study drug GI AEs. According to the investigators, the incidences of early withdrawal due to TEAEs were low, with GI disorders being the most common reason for withdrawal (Table 3).

SAEs reported in this study were represented in Table 3. During the extended treatment period, one SAE: acute pancreatitis, was accessed to be treatment-related (both visepegenatide and metformin) in the placebo→visepegenatide group, and this patient recovered after the treatment.

The number of patients with the incidence of hypoglycaemia was 8 (2.6%) in the visepegenatide group and 10 (3.2%) in the placebo group (Table 3). During the double-blind period, no incidences of severe hypoglycaemia and no hypoglycaemia <3.0 mmol/L occurred in the visepegenatide group. During the extended treatment period, 7 (2.3%) patients in the visepegenatide group and 23 (7.4) patients in the placebo→visepegenatide group had hypoglycaemia (Table 3 and Table S2).

No significant differences in vital parameters were observed between the groups. All laboratory parameters related to liver function were within the normal limits during the study.

	Visepegenatide N = 310	Placebo N = 310	Total N = 620
(Continued from previous page)			
Exposure of Metformin during run-in period, g			
Mean (SD)	44.3 (8.28)	44.2 (8.73)	44.3 (8.50)

Values are presented as mean (SD). Note: Baseline is defined as the last non-missing measurement before the first dose during the double-blind treatment period. [a]BMI, Body-mass index is the weight in kilograms divided by the square of the height in meters; HbA_{1c}, Glycated hemoglobin; FPG, fasting plasma glucose; eGFR, Glomerular filtration rate. [b]Duration of diabetes (years) = (date of signing the informed consent form–date of diagnosis of type 2 diabetes)/365.25, rounded to two decimal places.

Table 1: **Baseline demographics and disease characteristics.**

Discussion

In this confirmatory phase 3 study, visepegenatide administered at a dose of 150-μg, once-weekly, s.c. injection without the need for dose titrations significantly improved glycaemic control with a rapid-onset of treatment response, and increased the proportion of patients reaching the HbA_{1c} target in Chinese patients with T2DM uncontrolled with metformin monotherapy. These effects could sustain till 52 weeks during the entire treatment period. Meanwhile, the safety profile of visepegenatide was satisfactory in the study. Visepegenatide achieved significant glycaemic control with a lower risk of hypoglycaemia and GI AEs. Most AEs were mild to moderate and occurred at the initial phase of the treatment and improved over time on continuous treatment.

Early add-on interventions to metformin achieved a better glycaemic control, and antidiabetic agents combined with metformin offered durable glycaemic control, improved tolerance, and potentially delaying or reducing the complications.[13,14] In this study, visepegenatide exhibited effective glycaemic control. An early response was observed, with approximately 73% of patients in the visepegenatide group achieving ≥0.5% [≥5.5 mmol/mol]) reduction from baseline in HbA_{1c} level at week 4. Further, more patients in the visepegenatide group have achieved HbA_{1c} target level (<7%) compared to placebo at week 4. The treatment benefits continued for a longer duration through 52 weeks. In this study, the sample size is not large enough to detect a statistical difference in each subgroup, i.e., the sample size was not powered for each subgroup. However, the tread in the subgroup was consistent with the whole population. Further studies will be conducted to investigate the benefit in different subgroups including the patients with and without CVD or related risk factors.

Previous studies have indicated that early glycemic control reduces the risk of diabetic complications and mortality, while HbA_{1c} levels ≥7.0% (≥53 mmol/mol) and ≥8.0% (≥64 mmol/mol) are higher risk factors for microvascular event and mortality.[15] The ADA recommends an HbA_{1c} target goal of <7.0% for patients with T2DM.[4] In this study, we found a significantly higher proportion of patients achieving HbA_{1c} target levels of <7.0% [<53 mmol/mol] and ≤6.5% [≤48 mmol/mol] with visepegenatide treatment

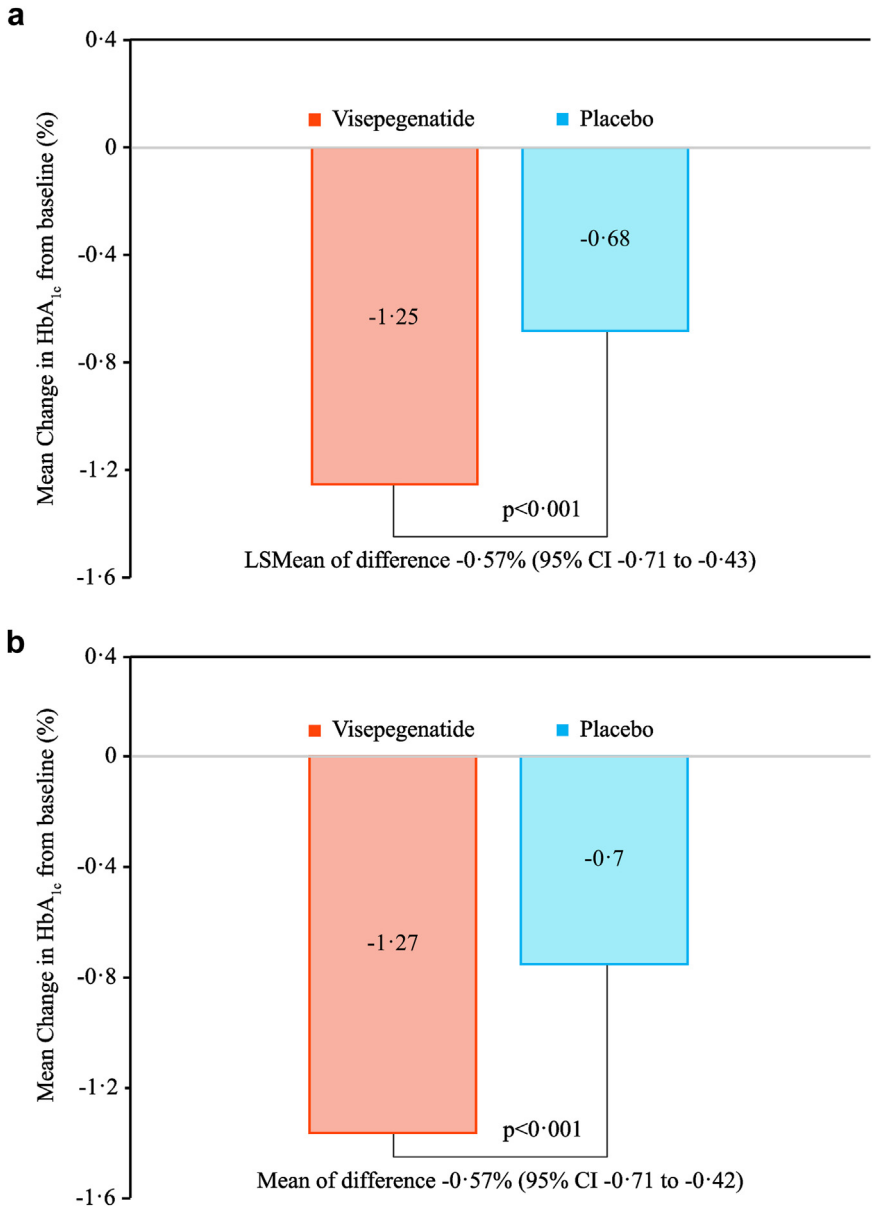

Fig. 2: **Reductions in HbA_{1c} levels at week 24. a) Treatment policy; b) Hypothetic strategy**. HbA_{1c} = glycated haemoglobin; Both visepegenatide and placebo groups received metformin ≥1500 mg/day or the maximum tolerated dose (<1500 mg/day but ≥1000 mg/day) throughout the study. Treatment policy: as per the ICH E914 considered data of patients who had undergone randomisation, regardless of treatment discontinuation and influence of rescue therapy. Hypothetical strategy: considered data of patients taking into account the intercurrent events (excluding data after initiation of rescue therapy and after treatment discontinuation).

compared with placebo. Additionally, in line with guidelines and considering real-world patient characteristics, further sensitivity analysis for the primary endpoint was performed based on baseline HOMA-B, age, gender, duration of disease, BMI, body weight, HbA_{1c} and eGFR. We found that the treatment with visepegenatide led to greater reductions in HbA_{1c} levels compared with placebo in all analyses, indicating that treatment with visepegenatide could benefit patients with different baseline characteristics.

In the present study, a significant decrease in FPG and 2hPG was observed in the visepegenatide group compared with the placebo group at the end of the double-blind period, which also confirmed the hypoglycaemic effect of visepegenatide in our study. Blood glucose fluctuations and uncontrolled hyperglycaemia led to various macrovascular and microvascular

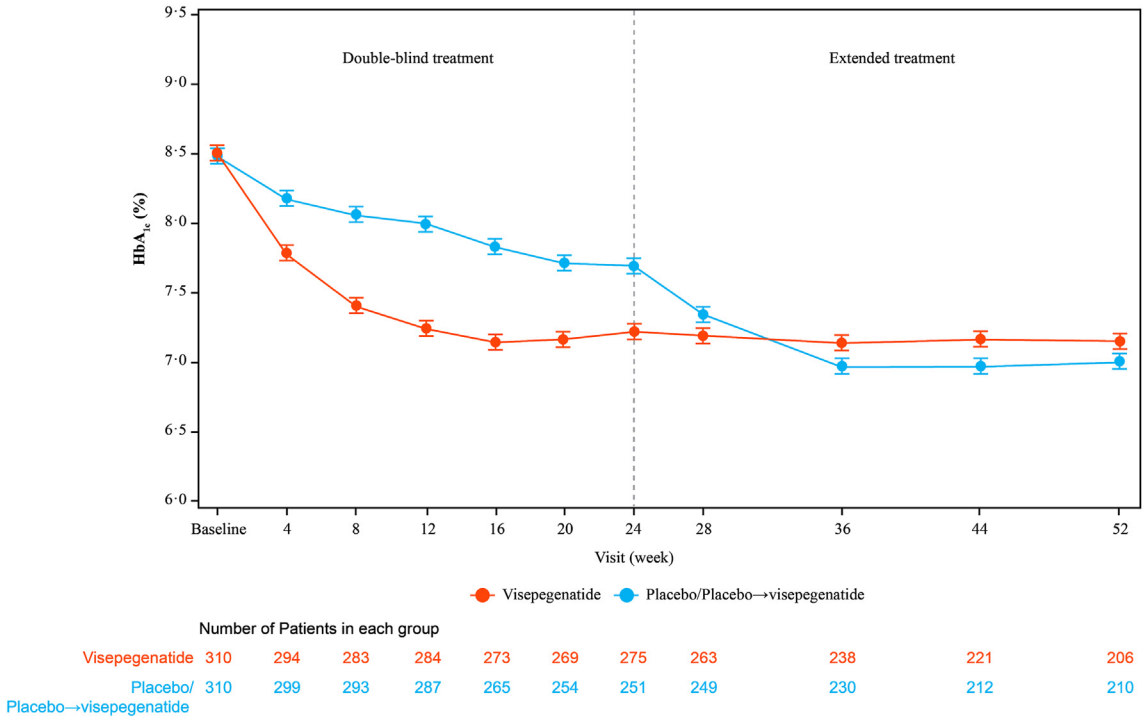

***Fig. 3*: Changes in HbA_{1c} at different timepoints throughout the study period**. HbA_{1c} = glycated haemoglobin. Both visepegenatide and placebo groups received metformin ≥1500 mg/day or the maximum tolerated dose (<1500 mg/day but ≥1000 mg/day) throughout the study.

complications,[15] and combination treatments help in achieving glycaemic goals and balancing with risks such as reduced or without the risk of hypoglycaemia.[14] In this study, visepegenatide exhibited effective glycaemic control. An early response was observed, with approximately 73% of patients in the visepegenatide group achieving ≥0.5% [≥5.5 mmol/mol]) reduction from baseline in HbA_{1c} level at week 4. Further, more patients in the visepegenatide group have achieved HbA_{1c} target levels compared to placebo at week 4. The treatment benefits continued for a longer duration through 52 weeks.

HOMA-β assessment monitors the long-term effectiveness of various treatments in patients with T2DM. A significant improvement in HOMA-β up to week 52 in the present study indicated improved insulin sensitivity and β-cell function in patients with T2DM.[16] We observed beneficial improvements in glucose monitoring parameters such as 2-h postprandial C-peptide and 2-h postprandial insulin, both from baseline and compared with the placebo group. These glucose-dependent changes in postprandial insulin and C-peptide were consistent with the mechanism of long-acting GLP-1 RAs, being glucose-lowering primarily through glucagonostatic and insulinotropic properties.[17] Further comparing with the placebo group ($p < 0.001$), fewer patients in the visepegenatide group received rescue therapy, indicating the visepegenatide's treatment effectiveness.

Weight management is recommended for patients with T2DM as per the ADA and the European Association for the Study of Diabetes guidelines. The American Association of Clinical Endocrinology recommends BMI-based care for persons with obesity and adiposity-based chronic disease complications.[5] We observed a significant but slight reductions in body weight with visepegenatide treatment at each interval from the baseline, which prolonged during the open-label extended treatment period with significantly greater reductions till week 52. The weight loss associated with visepegenatide treatment could benefit the patients.

In this study, visepegenatide treatment was well tolerated as monitored during the double-blind period and the open-label extended treatment period. TEAEs were similar in both groups, and most of the events were mild and transient in nature. Visepegenatide was well tolerated long-term, with initially observed AEs being reduced or resolved on continuous treatment during the 52-week extended treatment period. In general, GLP-1 RAs with metformin as background therapy have exhibited higher rates of nausea, vomiting,

	Visepegenatide 150 µg N = 310	Placebo/Placebo→ Visepegenatide N = 310
HbA_{1c} %		
Baseline, Mean (SD), %	8.48 (0.86)	8.46 (0.79)
Baseline, Mean (SD), mmol/mol	69.23 (9.43)	69.01 (8.64)
Change from baseline at 4-week, Mean (95% CI), %[b]	−0.72 (−0.78 to −0.67)***	−0.28 (−0.34 to −0.23)***
Change from baseline at 4-week, Mean (95% CI), mmol/mol[b]	−7.90 (−8.49 to −7.31)	−3.11 (−3.70 to −2.53)
Compared with placebo, %	−0.44 (−0.51 to −0.36) p < 0.001	
Compared with placebo, mmol/mol	−4.79 (−5.62 to −3.96) p < 0.001	
Change from baseline at 24-week, LSMean (95% CI), %[a]	−1.25 (−1.35 to −1.16)	−0.68 (−0.78 to −0.59)
Change from baseline at 24-week LSMean (95% CI), mmol/mol[a]	−13.71 (−14.76 to −12.66)	−7.49 (−8.53 to −6.44)
Compared with placebo, %	−0.57 (−0.71 to −0.43); p < 0.001	
Compared with placebo, mmol/mol	−6.23 (−7.71 to −4.74) p < 0.001	
Change from baseline at 24-week, Mean (95% CI)[b]	−1.27 (−1.37 to −1.16)***	−0.70 (−0.80 to −0.60)***
Change from baseline at 24-week, Mean (95% CI), mmol/mol[b]	−13.83 (−14.99 to −12.67)	−7.62 (−8.71 to −6.52)
Compared with placebo, %	−0.57 (−0.71 to −0.42), p < 0.001	
Compared with placebo, mmol/mol	−6.21 (−7.80 to −4.62), p < 0.001	
Change from baseline at 52-week, Mean (95% CI), %[b]	−1.19 (−1.32 to −1.05) ***	−1.29 (−1.40 to −1.18) ***
Change from baseline at 52-week, mmol/mol	−12.98 (−14.46 to −11.51)	−14.12 (−15.32 to −12.92)
Proportion of patients achieving HbA_{1c} target (%)		
HbA_{1c} < 7.0% (<53 mmol/mol) at 24-week	115 (40.5%)	50 (17.9%)
Compared with placebo	p < 0.001	
HbA_{1c} < 7.0% (<53 mmol/mol) at 52-week	99 (37.9%)	119 (45.2%)
HbA_{1c} ≤ 6.5% (≤48 mmol/mol) at 24-week	60 (21.1%)	17 (6.1%)
Compared with placebo	p < 0.001	
HbA_{1c} ≤ 6.5% (≤48 mmol/mol) at 52-week	52 (19.9%)	68 (25.9%)
Fasting plasma glucose (mmol/L)		
Baseline	9.30 (2.14)	9.29 (2.12)
Change from baseline at 24-week	−1.30 (2.23)***	−0.68 (2.26)***
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	−1.21 (2.21)***	−1.19 (2.16)***
2-h postprandial plasma glucose (mmol/L)		
Baseline	15.30 (3.30)	15.15 (3.24)
Change from baseline at 24-week	−1.74 (−3.28)***	−0.62 (3.18)**
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	−1.61 (3.28)***	−1.59 (3.42)***
Fasting insulin (pmol/L)		
Baseline	84.35 (62.64)	79.70 (61.22)
Change from baseline at 24-week	12.78 (60.79)***	3.65 (66.74)
Compared with placebo	p = 0.092	
Change from baseline at 52 weeks	16.81 (88.35)**	4.79 (58.25)
2-h postprandial insulin (pmol/L)		
Baseline	268.81 (167.14)	249.47 (151.99)
Change from baseline at 24-week	52.00 (142.60)***	30.83 (128.95)***
Compared with placebo	p = 0.036	
Change from baseline at 52 weeks	69.23 (181.31)***	75.48 (141.46)***
Fasting C peptide (nmol/L)		
Baseline	0.89 (0.35)	0.86 (0.36)
Change from baseline at 24-week	0.08 (0.30)	0.02 (0.32)***
Compared with placebo	p = 0.016	
Change from baseline at 52 weeks	0.077 (0.32)***	0.05 (0.33)*

(Table 2 continues on next page)

	Visepegenatide 150 μg N = 310	Placebo/Placebo→ Visepegenatide N = 310
(Continued from previous page)		
2-h postprandial C peptide (nmol/L)		
Baseline	2.00 (0.77)	1.91 (0.71)
Change from baseline at 24-week	0.34 (0.58)***	0.14 (0.51)***
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	0.36 (0.67) ***	0.38 (0.62) ***
HOMA-β		
Baseline	47.04 (41.69)	44.48 (39.29)
Change from baseline at 24-week	22.86 (59.83)***	7.19 (37.98)**
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	25.72 (93.38)***	14.95 (36.73)***
Proportion of participants undergoing rescue therapy		
At 24-week	9 (2.9%)	30 (9.7%)
Compared with placebo	p < 0.001	

Values are presented as mean (SD) unless stated otherwise. *p < 0.05. **p < 0.01, ***p < 0.001 compared to baseline. [a]Results of using treatment policy strategy, regardless of treatment discontinuation and influence of rescue therapy. [b]Results of using the hypothetical strategy, excluding data after permanent discontinuation of study drug or initiation of rescue medication.

Table 2: **Efficacy endpoints of visepegenatide treatment.**

diarrhoea, and occurrence of severe hypoglycaemic episodes.[18–20] Meanwhile, treatment/study withdrawal was only in 1.6% of patients related to the study drug GI AEs.

In our present study, a 2.6% incidence of hypoglycaemia in the visepegenatide group compared with 3.2% in the placebo group during the double-blind period indicated no additional hypoglycaemia risk with visepegenatide add-on therapy. Amongst all hypoglycaemia events during the double-blind period, no severe hypoglycaemia or hypoglycaemia of grade 2 (plasma glucose <3.0 mmol/L) was observed in the visepegenatide group, and no patients discontinued the treatment or withdrew from the study due to hypoglycaemic events. However, the incidence of hypoglycaemia was 7.4% in the placebo→visepegenatide group, which may be related to the corresponding use of rescue medication (Table S2). Liver enzymes were not changed after treatment compared to the baseline, and no adverse event of liver enzymes elevation was reported.

One SAE in the placebo→visepegenatide group, acute pancreatitis, was judged by the investigator to be related to the study drug. However, visepegenatide is not considered to increase the risk of pancreatitis, and may not be concluded based on this case. Evidence from meta-analyses and cardiovascular outcomes studies indicate that GLP-1RA treatment do not increase the risk of acute pancreatitis compared with placebo.[21–29]

This is the first confirmatory study evaluating the efficacy and safety of visepegenatide as an add on to background metformin therapy in a randomized, double-blind trial. As the study extended to 52-week treatment, the long-term effectiveness of visepegenatide in this cohort was also confirmed.

The present study has some limitations. First, T2DM is a chronic and progressive disease, and a long-term study beyond 52 weeks may be needed to further evaluate the efficacy, durability, and safety of visepegenatide combined with metformin. Second, the relatively smaller sample size of our study limits the extrapolation of results to a larger population. Further, the mixed model was not applied to secondary outcomes and hence may not be very robust to missing data. In addition, the second estimand may be biased if it is confounded by a post-randomization variable affected by treatment. The efficacy and safety of visepegenatide across ethnicity and larger populations are warranted to confirm the findings of the present study. In summary, 150-μg visepegenatide, once-weekly, s.c. injection achieved significant reductions in HbA_{1c} and attained an early treatment response in Chinese patients with T2DM inadequately controlled with metformin monotherapy without the requirement of dose titration. Prolonged effects were observed during the open-labelled extended period. Visepegenatide also improved the HOMA-β and induced body weight loss. Visepegenatide had a good safety profile. Comparatively, incidences of GI AEs and hypoglycaemia were lower than other GLP-1 RAs. Overall, a satisfactory benefit-risk ratio was observed with visepegenatide in this study, representing a potential treatment option for patients with T2DM.

Events	Double-blind treatment period				Extended treatment period			
	Visepegenatide N = 310		Placebo N = 310		Visepegenatide N = 310		Placebo/Placebo→ Visepegenatide N = 310	
	Number of patients (%)	Episodes	Number of patients (%)	Episodes	Number of patients (%)	Episodes	Number of patients (%)	Episodes
All adverse events (AE)	248 (80.0)	855	226 (72.9)	626	214 (69.0)	681	219 (70.6)	680
Treatment Emergent Adverse Events (TEAE)	221 (71.3)	691	201 (64.8)	475	196 (63.2)	607	207 (66.8)	598
Mild TEAE	147 (47.4)	574	137 (44.2)	380	127 (41.0)	454	147 (47.4)	473
Moderate TEAE	67 (21.6)	109	61 (19.7)	91	59 (19.0)	138	55 (17.7)	118
Severe TEAE	7 (2.3)	8	3 (1.0)	4	10 (3.2)	15	5 (1.6)	7
Gastrointestinal (GI) diseases	62 (20.0)	188	41 (13.2)	55	23 (7.4)	108	31 (10.0)	77
Mild	43 (13.9)	157	26 (8.4)	39	13 (4.2)	52	20 (6.5)	41
Moderate	19 (6.1)	31	15 (4.8)	16	9 (2.9)	55	11 (3.5)	36
Severe	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1	0 (0.0)	0
GI AEs by preferred term (in >2% of patients)								
Diarrhea	23 (7.4)	52	15 (4.8)	19	10 (3.2)	22	10 (3.2)	21
Vomiting	15 (4.8)	30	1 (0.3)	1	3 (1.0)	6	2 (0.6)	3
Nausea	13 (4.2)	31	1 (0.3)	1	3 (1.0)	3	7 (2.3)	17
Abdominal discomfort	10 (3.2)	28	0 (0.0)	0	1 (0.3)	12	0 (0.0)	0
Abdominal distension	5 (1.6)	15	5 (1.6)	6	1 (0.3)	1	1 (0.3)	1
TRAE leading to early withdrawal	6 (1.9)	11	1 (0.3)	1	0 (0.0)	0	2 (0.6)	4
GI AE related to investigational drug leading to early withdrawal	5 (1.6)	7	0 (0.0)	0	0 (0.0)	0	2 (0.6)	3
Nausea	3 (1.0)	3	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Abdominal discomfort	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Diarrhea	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Bloating	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Vomiting	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Acute pancreatitis	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)	2
Hypoglycemia[a]	8 (2.6)	9	10 (3.2)	20	7 (2.3)	11	23 (7.4)	52
Asymptomatic hypoglycemia	4 (1.3)	5	4 (1.3)	8	2 (0.6)	2	13 (4.2)	26
Definite symptomatic hypoglycemia	2 (0.6)	2	4 (1.3)	8	4 (1.3)	5	8 (2.6)	10
Relatively low plasma glucose	1 (0.3)	1	3 (1.0)	4	3 (1.0)	4	6 (1.9)	14
Suspected symptomatic Hypoglycemia	1 (0.3)	1	0 (0.0)	0	0 (0.0)	0	2 (0.6)	2
Severe hypoglycemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Serious adverse events (SAEs)	9 (2.9)	10	12 (3.9)	14	18 (5.8)	22	9 (2.9)	9
SAEs related to study drug	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.3)[b]	1
Death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

TRAE, treatment-related adverse event. Asymptomatic hypoglycemia: the blood glucose level was ≤3.9 mmol/L when tested with a glucometer provided by the sponsor or by the local laboratory/central laboratory, but without symptoms of hypoglycemia. Relatively hypoglycemia, reported symptoms were consistent with hypoglycemia, but the blood glucose level >3.9 mmol/L was tested by the glucometer provided by the sponsor or by the local laboratory/central laboratory. Definite symptomatic hypoglycemia: having typical symptoms of hypoglycemia, meanwhile with blood glucose level ≤3.9 mmol/L which was tested by the glucometer provided by the sponsor or by the local laboratory/central laboratory. Suspected symptomatic hypoglycaemia: having the typical symptoms of hypoglycemia but the blood glucose level was not tested, and it was speculated that symptoms may be caused by a blood glucose level of ≤3.9 mmol/L. Severe hypoglycaemia: hypoglycemia with severe cognitive impairment, requiring medical treatment to recover. [a]The definition of hypoglycemia in this study. [b]Acute pancreatitis reported as severe unexpected serious adverse reaction.

Table 3: **Treatment-emergent adverse events in the safety analysis set.**

Contributors

LJ, XC, KD, and MX contributed to the study design. LJ, XC, MY, JM, FB, SL, WP, SY, HZ, MH, and WL conducted and provided medical oversight during the trial. YJ, KD, and LL were responsible for the statistical analyses. XC, LJ, KD, YJ, LL directly accessed and verified the data presented in the paper. All authors are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all the data in the study and interpreted the data. The principal investigator and corresponding author, LJ had final responsibility for the decision to submit for publication. All the authors participated in the writing and critical review of the manuscript with the support of medical writing services provided by the funder. All authors approved this manuscript to be submitted for publication.

Data sharing statement

The data related to this study are presented in the manuscript and supplement files. Further deidentified data can be obtained from the corresponding author on reasonable request.

Declaration of interests

LL, KD, YJ, and MX are employees of PegBio Co., Ltd.

All other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101197.

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