Efficacy and safety of visepegenatide, a long-acting weekly GLP-1 receptor agonist as monotherapy in type 2 diabetes mellitus: a randomised, double-blind, parallel, placebo-controlled phase 3 trial

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Summary

Background Type 2 diabetes (T2DM) remains a challenge to treat despite the expansion of various therapeutic classes. Visepegenatide (PB-119) is a once a week, subcutaneous, glucagon-like peptide-1 receptor agonist (GLP-1 RA) injection without the requirement of dose titration that has shown glycaemic control and safety profile in two phase 2 studies conducted in China and the United States, respectively. The aim of this study was to evaluate the efficacy and safety of visepegenatide as a monotherapy in treatment-naïve patients with T2DM.

Methods This was a multicentre, double-blind, parallel, placebo-controlled, phase 3 trial conducted in 30 centres in China. Adult participants (aged 18–75 years) with T2DM, glycated haemoglobin (HbA1c) of 7.5%–11.0% [58.47–96.73 mmol/mol], body mass index (BMI) of 18–40 kg/m^2, and who had been treated with diet and exercise alone for at least 8 weeks before the screening visit were eligible for enrolment. After a 4-week placebo injection run-in period, participants with HbA1c of 7.0%–10.5% [53.0–91.3 mmol/mol] and fasting plasma glucose (FPG) < 15 mmol/L were randomised in a ratio of 1:1 to receive visepegenatide (150 μg) or placebo subcutaneous injections once a week for 24 weeks. The treatment was extended to another 28 weeks during which all participants received visepegenatide. The primary outcome was a change in HbA1c from baseline to week 24. This study was registered with ClinicalTrials.gov, as NCT04504370.

Findings Between November 2, 2020, and November 2, 2022, we randomly assigned 273 adult participants to the visepegenatide (n = 137) and placebo (n = 136) groups. In total, 257 (94.12%) participants, 131 (95.6%) on visepegenatide, and 126 (92.6%) on placebo, completed the double-blinded treatment period. At baseline, the mean (SD) HbA1c was 8.47% (0.81) [69.07 [8.81] mmol/mol], which rapidly decreased to 7.63% (0.80) [59.94 [8.70] mmol/mol] with visepegenatide by week 4 of treatment, and the change from baseline was significantly greater than that in the placebo group (–0.82% [–0.90 to –0.74]; [–8.99 [–9.89 to –8.10] mmol/mol] *vs* –0.30% [–0.41 to –0.19]; [–3.30 [–4.50 to –2.09] mmol/mol]). At week 24, when evaluating the effects of treatment with treatment policy estimand, the least square mean (LSM change in HbA1c from baseline was –1.36 (95% confidence interval [CI] –1.52 to –1.20) [–14.84 [–16.60 to –13.08] mmol/mol] in the visepegenatide group *vs* –0.63 (–0.79 to –0.46) [–6.84 [–8.61 to –5.07] mmol/mol] in the placebo group. The reduction in HbA1c was significantly greater with

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visepegenatide than placebo (LSM difference –0.73, 95% CI –0.96 to –0.50; p < 0.001). When evaluating the treatment estimand with hypothetic policy, the LSM change in HbA1c from baseline in the visepegenatide group (–1.37 [–1.53 to –1.20]) [–14.95 [–16.76 to –13.14] mmol/mol] was significantly greater than the placebo group (–0.63 [–0.81 to –0.45]) [6.90 (–8.89 to –4.90) mmol/mol]. The LSM difference was (–0.74, 95% CI –0.98 to –0.49; [–8.00 [–10.50 to –5.50] mmol/mol]; p < 0.001]. A significantly greater proportion of the visepegenatide group achieved a target HbA1c level of <7% (<53 mmol/mol) than the placebo (50.4% *vs* 14.2%; p < 0.05) and stringent HbA1c level of ≤6.5% (≤48 mmol/mol) (26.7% *vs* 7.9%), respectively. There was also a significantly greater improvement in FPG, 2-h postprandial glucose, homeostasis model assessment (HOMA) of beta cell function, post-prandial insulin, fasting, and post-prandial C-peptide level (p < 0.05) with visepegenatide treatment. The number (3 [2.2%]) of participants who received rescue therapy in the visepegenatide group was remarkably lower compared with those (17 [12.5%]) in the placebo group (p < 0.05). During the extended treatment period, visepegenatide consistently maintained the efficacy till week 52 confirmed by all the above endpoints. The reduction in HbA1c at week 52 was –1.39% (–1.58 to –1.19) [–15.14 [–17.28 to –13.01] mmol/mol], which was even greater than that at week 24. There was also a significant improvement in HOMA-insulin resistance (p = 0.004) at week 52 compared with the baseline value. For the placebo→visepegenatide group, which received visepegenatide in the extended treatment period, a notable decrease in HbA1c at week 52 compared to baseline was observed. The change from baseline in HbA1c was –1.49% (–1.68 to –1.30) [–16.27 [–18.37 to –14.16] mmol/mol]. The outcome was in the same direction as the visepegenatide group from the double-blind treatment period. Comprehensive benefits of visepegenatide including weight loss, improvement in lipid profile, and reduction in blood pressure have been demonstrated in this study. Visepegenatide reduced the body weight in a BMI-dependent manner that was prominent in BMI >32 kg/m^2 with a mean (SD) reduction of –4.77 (13.94) kg at week 52 (p < 0.05). Incidences of gastrointestinal adverse events were less common than other weekly GLP-1 RA in the market, and most of the adverse events were mild and moderate in nature, occurring in the first weeks of the treatment, and were transient. No serious hypoglycaemia or grade 2 hypoglycaemia (blood glucose: ≤3 mmol/L) was reported during the study.

Interpretation As a monotherapy, visepegenatide provided rapid without the risk of hypoglycaemia, significant, and sustainable glycaemic control by improving islet β-cell function and insulin resistance. Treatment with visepegenatide induced early treatment response in reducing HbA1c and maintaining glycaemic control for 52 weeks. Meanwhile, visepegenatide provided a comprehensive benefit in body weight loss, lipids, and blood pressure reduction. Visepegenatide had a better safety profile than other weekly GLP-1 RA in participants with T2DM even without the requirement of dose titration. Visepegenatide would provide an optimal treatment approach with its high benefit and low-risk balance.

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Keywords: Visepegenatide; HbA1c; Glycaemic control; Diabetes; BMI; GLP-1 RA

Introduction

Glycaemic control and maintenance are crucial targets in managing type 2 diabetes mellitus (T2DM) and remain a challenge despite advances in novel pharmacotherapies.[1–3] Even more, alarming is the current estimate that by 2050, approximately 1.31 (1.22–1.39) billion people worldwide could be living with diabetes, and according to another estimate, the incidence of diabetes is projected to rise to 783 million by the year 2045.[4,5] T2DM is characterised by insulin resistance and β-cell function deficiency managed by non–insulin-based antidiabetic and lifestyle changes that may eventually lead to insulin dependency.[6] Novel therapies with different mechanisms of action to lower the glucose in T2DM are approved in up to 12 classes of drugs.[7] Among these, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated a promising cardioprotective effect/cardiovascular outcome by reducing microvascular and major adverse cardiovascular events (MACE-3).[7]

Exenatide was the first approved drug in the GLP-1 RA class by the United States Food and Drug Administration (US FDA) and European Medicines Agency.[8] These short-acting GLP-1 RAs are administered daily as injections, and patients are responsible for proper dosing or require titration.[8] In addition, the risk of hypoglycaemia especially with combination therapy, the convenience of dose administration, compliance, the comparatively shorter half-life in pharmacokinetics, and faster to reach maximum plasma concentration

Research in context

Evidence before this study

We searched PubMed for research articles published in English up to October 15, 2023, using the terms "glucagon-like peptide-1 receptor agonist", "GLP-1", and "type 2 diabetes". Reference lists of relevant studies were also searched. The search indicated that, although there was substantial research on GLP-1 receptor agonists, there was less evidence on the rapid or early glycaemic efficacy and the efficacy sustainability of GLP-1 RA. Furthermore, high incidences of gastrointestinal adverse events were associated with GLP-1 RA. Earlier, phase 1 studies support visepegenatide as the long-acting GLP-1 RA, having antidiabetic activity. In the phase 1 and two phase 2 studies conducted in China and the United States, visepegenatide brought clinically meaningful results in efficacy and safety results, both as monotherapy and as an add-on to metformin treatment, without the need for dose titration.

Added value of this study

In this phase 3 study, we report the efficacy and safety of once-a-week visepegenatide injection in treatment naïve patients with T2DM. Dose adjustments are not required in this long-acting easy-to-use subcutaneous injection of visepegenatide. Treatment with visepegenatide resulted in significant and clinically meaningful improvements in glycaemic control. Especially noteworthy is the early onset of treatment response and sustaining the response to treatment in the 52-week study duration. To our knowledge, this is the first report showing rapid response without the risk of hypoglycaemia and with a significant reduction in HbA1c at week 4 of treatment, and sustaining the efficacy till 52 weeks after treatment. Visepegenatide greatly improved β-cell function and sustained the effect with prolonged treatment. Insulin resistance was also significantly reduced. Robust body weight reductions were also observed in a BMI-dependent manner. Visepegenatide improved the lipid profile and reduced blood pressure, indicating overall improved cardiometabolic outcomes. The safety profile was consistent with other GLP-1 RAs. However, the incidence of gastrointestinal adverse events was remarkably lower than those reported in other studies of GLP-1 RAs.

Implications of all the available evidence

To reduce the progression of diabetic complications such as cardiovascular and renal events, it is crucial to attain, early treatment response in reducing HbA1c levels and maintaining HbA1c in the guideline's set target range. Visepegenatide induced rapid response without the risk of hypoglycaemia, sustained the efficacy for the long-term, improved body weight loss and blood pressure, and has a better safety profile.
Visepegenatide as an easy-to-use, self-administered injection, without the burden of dose adjustment, is an optimal treatment option for long-term treatment in people with T2DM.

necessitate an alternative, convenient therapy. Long-acting GLP-1 RAs, such as semaglutide, dulaglutide, exenatide microspheres, usually require dose titration and exhibit relatively higher incidences of gastrointestinal side effects.[8]

Visepegenatide (PB-119), a safer, effective, and convenient to use, long-acting GLP-1 RA, was developed to fill the therapeutic gap. Conjugation of polyethylene glycol (PEG) to peptides increases the molecular size of the peptide, decreases renal filtration/slows excretion, and prevents or reduces proteolysis of the peptides.[9] The pharmacokinetics of visepegenatide showed slow absorption with a mean peak time of 20–40 h and a mean elimination half-life of 60–70 h with better safety and tolerable profile.[10] From the phase 2 clinical study, visepegenatide at a dose of 150 μg without titration, was recommended for the phase 3 study. Even though all three doses exhibited efficacy, optimal efficacy, and safety were observed at 150 μg with a significant reduction in HbA1c, fasting plasma glucose, and 2 h postprandial glucose, and a low incidence of adverse events, especially gastrointestinal events.[11]

The objective of the present study was to evaluate the efficacy and safety of once-a-week subcutaneous injection of visepegenatide as a monotherapy in treatment-naive patients with T2DM.

Methods

Study design and participant

This multicentre, double-blinded, randomised, phase 3 study was conducted in 30 sites across China. A detailed study design is given in Fig. 1a. The eligible participants were Chinese adults, aged ≥18 and ≤ 75 years, diagnosed with type 2 diabetes as per the diagnostic criteria of World Health Organization (1999), had only been managed with diet and exercise interventions without any antidiabetic medication, with a glycosylated haemoglobin (HbA1c) range of ≥7.5% and ≤11.0% (58.47–96.73 mmol/mol), before screening as well as with a range of ≥7.0% and ≤10.5% (53.0–91.3 mmol/mol) before randomisation, fasting plasma glucose (FPG) of <15 mmol/L before both screening and randomisation, and body mass index (BMI) of ≥18.5 and ≤40.0 kg/m^2 (change not higher than 5%, 3 months before randomisation). The main exclusion criteria were; the participants with type 1 diabetes, pancreatic injury, concomitant use of other antidiabetic medications or drugs that may affect blood glucose metabolism 3 months before randomisation, acute and severe chronic diabetic complications, history of two or more episodes of severe hypoglycaemia within 6 months before the start of the study, an estimated glomerular filtration rate (eGFR) of <60 mL/min

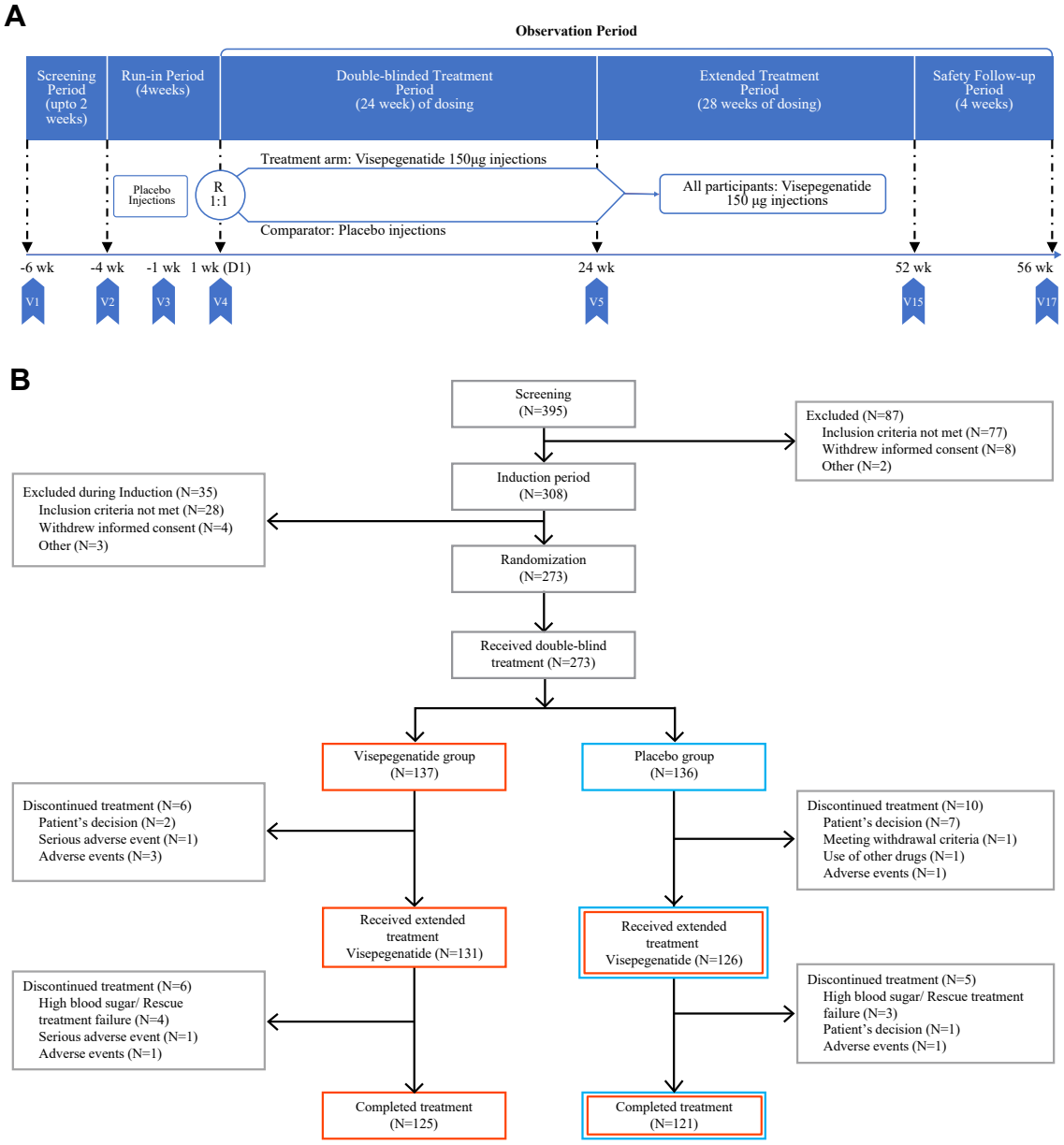

***Fig. 1:* a, Study design**. V1 to V17. visit 1 to 17; wk. week; R. Randomization; D1. Day 1; rescue therapy. Metformin. **b, Consort flow-chart: patient flow**.

per 1.73 m^2. The detailed inclusion and exclusion criteria are presented in the study protocol (Appendix 1).

The study was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines[12] and the principles of the Declaration of Helsinki.[13] The study protocol was approved by the Institutional Review Board/ethical committee of the respective study centres. The study protocol is available in the appendix. All participants provided written informed consent before the enrolment in the study. The study was registered at clinical.gov, number NCT04504370.[14]

Randomisation and masking

Participants who were eligible after the run-in period were randomised by parallel assignment in a 1:1 ratio to either the visepegenatide (150 µg) or placebo group, using a computer-generated random sequence with an Interactive Web Response System. Participants were stratified based on the baseline HbA1c (≤8.5%

[≤69.40 mmol/mol] or >8.5% [>69.40 mmol/mol]). Except for the coding number, both visepegenatide and placebo were identical in appearance and packaging. Adequate measures were taken to blind investigators, participants, site staff, data analysts, and sponsor until unblinding due to emergency (detailed in the protocol).

Procedure

This study had a 2-week screening period, 4-week run-in period, 24-week double-blinded treatment period, followed by a 28-week extended treatment period and a 4-week safety follow-up period. In the run-in period, participants were instructed to maintain a healthy life style and were administered with a placebo matched to visepegenatide injection. Then, eligible participants were randomly assigned in a 1:1 ratio to either the visepegenatide group (150 μg) or placebo group to receive once a week subcutaneous (s.c.) injection for 24 weeks. In the extended treatment period, the participants initially assigned to the placebo group were crossed over to receive visepegenatide. This group is referred as placebo→visepegenatide group. The participants initially assigned to the treatment group continued to receive visepegenatide s.c. injection. In the safety follow-up period, antidiabetic medications were allowed at the discretion of the investigators. Participants were accessed at regular, pre-defined intervals for clinical and laboratory assessments. Throughout the study, the participants were advised on diet and exercise plans. Training was provided to ensure adherence and the participants were instructed to self-monitor the blood glucose, administer subcutaneous injections, and record the suspected symptoms of hypoglycaemia or any adverse events (AEs). Use of antihypertensive or antidiabetic drugs before the start of the study and drugs to treat AE during the study was allowed, whereas other concomitant drugs having hypoglycaemic effect were prohibited. Participants who discontinued the treatment could remain in the trial until the study end.

To safeguard the safety of the participants, rescue medication (metformin) was added to the treatment by the investigators if the FPG level (confirmed by another FPG) was beyond the following threshold according to the FDA[15]: FPG >15.0 mmol/L during weeks 1–6, FPG >13.3 mmol/L during weeks 7–12, FPG >11.1 mmol/L during weeks 13–24 in the double-blinded treatment period. Recuse therapy was permitted if FPG >11.1 mmol/L or HbA1c >8% (63.94 mmol/mol) during the extended treatment period. Before the rescue medication administration, investigators first ensured the reversible causes for the hyperglycaemia have been relieved, eg, cold, diet. Those participants who switched from placebo to visepegenatide treatment in the extension treatment period were expected to have better glycaemic control, so the rescue medication was adjusted or discontinued after the evaluation by the investigator.

The flow of participants and trial profile are illustrated in Fig. 1a.

Outcomes and assessments

The primary endpoint was the change from baseline in the HbA1c levels at week 24 in the full analysis set (FAS), which included all participants who received at least one dose and achieved a measurable outcome after dosing. The secondary efficacy endpoints included (i) proportion of participants achieving HbA1c <7% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol) at weeks 24 and 52; (ii) changes in HbA1c at weeks 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52 and changes in body weight, BMI, lipid profile, blood pressure, β-cell function (HOMA-β), HOMA-insulin resistance (HOMA-IR) at weeks 24 and 52; (iii) changes in FPG, 2-h postprandial plasma glucose (2hPG), insulin, c-peptide at weeks 24 and 52; (iv) proportion of participants receiving rescue therapy. Safety was assessed by incidences and severity of AEs including treatment-emergent adverse event (TEAE), serious adverse event (SAE) as stated in the Medical Dictionary for Regulatory Activities version 22.0. Other safety endpoints included the mean changes in calcitonin levels, biochemical parameters, vital signs, local reactions at the injection site, 12-lead electrocardiogram, and physical examination.

Statistical analysis

Statistical analysis was performed using SAS9.4 software or higher version. The sample size was calculated to ensure a power of at least 90% for testing the superiority of visepegenatide *vs* placebo in change of HbA1c from baseline to week 24. Assuming a treatment effect of –0.7%, a standard deviation (SD) of 1.5%, a two-sided α level of 0.05, and a dropout rate of 20%, it was estimated that a total sample size of 260 randomly assigned participants was needed. The detailed methods are presented in the pre-specified statistical analysis plan (Appendix 2).

Efficacy endpoints were analysed with the data from all randomly assigned participants (intention-to-treat population). The FAS included all participants in intended-to-treat who received at least one treatment dose during the double-blinded treatment period and had at least one post-baseline measurement of the primary endpoint. Per-protocol set (PPS) was a subset of FAS and the criteria for PPS is given in Supplementary Table S1. The mixed model for repeated measures (MMRM) was used to analyse the primary efficacy endpoint of change in HbA1c from baseline between the groups. The MMRM included the fixed class effects of treatment group, visit, and treatment-by-visit interaction. The baseline HbA1c value was used as a fixed covariate. For other continuous variables, a MMRM was also used to evaluate the treatment effect between the groups during the double-blinded treatment period. For binary efficacy variables (proportion of participants

reaching an HbA1c of ≤7% (<53 mmol/mol) or ≤6.5% (≤48 mmol/mol), a chi-square test was used for treatment comparisons. Paired t-test or signed rank sum was used to compare the intra-group comparison of quantitative changes relative to baseline. For the extended treatment period, analysis of change from baseline was implemented using the Paired t-test or signed rank sum, and the effect difference 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[16] (Statistical Principles for Clinical Trials [E9], addendum on statistical principles related to estimand and sensitivity analysis), representing the average treatment effect of visepegenatide relative to placebo for all participants who had undergone randomisation, regardless of treatment discontinuation and influence of rescue therapy. The secondary efficacy estimand, using the hypothetical strategy as per ICH E9[16] 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 participants, excluding data after permanent discontinuation of the study drug or initiation of rescue medication.

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

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

In this pivotal study conducted between November 2, 2020, and November 2, 2022, a total of 395 participants were screened for eligibility with 308 participants being enrolled into the run-in period. Among them, 273 eligible participants were randomised to receive visepegenatide 150 μg (n = 137) or placebo (n = 136). Six (4.4%) participants received visepegenatide and 10 (7.4%) participants received placebo discontinued the treatment in the double-blinded treatment period. The common cause of treatment discontinuation was AE in three (2.2%) participants of the visepegenatide group and patients' decision in seven (5.6%) participants of the placebo group. Of the 257 participants who entered the extended treatment period, 246 (90.11%) participants completed the treatment. The proportion of participants from each group who completed the overall 52-week treatment and safety follow-up is presented in the patient disposition flow chart (Fig. 1b).

Patient demographics and clinical characteristics were well balanced across the groups (Table 1). At baseline, the mean (SD) age was 50.4 (11.41) years in the placebo group and 50.3 (10.25) years in the visepegenatide group with BMI of 26.52 (3 .73) and 26.53 (3.51) kg/m^2, respectively. More male participants were randomly enrolled (75.7% *vs* 70.6% in the two groups). Fifty (18.3%) participants were aged between ≥60 and < 75 years. Overall, the mean (SD) duration of diabetes was 2.18 (2.50) years with 59 (21.6%) participants having diabetes complications. Mild renal impairment with eGFR of 60–90 mL/min/1.73 m^2 was found in 35 (12.8%) participants. At baseline, the mean (SD) HbA1c was 8.50% (0.81) [69.40 mmol/mol].

Efficacy in the double-blinded treatment period

Primary outcome

Visepegenatide significantly reduced the HbA1c compared with placebo in the primary estimand (treatment policy strategy) and secondary estimand (hypothetical strategy) assessments (Fig. 2 a, b). At week 24, when evaluating the average treatment effect of visepegenatide relative to placebo as per the treatment policy strategy (regardless of treatment discontinuation and influence of rescue therapy), the least squares mean (LSM) change from baseline in HbA1c was –1.36% (95% CI 1.52 to –1.20) [–14.84 [–16.60 to –13.08] mmol/mol] in the visepegenatide group and –0.63% (95% CI –0.79 to –0.46) [–6.84 [–8.61 to –5.07] mmol/mol] in the placebo group. The estimand treatment difference *vs* placebo was –0.73% (95% CI –0.96 to –0.50; [–8.00 [–10.50 to –5.50] mmol/mol] p < 0.001) (Fig. 2a). In the PPS set, 17 participants were excluded and the trend of the analysis were consistent between the FAS and PPS (Supplementary Table S1). When assessing the primary efficacy endpoint as per estimand using the hypothetical strategy (excluding the data after rescue therapy and treatment discontinuation), the change from baseline in HbA1c was –1.37 (–1.53 to –1.20) [–14.95 [–16.76 to –13.14] mmol/mol] in the visepegenatide group and –0.63 (–0.81 to –0.45) [–6.90 [–8.89 to –4.90] mmol/mol] in the placebo group with a statistical difference between the groups (–0.74, 95% CI –0.98 to –0.49; [–8.06 [–10.73 to –5.38] mmol/mol]; p < 0.001). Further, sensitivity analysis was performed to assess the robustness of the primary analysis results to explore missing data assumptions, as pre-specified in the statistical analysis plan under the section 6.3.1. Sensitivity analysis of the primary outcome was consistent with the results of the main analysis (Supplementary Table S2a, b, and c).

Early response to visepegenatide was observed at week 4 with a rapid reduction of –0.82% (95% CI –0.90

Characteristics	Visepegenatide N = 137	Placebo N = 136	Total N = 273
Age (years)	50.3 (10.25)	50.4 (11.41)	50.3 (10.82)
Gender n (%)			
Male	104 (75.9)	96 (70.6)	200 (73.3)
Female	33 (24.1)	40 (29.4)	73 (26.7)
Nationality n (%)			
Han nationality	134 (97.8)	129 (94.9)	263 (96.3)
Other	3 (2.2)	7 (5.1)	10 (3.7)
Weight (kg)	74.34 (12.44)	73.71 (13.40)	74.03 (12.91)
BMI[a] (kg/m^2)	26.53 (3.51)	26.52 (3.73)	26.52 (3.62)
Duration of diabetes[b] (years)	2.20 (2.41)	2.16 (2.60)	2.18 (2.50)
Diabetes duration group n (%)			
≤1 year	62 (45.3)	61 (44.9)	123 (45.1)
>1 year and ≤3 years	36 (26.3)	42 (30.9)	78 (28.6)
>3 years	39 (28.5)	33 (24.3)	72 (26.4)
HbA1c (%)	8.47 (0.81)	8.53 (0.81)	8.50 (0.81)
HbA1c (mmol/mol)	69.07 (8.81)	69.78 (8.88)	69.40 (8.81)
HbA1c level group, n (%)			
≤8.5% (≤69.40 mmol/mol)	76 (55.5)	74 (54.4)	150 (54.9)
>8.5% (>69.40 mmol/mol)	61 (44.5)	62 (45.6)	123 (45.1)
FPG (mmol/L)	9.15 (2.00)	9.26 (2.01)	9.21 (2.00)
eGFR ($mL/min/1.73\ m^2$)	105.96 (13.76)	107.82 (14.54)	106.88 (14.16)
60–90 rate, n (%)	20 (14.6)	15 (11.0)	35 (12.8)
Diabetes complications n (%)			
At least one complication	32 (23.4)	27 (19.9)	59 (21.6)

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; HbA1c, 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.**

to –0.74) [–8.99 [–9.88 to –8.10] mmol/mol] in HbA1c levels ($p < 0.001$), and the reduction in HbA1c was sustained during the extended treatment period with –1.39 (95% CI –1.58 to –1.19) [–15.14 [–17.28 to –13.01] mmol/mol] at week 52 in the study group (Fig. 3, Table 2).

The placebo→visepegenatide group, which received visepegenatide during the extended treatment period, had an outcome in the same direction as the visepegenatide group during the double-blind treatment period. At week 52, the change from baseline in HbA1c was –1.49% (–1.68 to –1.30) [–16.27 [–18.37 to –14.16] mmol/mol], which was greater than week 24.

Visepegenatide on the secondary efficacy endpoints at the end of weeks 24 and 52

At week 24, a greater proportion of participants in the visepegenatide group (50.4%) achieved an HbA1c target level of <7% [<53 mmol/mol] than that in the placebo group (14.2%) ($p < 0.05$). Likewise, a significant proportion of participants treated with visepegenatide (26.7%) achieved an HbA1c of ≤6.5% [≤48 mmol/mol] compared with that of placebo (7.9%; $p < 0.05$). At week 52, the proportion of participants sustaining target HbA1c levels of <7% [<53 mmol/mol] and ≤6.5% [≤48 mmol/mol] in the visepegenatide group were 43% and 22.7%, respectively. On the other hand, after receiving visepegenatide treatment in the extended treatment period, the placebo→visepegenatide group had a significantly higher proportion of participants achieving an HbA1c level of <7% [<53 mmol/mol] compared with 24 weeks (47.2% *vs* 14.2%), and HbA1c ≤ 6.5% [≤48 mmol/mol] was achieved by 33.6% of participants, which was an improvement compared with its week 24 placebo treatment (Table 2). Overall, reductions in HbA1c were higher in the visepegenatide group regardless of BMI or gender than in the placebo group and were significant compared with the baseline values (Supplementary Tables S3 and S4). Gender subgroup analysis showed that, in males, the reduction in HbA1c from baseline was significant at week 24, and a greater reduction was observed in the Visepegenatide group compared to the placebo group (–1.44% *vs* –0.66%). The reduction from baseline in the female subgroup was significant, and numerically greater in the visepegenatide group than in the placebo group (–1.08% *vs* –0.63%) (Supplementary Table S4). Visepegenatide brought significant reductions in HbA1c in subgroup analysis of baseline HbA1c (≤8.5% and >8.5%) than the placebo. Greater HbA1c reductions were observed

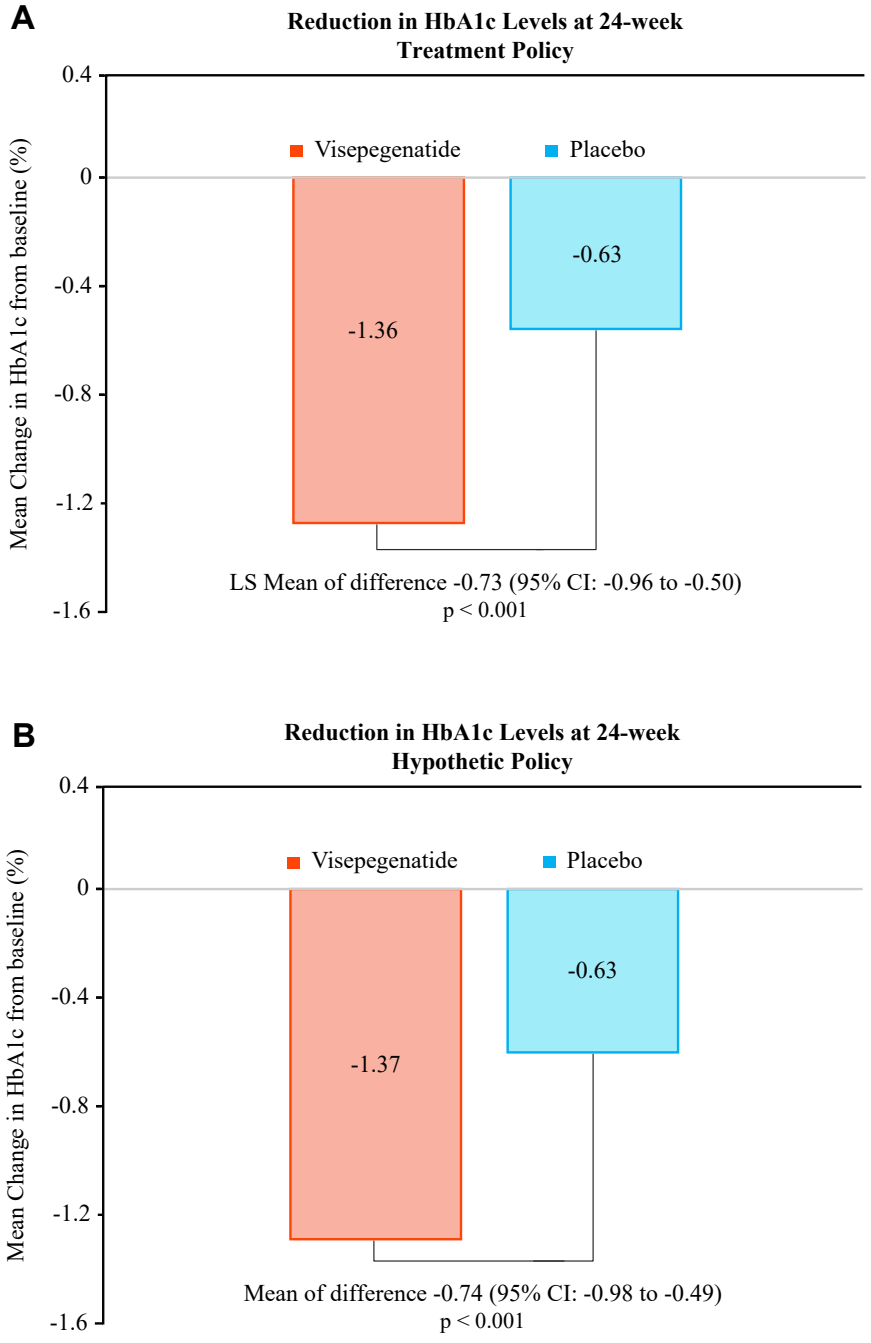

Fig. 2: **Change in mean HbA1c from baseline at 24-week. a, Treatment policy; b, Hypothetic policy**. HbA1c, glycated haemoglobin.

in the higher baseline HbA1c (>8.5%) subgroup (Supplementary Table S5).

At week 24, both mean FPG and mean 2hPG levels showed a statistically significant reduction ($p < 0.05$) in the visepegenatide group than in the placebo group (Table 2). The change in FPG from baseline in each group was –1.26 (1.78) *vs* –0.52 (1.92) mmol/L, and the change in 2hPG was –2.52 (3.12) *vs* –0.85 (3.44) mmol/L. These reductions in the visepegenatide group remained stable until week 52 during the extended treatment. At week 52, the placebo→visepegenatide group exhibited superior reductions compared with its baseline levels (both $p < 0.001$).

At week 24, fasting C-peptide, 2-h postprandial C-peptide, and insulin levels were significantly increased compared with baseline in the visepegenatide

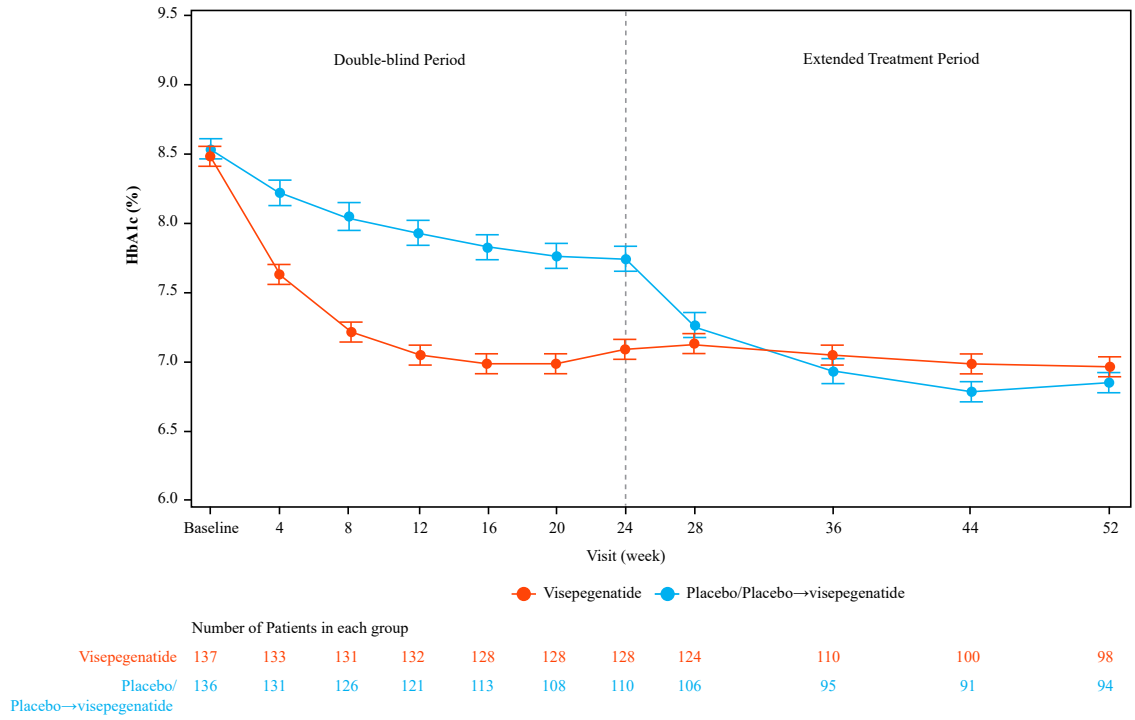

***Fig. 3:* Changes in HbA1c from baseline throughout the 52week treatment**. HbA1c, glycated haemoglobin; Note: Placebo→Visepegenatide group received visepegenatide injection in the extended treatment period.

group and significantly higher than the placebo group ($p = 0.040$, $p < 0.001$, $p < 0.001$). Although the levels of fasting insulin were also numerically higher, no significant difference was observed between the groups. At week 52, postprandial C-peptide and insulin continued to increase in the visepegenatide group and were significantly higher than their baseline levels ($p < 0.001$ for both). However, fasting insulin level was numerically decreased compared with its baseline. At week 52, the postprandial C-peptide and insulin level in the placebo→visepegenatide also increased compared with their week 24 levels, and significantly higher than their baseline levels (Table 2).

HOMA model was applied to evaluate the β-cell function and insulin resistance. HOMA-β of the visepegenatide group increased at week 24 from its baseline value and was significantly higher than the placebo (18.21 [44.90] *vs* 1.83 [19.98]; $p < 0.001$). This increase was prolonged with the extended treatment (16.45 [39.72] at week 52). The placebo→visepegenatide group also showed a significant improvement in the HOMA-β (21.29 [33.81] at week 52, $p < 0.05$ compared with the baseline) in the extended treatment period (Table 2).

At week 24, there was no significant difference in the HOMA-IR change from baseline between the groups. However, with extended treatment, HOMA-IR significantly reduced from baseline in the visepegenatide group (–0.96 [3.71]; $p < 0.01$ compared with the baseline.

The number of participants who received rescue therapy during the double-blinded treatment period was significantly lower in the visepegenatide group (2.2% *vs* 12.5%, $p < 0.05$).

The baseline BMI and body weight was 26.5 kg/m^2 and 70.4 kg, respectively in the cohort. Body weight loss was observed at week 24. At week 52, the overall change in body weight from baseline was –0.69 (3.90) kg and –0.62 (2.69) kg in the visepegenatide and placebo→visepegenatide groups ($p < 0.05$ compared with the baseline for both groups), respectively. The effect of weight loss was in a baseline BMI-dependent manner. In the subgroups with BMI <24 kg/m^2, ≥24 to <28 kg/m^2, ≥28 kg/m^2, and ≥30 kg/m^2, the body weight change from baseline at week 52 was 0.11 (2.23) kg, –0.56 (2.19) kg, –1.42 (6.10) kg and –1.74 (8.19) kg, respectively. The reduction was more pronounced in the BMI ≥32 kg/m^2 subgroup with 4.77 kg observed at week 52 (Table 3).

Effect on the lipid profile and blood pressure

At week 24, the treatment with visepegenatide significantly reduced the mean total cholesterol from baseline by –0.12 (0.81) mmol/L *vs* an increase of 0.11 (0.82) mmol/L in the placebo group ($p < 0.05$). Low-density lipoprotein (LDL) cholesterol levels were significantly

	Visepegenatide 150 µg	Placebo/placebo→visepegenatide
HbA1c		
Baseline, Mean (SD), %	8.47 (0.81)	8.53 (0.81)
Baseline, Mean (SD), mmol/mol	69.07 (8.81)	69.78 (8.88)
Change from baseline at 4-week, Mean (95% CI), %[b]	−0.82 (−0.90 to −0.74)	−0.30 (−0.41 to −0.19)
Change from baseline at 4-week, Mean (95% CI), mmol/mol[b]	−8.99 (−9.89 to −8.10)	−3.30 (−4.50 to −2.09)
Compared with placebo %	−0.52 (−0.66 to −0.38); p < 0.001	
Compared with placebo, mmol/mol	−5.69 (−7.19 to −4.20); p < 0.001	
Change from baseline at 24-week, LSMean (95% CI), %[a]	−1.36 (−1.52 to −1.20)	−0.63 (0.79 to −0.46)
Change from baseline at 24-week LSMean (95% CI), mmol/mol[a]	−14.84 (−16.60 to −13.08)	−6.84 (−8.61 to −5.07)
Compared with placebo	−0.73 (−0.96 to −0.50); p < 0.001	
Compared with placebo, mmol/mol	−8.00 (−10.50 to-5.50); p < 0.001	
Change from baseline at 24-week Mean (95% CI), %[b]	−1.37 (−1.53 to −1.20)	−0.63 (−0.81 to −0.45)
Change from baseline at 24-week, Mean (95% CI), mmol/mol[b]	−14.95 (−16.76 to −13.14)	−6.90 (−8.89 to −4.90)
Compared with placebo, %	−0.74 (−0.98 to −0.49); p < 0.001	
Compared with placebo, mmol/mol	−8.06 (−10.73 to −5.38); p < 0.001	
Change from baseline at 52-week, Mean (95% CI), %[b]	−1.39 (−1.58 to −1.19)	−1.49 (−1.68 to −1.3)
Change from baseline at 52-week mmol/mol	−15.14 (−17.28 to −13.01)	−16.27 (−18.37 to −14.16)
Proportion of patients achieving HbA1c target (%)		
HbA1c < 7.0% (<53 mmol/mol) at 24-week	50.4	14.2
Compared with placebo	p < 0.001	
HbA1c< 7.0% (<53 mmol/mol) at 52-week	43.0	47.2
HbA1c ≤ 6.5% (≤48 mmol/mol) at 24-week	26.7 (p < 0.001)	7.9
Compared with placebo	p < 0.001	
HbA1c ≤ 6.5% (≤48 mmol/mol) at 52-week	22.7	33.6
Fasting plasma glucose (mmol/L)		
Baseline	9.15 (2.00)	9.26 (2.01)
Change from baseline at 24-week	−1.26 (1.78)[c]	−0.52 (1.92)[c]
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	−1.39 (1.79)[c]	−1.46 (2.11)[c]
2-h postprandial plasma glucose (mmol/L)		
Baseline	15.61 (3.14)	15.55 (3.35)
Change from baseline at 24-week	−2.52 (3.12)[c]	−0.85 (3.44)[c]
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	−2.29 (2.89)[c]	−2.38 (3.90)[c]
Fasting insulin (pmol/L)		
Baseline	93.30 (65.48)	93.44 (56.87)
Change from baseline at 24-week	2.17 (57.09)	−3.07 (37.46)
Compared with placebo	p = 0.315	
Change from baseline at 52 weeks	−1.36 (55.463)	5.36 (42.802)
2-h postprandial insulin (pmol/L)		
Baseline	316.58 (206.74)	340.29 (200.18)
Change from baseline at 24-week	60.83 (156.90)[c]	−9.75 (152.523)
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	78.11 (148.64)[c]	62.46 (157.74)[c]
Fasting C peptide (nmol/L)		
Baseline	0.96 (0.33)	0.96 (0.34)
Change from baseline at 24-week	0.03 (0.28)	−0.02 (0.21)
Compared with placebo	p = 0.040	
Change from baseline at 52 weeks	0.03 (0.26)	0.04 (0.248)
2-h postprandial C peptide (nmol/L)		
Baseline	2.21 (0.79)	2.28 (0.76)
Change from baseline at 24-week	0.38 (0.57)[c]	−0.02 (0.55)
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	0.49 (0.58)[c]	0.40 (0.64)[c]

(Table 2 continues on next page)

	Visepegenatide 150 μg	Placebo/placebo→visepegenatide
(Continued from previous page)		
HOMA-β		
Baseline	52.23 (36.89)	51.59 (33.56)
Change from baseline at 24-week	18.21 (44.90)[c]	1.83 (19.98)
Compared with placebo	p < 0.001	
Change from baseline at 52 weeks	16.45 (39.72)[c]	21.29 (33.81)[c]
HOMA-IR		
Baseline	4.97 (3.90)	4.85 (4.55)
Change from baseline at 24-week	−0.64 (3.97)	−0.37 (2.89)
Compared with placebo	p = 0.589	
Change from baseline at 52 weeks	−0.96 (3.71)[c]	−0.45 (2.81)
Proportion of participants undergoing rescue therapy		
At 24-week	3 (2.2%)	17 (12.5%)
Compared with placebo	p = 0.001	
Total cholesterol (mmol/L)		
Baseline	5.02 (0.85)	5.02 (1.13)
Change from baseline at 24-week	−0.12 (0.81)	0.11 (0.82)
Compared with placebo	p = 0.030	
Change from baseline at 52 weeks	−0.20 (0.95)[c]	−0.25 (0.96)[c]
Low-density lipoprotein cholesterol (mmol/L)		
Baseline	3.06 (0.70)	3.04 (0.84)
Change from baseline at 24-week	−0.12 (0.67)[c]	0.01 (0.71)
Compared with placebo	p = 0.104	
Change from baseline at 52 weeks	−0.192 (0.65)[c]	−0.168 (0.66)[c]
Triglycerides (mmol/L)		
Baseline	2.14 (1.16)	2.0 (1.09)
Change from baseline at 24-week	−0.09 (1.18)	0.22 (1.86)
Compared with placebo	p = 0.166	
Change from baseline at 52 weeks	0.33 (3.12)	0.07 (1.04)
Systolic blood pressure (mmHg)		
Baseline	123.8 (11.69)	122.3 (11.69)
Change from baseline at 24-week	−1.5 (10.55)	0.3 (11.23)
Compared with placebo	p = 0.218	
Change from baseline at 52 weeks	−2.1 (12.34)	−0.4 (11.71)
Diastolic blood pressure (mmHg)		
Baseline	81.5 (7.95)	80.4 (7.59)
Change from baseline at 24-week	−2.2 (6.77)[c]	−0.1 (7.61)
Compared with placebo	p = 0.055	
Change from baseline at 52 weeks	−1.8 (8.46)[c]	−1.7 (8.49)[c]

Values are presented as mean (SD) unless stated otherwise. [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. [c]Compared to baseline, p < 0.05.

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

reduced from baseline (p < 0.05 *vs* baseline) in the visepegenatide group, whereas in the placebo group, LDL increased compared with the baseline (–0.12 [0.67] *vs* 0.01 [0.71] mmol/L). Progressively greater reductions in total cholesterol (–0.20 [0.95]; p = 0.021 *vs* baseline) and LDL-cholesterol (–0.19 [0.65]; p = 0.001 *vs* bassline) were observed until week 52 with the extended treatment. Regarding the triglycerides, they were reduced in the visepegenatide group, whereas they increased in the placebo group (–0.09 [1.18] *vs* 0.22 [1.86] mmol/L) at week 24. The placebo→visepegenatide group exhibited similar improvement in the lipid profile in the extended treatment period (Table 2). Among the subgroup participants with dyslipidaemia, visepegenatide induced greater improvement at week 24 and similar improvement at week 52 compared with overall participants population (Supplementary Table S6).

Visepegenatide treatment led to reduction in both systolic blood pressure (SBP) and diastolic blood pressure (DBP). At week 24, the visepegenatide group had a

	Visepegenatide 150 µg	Placebo group Placebo→Visepegenatide
	N = 137	N = 136
Change in body weight from baseline: subgroup BMI <24 kg/m^2,		
24-week, Mean (SD) kg	0.49 (2.25)	−0.21 (1.80)
52-week, Mean (SD) kg	0.11 (2.23)	−0.34 (2.83)
Change body weight from baseline: subgroup BMI ≥24 to <28 kg/m^2, Mean (SD) kg		
24-week, Mean (SD) kg	−0.39 (2.56)	−0.15 (1.96)
52-week, Mean (SD) kg	−0.56 (2.19)	−0.24 (1.79)
Change body weight from baseline: subgroup BMI ≥28 kg/m^2, Mean (SD) kg		
24-week, Mean (SD) kg	−0.97 (5.50)	−1.39 (2.61)
52-week, Mean (SD) kg	−1.42 (6.10)	−1.58 (3.29)
Change in body weight from baseline: subgroup BMI ≥30 kg/m^2, Mean (SD) kg		
24-week, Mean (SD) kg	−1.79 (7.27)	−1.52 (2.75)
52-week, Mean (SD) kg	−1.74 (8.19)	−1.77 (3.59)
Change in body weight from baseline: subgroup BMI ≥32 kg/m^2, Mean (SD) kg		
24-week, Mean (SD) kg	−5.13 (12.38)	−1.66 (3.27)
52-week, Mean (SD) kg	−4.77 (13.94)	−2.06 (3.87)

Table 3: **Change in body weight (by baseline BMI subgroup) analysis.**

numerically higher reduction in both SBP (−1.5 [10.55] mmHg *vs* 0.3 [11.23] mmHg) and DBP (−2.2 [6.77] mmHg *vs* −0.1 [7.61] mmHg) compared with the placebo group. At week 52, there was a greater reduction in the SBP (−2.1 [12.34] mmHg) and a sustained reduction in the DBP (−1.8 [8.46] mmHg). The reduction in SBP and DBP was numerically greater in the subgroup participants with hypertension (Supplementary Table S7). The placebo→visepegenatide group had similar effect on lipid profile and blood pressure after receiving the study drug in the extended treatment period (Table 2).

Safety profile

Overall, at least one TEAE was reported in 111 (81.0%) participants in the visepegenatide group *vs* 85 (62.5%) participants in the placebo group during the double-blinded treatment period. However, with continuous treatment, it was reduced to 85 (62.0%) and 84 (61.8%) participants in the extended treatment period. Gastrointestinal AE was reported in 42 (30.7%) participants of the visepegenatide group *vs* 15 (11.0%) participants of the placebo group during the double-blinded period, mostly commonly 11 (8.0%) of diarrhoea, 11 (8.0%) of nausea, and 8 (5.8%) of vomiting in the visepegenatide group. The incidence of gastrointestinal AE was lower in the extended treatment period (12.4% and 16.9%). Most of the AEs were of mild and moderate in nature appearing at the initial phase of the treatment and resolved or reduced in frequency as the treatment progressed. There was only one severe gastrointestinal event occurring in the extended treatment period (Table 4).

During the 24-week, double-blinded treatment period, five (3.6%) and one (0.7%) participants discontinued the study due to TEAE in the visepegenatide and placebo groups, respectively; of whom, three (2.2%) and one (0.7%) participants were due to gastrointestinal AE. During the extended treatment, no patient discontinued from the study due to TEAE.

One incidence of SAE (0.7%), acute pyelonephritis, was reported in the visepegenatide group during the double-blinded treatment period, and was judged as related to the study drug by the investigator. However, considering female participants of the reproductive age with T2DM were a high-risk population for urinary tract infection, and GLP-1 RA was not a risk factor, the sponsor assessed this SAE not related to the study drug.

Low incidences of hypoglycaemia, six (4.4%) consisting of three (2.2%) asymptomatic hypoglycaemia, two (1.5%) relative hypoglycaemia, one (0.7%) symptomatic hypoglycaemia, were reported in the visepegenatide group *vs* one (0.7%) asymptomatic hypoglycaemia in the placebo group. The incidence was further reduced during the extended treatment period, whereas the placebo→visepegenatide group exhibited similar trend. No incidences of severe hypoglycaemia or grade 2 hypoglycaemia (<3 mmol/L) and no death were reported in the entire 52-week study period (Table 4). Vital signals including change in heart rate were similar between the groups and no significant deviation was observed during the extended treatment period. No pancreatitis, no thyroid cancer, and no difference in calcitonin levels between the groups were observed.

Discussion

In this pivotal phase 3, visepegenatide as monotherapy led to a rapid onset without the risk of hypoglycaemia, significant, and sustained effect in hyperglycaemic control up to 52 weeks, as well as sustained improvement in insulin and C-peptide secretion, islets-β cellular function, and insulin resistance. It also demonstrated the comprehensive benefit in body weight, blood lipids profile, and blood pressure. The improvements were generally greater at 52 weeks than 24 weeks. Most importantly, visepegenatide has an outstanding safety profile even without dose titration scheme. Gastrointestinal side effects were significantly lower than other GLP-1 RAs in the market. Number of participants discontinuing the treatment due to gastrointestinal AE were less. No new safety signals other than the GLP-1 RAs associated AEs were observed. The good safety profile and compliance were also evident in the low dropout rate of the study, particularly during the COVID-19 pandemic. The overall completion rate for week 24 was more than 94% and more than 90% for the whole 52 weeks.

In this study, visepegenatide was administrated at a dose of 150 µg s.c. injection once a week, without dose titration based on the good safety and tolerability exhibited in the earlier two phase 2 studies.[11] As the

Events	Double-blind treatment period				Extended treatment period			
	Visepegenatide N = 137		Placebo N = 136		Visepegenatide N = 137		Placebo→Visepegenatide N = 136	
	Number of patients (%)	Episodes	Number of patients (%)	Episodes	Number of patients (%)	Episodes	Number of patients (%)	Episodes
All adverse events (AE)	117 (85.4)	468	94 (69.1)	265	94 (68.6)	305	88 (64.7)	264
Treatment Emerging Adverse Events (TEAE)	111 (81.0)	406	85 (62.5)	211	85 (62.0)	256	84 (61.8)	233
Mild TEAE	64 (46.7)	342	63 (46.3)	172	61 (44.5)	214	55 (40.4)	186
Moderate TEAE	42 (30.7)	59	20 (14.7)	37	23 (16.8)	41	26 (19.1)	44
Severe TEAE	5 (3.6)	5	2 (1.5)	2	1 (0.7)	1	3 (2.2)	3
Gastrointestinal (GI) Diseases	42 (30.7)	170	15 (11.0)	19	17 (12.4)	52	23 (16.9)	44
Mild	28 (20.4)	150	12 (8.8)	16	14 (10.2)	49	19 (14.0)	39
Moderate	14 (10.2)	20	3 (2.2)	3	3 (2.2)	3	3 (2.2)	4
Severe	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (0.7)	1
GI AEs by preferred term (in ≥5% of patients)	25 (18.2)	100	3 (2.2)	4	13 (9.5)	44	12 (8.8)	29
Diarrhea	11 (8.0)	31	2 (1.5)	2	13 (9.5)	44	12 (8.8)	29
Nausea	11 (8.0)	32	1 (0.7)	1	9 (6.6)	15	4 (2.9)	4
Abdominal distension	9 (6.6)	23	1 (0.7)	1	3 (2.2)	17	6 (4.4)	6
Vomiting	8 (5.8)	14	0 (0.0)	0	2 (1.5)	11	3 (2.2)	14
TEAEs leading to early withdrawal	5 (3.6)	6	1 (0.7)	1	0 (0.0)	0	0 (0.0)	0
GI AE leading to early withdrawal	3 (2.2)	4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Constipation	1 (0.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Nausea	1 (0.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Abdominal distension	1 (0.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Vomiting	1 (0.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Hypoglycemia[b]	6 (4.4)	6	1 (0.7)	1	3 (2.2)	5	5 (3.7)	7
Asymptomatic hypoglycemia	3 (2.2)	3	1 (0.7)	1	2 (1.5)	3	3 (2.2)	5
Relatively hypoglycemia	2 (1.5)	2	0 (0.0)	0	0 (0.0)	0	1 (0.7)	1
Definite symptomatic hypoglycemia	1 (0.7)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Suspected symptomatic Hypoglycemia	0 (0.0)	0	0 (0.0)	0	1 (0.7)	2	1 (0.7)	1
Severe hypoglycemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Serious Adverse Events (SAEs)	9 (6.6)	10	2 (1.5)	3	2 (1.5)	2	5 (3.7)	6
SAEs related to study drug	1 (0.7)[a]	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

[a]Acute pyelonephritis. The sponsor assessed that the SAE was not related to the study drug. [b]The definition of hypoglycemia in this study: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.

Table 4: **Treatment-emergent adverse events in the safety analysis set.**

primary endpoint at week 24 of the study, visepegenatide provided a superior effect compared to placebo in reducing the HbA1c levels in treatment-naïve patients with T2DM (Fig. 2a and b). The HbA1c change from baseline in our study is similar to other GLP-1 RAs as a monotherapy; 0.5 mg and 1.0 mg of semaglutide had a reduction of –1.45% and –1.55% at week 30 in the SUSTAIN 1 study,[17] while 0.75 mg and 1.5 mg of dulaglutide reduced HbA1c by –0.71% and –0.78% at week 26 in the AWARD 3 study,[18] whereas exenatide (2.0 mg once-a-week) reduced HbA1c by –1.53% at week 26 in the DURATION 4 study.[19]

At week 4, a rapid reduction in HbA1c levels –0.82% (–0.90 to –0.74) [–8.99 [–9.89 to –8.10] mmol/mol] was observed without the risk of hypoglycaemia and 18.8% of participants achieved the treatment target of HbA1c < 7.0% (<53 mmol/mol) with visepegenatide. Gender subgroup analysis showed that males in the Visepegenatide group had numerically greater reductions in HbA1c at week 24 than females. The same trend has been observed in the Dulaglutide study.[20] Of note, this study had a total sample size of 273 participants with limited numbers in each subgroup. As a result, this subgroup analysis was not powered to investigate the statistical treatment difference in each subgroup. We conducted a series of quantitative pharmacological studies based on all phase 1 to phase 3 clinical trials, and found no factor including gender, to significantly impact the reduction of HbA1c by visepegenatide.

Studies have shown the benefits of early and intensive antidiabetic treatment on the macrovascular outcome of diabetes. The early response may decrease the hyperglycaemia-associated toxicities and progression of diabetes complications including atherosclerotic cardiovascular disease and chronic kidney disease. According to 2023 American Association of Clinical Endocrinology statement, therapeutic inertia is a major threat to achieve improved health outcomes, and treatment should get to the goal as soon as possible. Notably, unlike other antidiabetic drugs in which loss of efficacy has been observed with the prolonged treatment,[21–24] in our present study, visepegenatide exhibited a prolonged and sustained effect on glycaemic control as well as the associated complementary benefits in the extended treatment duration till 52 weeks. Efficacy plateau was not observed. Taken these observations together, visepegenatide may confer potential long-term benefits to patients with T2DM. Similarly, visepegenatide lowered the FPG and 2hPG significantly greater than the placebo and maintained throughout the study.

Results from this study showed that visepegenatide is therapeutically superior in achieving the HbA1c target range of <7% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol) levels (Table 2). Remarkable response with visepegenatide was observed in 35 (26.7%) participants who achieved an optimal HbA1c level of ≤6.5% (≤48 mmol/mol) and 66 (50.4%) achieved HbA1c target level of <7% (<53 mmol/mol) during the double-blinded treatment period, which was maintained in the extended treatment period. The American Diabetes Association (ADA) 2023 Standard of Care in Diabetes, recommends a more stringent glycaemic goal as HbA1c at ≤6.5% (≤48 mmol/mol) for selected individual based on the duration of diabetes, age/life expectancy, comorbid conditions, hypoglycaemia unawareness, and individual patient considerations.[25,26]

The treatment with visepegenatide greatly enhanced the islet β-cell function shown by significant improvement in HOMA-β from baseline and reducing HOMA-IR, the two most important underlying causes of T2DM. In parallel, the use of visepegenatide increased the levels of fasting C-peptide, 2-h postprandial C-peptide, and 2-h postprandial insulin with no significant change in fasting insulin. Considering that longer half-life and constant clearance rate, measurement of C-peptide is a practical approach and more specific indicator of β-cell function.[21] These effects were greater at week 52 than week 24, supporting the lasting benefit of visepegenatide treatment. At week 52, the fasting insulin level of visepegenatide group was decreased compared with baseline and week 24, which is consistent with the reduced HOMA-IR at week 52.

In the present study, visepegenatide provided a comprehensive benefit on body weight, blood pressure, and lipid profiles compared with placebo and the effects were progressive, maintained for a long duration of 52 weeks. Diabetes and obesity share a common pathophysiological mechanism[22] and are the risk factors for cardiovascular diseases (CVD)/cardiometabolic diseases.[23] Effective management of obesity could delay the disease progression and aid in controlling the insulin resistance.[24,25,27] The ADA and European Association for the Study of Diabetes guidelines recommend including GLP-1 RA in the management of T2D to ensure adequate glycaemic control and its beneficial effect on obesity and CVD.[25] Treatment with visepegenatide resulted in a significant body weight loss compared with baseline. Other GLP-1 RAs showed significant reductions in body weight in obese/overweight adults[28] and in adult patients with T2DM[29] but at high doses. Visepegenatide at 150 μg was intended for effective glycaemic control with better tolerability. Importantly, the mean BMI of this study was only 26.0 kg/m^2; however, the mean BMI in the phase 3 studies of semaglutide and dulaglutide in T2DM population was more than 32.0 kg/m^2. In the current relatively low BMI population and at this low therapeutic dosage, visepegenatide still showed a remarkable weight loss effect and appeared to be in a BMI-dependent manner. The weight loss effect was more pronounced in the BMI ≥32 kg/m^2 subgroup with a mean reduction of 4.77 kg observed at week 52. This reduction was similar with what has been demonstrated in other phase 3 studies in diabetes as monotherapy and had the similar BMI, for example, semaglutide SUSTAIN 1 study (4.53 kg) and higher than that in the Dulaglutide AWRAD-3 study (2.29 kg).[17,18] Anti-diabetic drugs have differential effects on sarcopenia especially on muscle health. In addition to age-related sarcopenia in diabetes, lean individuals with T2DM may have life-long exposure disadvantageously affecting lean body mass and fat mass. Studies have shown certain classes of antidiabetic drugs linked with loss of skeletal muscle mass.[30] However, GLP-RA induces weight loss by reducing fat mass and not affecting lean mass.[31,32] This could explain the remarkable weight reduction in the BMI ≥32 kg/m^2 subgroup in our study indicating higher reductions with correspondingly higher fat mass in obese patients. Reducing lean mass would be unfavourable, especially in lean or sarcopenic individuals. Visepegenatide provided a remarkable glycemic lowering effect without significant weight loss in lean patients.

Crucially, visepegenatide also reduced total cholesterol, LDL-C, and total triglyceride during the double-blind treatment, whereas these lipid parameters all increased in the placebo group. Noteworthy is the clinical effect on patients with dyslipidaemia who had greater reductions in lipid profile at week 24 and reduced further at week 52 (Supplementary Table S6). In the placebo group, the blood pressure was not significantly changed or even elevated at week 24. Nevertheless, visepegenatide treatment led to numerically higher reductions in both systolic and diastolic

blood pressure and maintained in the study. The effects were more profound in patients with hypertension. The SBP and DBP reductions were as much as 3.3 mmHg and 2.8 mmHg in this subgroup population with the visepegenatide treatment (Supplementary Table S7). Other GLP-1 RAs have identified their effect in the reduction of SBP but only slight or neutral effect in DBP. However, in the present study, visepegenatide exhibited a remarkable benefit in reducing both SBP and DBP, suggesting potentially greater cardiovascular benefits.

In the extended treatment period, participants from the placebo group switched to visepegenatide treatment and presented similar efficacy as the visepegenatide group in both glycaemic control, β-cell function improvement, reversing insulin resistance and comprehensive benefits obtained including weight loss, lipid profile improvement, and reduction in blood pressure.

In terms of safety, throughout the entire study, visepegenatide treatment showed good tolerability and safety. Majority of TEAEs occurring were all mild to moderate in intensity. The most common adverse reactions are gastrointestinal reactions such as nausea, vomiting, and diarrhoea, which shared the same safety signal with other GLP-1 RAs, but the incidences were significantly lower than what they have reported. During the double-blinded treatment period, the incidence of most common gastrointestinal side effects was nausea (8.0%), vomiting (5.8%), and diarrhoea (8.0%). The aforementioned incidences reported in the SUSTAIN 1 study[17] were 20%, 4%, and 13%, in the AWARD 3 study[18] were 10.7%, 5.9%, and 5.2%, and in the DURATION-4 study[19] were 11.3%, 4.8%, and 10.9%. In the present study, most gastrointestinal AEs related to visepegenatide were transient and occurred within 4 weeks of initial treatment and with the treatment, they were gradually alleviated and significantly less common in the extended treatment period. Only five participants discontinued the treatment due to gastrointestinal AE related to visepegenatide and withdrew from the study; of whom, three participants were from the visepegenatide group during the double-blinded period, one patient from each group during the extended treatment period. The discontinuation rate due to gastrointestinal AE was also lower in the present study compared with the discontinuation in other GLP-1 RAs studies. Taken together, qualitatively visepegenatide demonstrates a high benefit and low-risk balance.

From the perspective of its mechanism of action, GLP-1 RA increases insulin secretion in a glucose concentration-dependent manner, for this reason, the risk of hypoglycaemia was low. This study again confirmed the safety of visepegenatide in hypoglycaemia. No patient had hypoglycaemia <3.0 mmol/L or severe hypoglycaemia. No participants interrupted the treatment or discontinued it due to hypoglycaemia.

The study design is one of the strengths of this study. We assigned approximately 50% of the participants to the placebo group for 24 weeks for active, parallel comparison. However, to ensure the patient safety, rescue therapy was administered when hyperglycaemia occurred. The efficacy data after receiving rescue therapy was included in the primary endpoint analysis. This efficacy estimand using the treatment policy strategy of including all the efficacy data after the post–rescue therapy and treatment discontinuation in the efficacy analysis may better reflect the situation in real clinical practice. Considering a low therapeutic dose, reduction in HbA1c, and various glycaemic as well as metabolic parameters, visepegenatide demonstrated rapid, significant efficacy and sustained response over the long term in the present study as we included and extended 28-week extended treatment period to observe the persistence response and safety profile.

There were few limitations in the present study. Lack of a positive control group for better comparison of efficacy with the study drug; however, the active, parallel, placebo group comparison attributed the effects to the study drug. Nonetheless, this study provides a definitive efficacy and an outstanding safety profile due to its sound clinical design and comprehensive efficacy outcomes in the treatment-naïve population with T2DM. In addition, more male participants were randomly enrolled in this study, possibly related to the COVID-19 pandemic during the study. However, the subgroup analysis results were consistent with the whole population. In the Unites States, both a phase 1 study and a phase 2 study of visepegenatide have been completed. Quantitative pharmacological research based on all the phase 1 to phase 3 studies has confirmed that there is no racial difference in either pharmacokinetic or pharmacodynamic characteristics. While further studies are required, our results remain reliable and applicable for generalisability.

In conclusion, visepegenatide at a dose of 150 μg as once a week monotherapy exerts early, significant, sustained glycaemic control in the treatment of naive adult patients with T2DM. Treatment with visepegenatide can induce the early onset of treatment response in reducing HbA1c and maintaining the efficacy for 52 weeks. Visepegenatide treatment enhanced the islet-β cell function, improved insulin resistance, and provided comprehensive benefits in lowering the body weight, lipid profile, and blood pressure constantly. These comprehensive benefits are maintained or enhanced with the treatment prolongation. Visepegenatide had a remarkable safety profile and was well tolerated in participants with T2DM. This study also demonstrated high levels of therapy adherence without the need for dose titration and convenient to use injections. The fast, sustained efficacy including the comprehensive benefit, the superior safety profile, and the no-titration regimen

support the long-term treatment and consequently great benefit for the patients with T2DM.

Contributors

ZZ, XY, KD, and MX contributed to the study design. JM, YL, XW, SL, SY, ZM, YZ, JL (Jingna Lin), JL (Jie Liu) conducted and provided medical oversight during the trial. KD, YJ, and LL were responsible for the statistical analyses. 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, interpreted the data, and participated in the writing and critical review of the manuscript with the support of medical writing services provided by the funder. All authors approve of this manuscript to be submitted for publication.

Data sharing statement

The data related to this study are presented in the manuscript, supplement, and appendix 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.2024.101101.

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