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Efficacy and Safety of Bilpatide, a Bi-weekly GIP/GLP-1 Receptor Agonist, in Chinese Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial

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Abstract

Bilpatide is a novel bi-weekly dual receptor agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) developed for the treatment of obesity and type 2 diabetes (T2D). Here we report the SHINING-1 randomized, double-blind, placebo-controlled phase 2 trial assessing the efficacy and safety of bilpatide compared with placebo in Chinese participants with T2D uncontrolled by lifestyle intervention or metformin combination therapy. In this study, 233 participants were randomized to receive bilpatide 3 mg, 6 mg, 9 mg, 12 mg or 15 mg, or placebo for 24 weeks. All bilpatide doses produced significant, dose-dependent reductions in glycated haemoglobin A1c (HbA1c) from baseline to week 24 versus placebo, with least-squares mean changes of -1.66% for 3 mg, -2.04% for 6 mg, -2.14% for 9 mg, -2.34% for 12 mg, and − 2.76% for 15 mg, compared with − 0.25% for placebo(all $P < 0.001$). More participants receiving bilpatide achieved HbA1c < 7.0% and < 6.5%, and body-weight loss ≥ 5% and ≥ 10%, than those receiving placebo. The most common treatment-emergent adverse events were gastrointestinal, predominantly mild or moderate in severity. No severe hypoglycemia, pancreatitis, injection-site reactions, or thyroid malignancy were reported. In summary, in Chinese participants with T2D, 24 weeks of bi-weekly bilpatide improved glycemic control and reduced body weight, with cardiometabolic benefits and acceptable safety and tolerability.ClinicalTrials.gov registration: NCT06254274.

Introduction

Diabetes is a chronic metabolic disorder characterized by persistent hyperglycemia and impaired glucose homeostasis. According to the International Diabetes Federation Atlas, China has the world's largest diabetic population, comprising approximately 148 million adults, predominantly with type 2 diabetes (T2D)[1]. T2D is often accompanied by obesity, hypertension, and dyslipidemia, which substantially elevate the risk of complications and underscore the necessity for management strategies that extend beyond glycemic control[2,3].

Glucagon-like peptide-1 (GLP-1) receptor agonists lower blood glucose through glucose-dependent insulin secretion with a low risk of hypoglycemia, and also improve weight, lipid profiles, and cardiovascular outcomes[4–7]. Combining GLP-1 receptor agonism with glucose-dependent insulinotropic polypeptide (GIP) receptor activation produces synergistic effects on glycemic control and weight loss, as GIP modulates insulin secretion, glucagon release, and lipid metabolism in a complementary manner[8,9]. Tirzepatide, a once-weekly dual GIP/GLP-1 receptor agonist, has demonstrated superior glucose-lowering efficacy compared with insulin degludec, insulin glargine, semaglutide, and dulaglutide in phase 3 trials, establishing the clinical value of this multi-target strategy[10–13].

Despite these advances, important unmet needs persist with currently approved once-weekly GLP-1-based therapies. Real-world data indicated that 30–50% of patients discontinued within the first year, driven in part by the burden of weekly injections, gastrointestinal intolerability, and injection-site reactions. Less frequent dosing regimens have been associated with improved medication persistence and compliance in patients with type 2 diabetes[14,15]. Moreover, injection-site reactions have been reported with various GLP-1 receptor agonists, including tirzepatide[16–18]. These observations underscore the clinical need for agents with extended dosing intervals—such as bi-weekly administration—that could achieve comparable or superior glycemic control while reducing injection frequency, improving gastrointestinal tolerability, and enhancing long-term adherence and outcomes.

Bilpatide (also known as RAY1225) is a novel bi-weekly dual GIP/GLP-1 receptor agonist. Its chemical structure, disclosed in patent WO2022247950A1[19], incorporates unnatural amino acids and a fatty acid side chain that promote albumin binding to prolong half-life, thereby enabling subcutaneous injection once every two weeks. Our preclinical data showed that RAY1225 has a greater affinity to GIP relative to GLP-1 receptors expressed on cells. In a phase 1 clinical trial (NCT05835752) in Chinese healthy and obese adults, RAY1225 demonstrated an acceptable safety and tolerability profile and a long half-life of approximately 10 days. At week 10, obese participants receiving RAY1225 (2/4/6mg) exhibited a reduction in serum insulin from baseline (-4.47 mIU//L) and a greater decrease in HOMA-β (-139.94 vs. -48.33 for placebo), indicating improved insulin sensitivity—a key therapeutic goal in T2D. However, the limited 4-week dosing period in that phase 1 trial did not allow for adequate dose titration, nor was it suitable for exploring higher tolerated doses. Therefore, dose exploration was continued in this phase 2 trial. Here, we report results from SHINING-1, which assessed the efficacy and safety of bilpatide in Chinese patients with type 2 diabetes uncontrolled bylifestyle intervention without or with stable doses of metformin.

Results

Patient disposition and baseline characteristics

Totally 329 participants were assessed for study eligibility, and 234 were randomly assigned to one of the six treatment groups (Fig. 1). One participant in the bilpatide 9 mg group was not treated; thus 233 participants were randomly assigned to receive at least one dose of study drug: bilpatide 3 mg (n = 41), 6 mg (n = 40), 9 mg (n = 40), 12 mg (n = 41), 15 mg (n = 8), or placebo (n = 63). 2 participants without any post-baseline glycated haemoglobin A1c (HbA1c) parameter measurements because of premature discontinuation were excluded from the full analysis set (FAS) population (n = 231). 218 (94%) participants completed the study, and 15 (6%) discontinued before the primary endpoint visit due to withdrawal from the study, rescue therapy, patient decision, or physician decision. 13 (8%) participants in the bilpatide groups and 3 (5%) in the placebo group discontinued the study.

Baseline demographic and clinical characteristics were similar across treatment groups (Table 1). Participants had a mean age of 47.8 years (standard deviation [SD] 9.76), body weight of 80.02 kg (16.66), body-mass index (BMI) of 29.07 kg/m² (4.56), diabetes duration of 4.53 years (4.30), and HbA1c of 8.05% (0.99).

Table 1
Baseline demographics and clinical characteristics

	Bilpatide 3mg	Bilpatide 6mg	Bilpatide 9mg	Bilpatide 12mg	Bilpatide 15mg	Placebo
	(N = 41)	(N = 39)	(N = 40)	(N = 41)	(N = 8)	(N = 62)
Age, years	48.3 (10.44)	47.6 (9.89)	48.7 (10.05)	48.5 (9.97)	42.5 (9.29)	47.2 (9.04)
Sex, n (%)						
Female	15 (36.6%)	21 (53.8%)	18 (45.0%)	17 (41.5%)	0	23 (37.1%)
Male	26 (63.4%)	18 (46.2%)	22 (55.0%)	24 (58.5%)	8 (100%)	39 (62.9%)
Asian race, n (%)	41 (100%)	39 (100%)	40 (100%)	41 (100%)	8 (100%)	62 (100%)
Body weight, kg	79.74 (15.75)	75.91 (15.30)	81.98 (18.01)	81.81 (18.25)	91.78 (21.83)	78.86(14.92)
BMI, kg/m2	28.69 (3.82)	28.22 (4.55)	29.82 (5.15)	29.94 (4.74)	30.43 (4.92)	28.63 (4.43)
Waist circumference, cm	98.95 (9.95)	95.95 (10.42)	100.91(14.33)	101.13(12.41)	103.31(11.92)	97.73 (11.20)
HbA1c, %	8.02 (0.89)	8.12 (1.14)	8.09 (0.81)	7.93 (0.92)	8.09 (0.93)	8.08 (1.12)
HbA1c <8.5%, n(%)	28 (68.3%)	25 (64.1%)	24 (60.0%)	31 (75.6%)	6 (75.0%)	43 (69.4%)
HbA1c ≥8.5%, n(%)	13 (31.7%)	14 (35.9%)	16 (40.0%)	10 (24.4%)	2 (25.0%)	19 (30.6%)
Fasting plasma glucose, mmol/L	9.37 (2.36)	9.16 (2.20)	9.08 (1.89)	9.48 (2.17)	10.78 (2.68)	9.23 (1.86)
Diabetes duration, years	5.48 (4.868)	4.12 (4.078)	5.37 (5.573)	3.74 (3.153)	3.35 (3.055)	4.29 (3.796)
Diabetes mellitus treatment status						
Naïve, n(%)	16 (39.0%)	16 (41.0%)	14 (35.0%)	10 (24.4%)	3 (37.5%)	23 (37.1%)
non-naïve, n (%)	25 (61.0%)	23 (59.0%)	26 (65.0%)	31 (75.6%)	5 (62.5%)	39 (62.9%)
Blood pressure, mmHg						
Systolic	127.2 (10.98)	120.5 (11.00)	122.6 (12.94)	129.0 (10.87)	122.0 (9.55)	121.8 (11.89)
Diastolic	84.5 (7.14)	81.0 (6.25)	82.1 (7.75)	85.8 (8.05)	82.7 (6.77)	82.2 (7.46)
Pulse rate, bpm	76.9 (11.64)	78.6 (11.11)	77.0 (9.67)	80.9 (9.56)	80.0 (9.97)	79.1 (8.35)

Data are mean (SD) or n (%), unless otherwise indicated. N, number of patients who were randomized and received at least one dose of study drug.

Efficacy

At week 24, the bilpatide groups exhibited significant, dose-dependent reductions in HbA1c versus placebo. These reductions were observed as early as week 4, approached maximal effect around week 20, and were sustained through week 24. At the end of treatment, the mean HbA1c level was 6.40% for 3 mg, 6.07% for 6 mg, 5.92% for 9 mg, 5.70% for 12 mg, and 5.34% for 15 mg of bilpatide compared with 7.82% for placebo (Fig. 2A; Table 2). The least squares mean changes from baseline in HbA1c were − 1.66% (95% CI -1.88 to -1.45) with 3 mg, -2.04% (-2.26 to -1.82) with 6 mg, -2.14% (-2.36 to -1.92) with 9 mg, -2.34% (-2.56 to -2.12) with 12 mg, and − 2.76% (-3.25 to -2.26) with 15 mg of bilpatide, compared with − 0.25% (-0.43 to -0.07) in the placebo group (all $p < 0.001$; Fig. 2B; Table 2). These reductions represent clinically meaningful improvements in glycemic control, with doses of 6 mg and higher achieving HbA1c reductions of ≥ 2.0%—a threshold associated with significant risk reduction for diabetes-related microvascular and macrovascular complications. Importantly, the resulting mean HbA1c at week 24 fell to near-normal or normal glycemic ranges across the 6–15 mg doses (5.34% to 6.07%), suggesting substantial glycemic normalization potential. The results of sensitivity analysis using alternative analytical methods were essentially consistent with those of the primary analysis (Sup. Table 1). In both models, all bilpatide groups demonstrated dose-dependent reductions in HbA1c. Subgroup analyses based on the full analysis set showed consistent HbA1c reductions across all bilpatide dose groups compared with placebo at week 24, regardless of baseline HbA1c (< 8.5% or ≥ 8.5%), diabetes duration (≤ 5 years or > 5–10 years), or prior diabetes treatment status (treatment-naive, defined as treated with diet and exercise alone, no prior antidiabetic drug used before screening; or continuous use of antidiabetic drugs for ≤ 1 week within 12 weeks before screening and no further use within 4 weeks before screening; or use of only one oral antidiabetic drug within 12 weeks before screening and no further use within 4 weeks before screening; or treated, defined as stable types and doses of 1–2 antidiabetic agents (including metformin, α-glucosidase inhibitor, or SGLT-2 inhibitor) within 12 weeks before screening) (all $p < 0.05$; Sup. Figure 2).

Table 2
Summary of key endpoints: Change from baseline at 24 weeks for glycemic variables and weight outcomes

	Bilpatide 3mg	Bilpatide 6mg	Bilpatide 9mg	Bilpatide 12mg	Bilpatide 15mg	Placebo
	(N = 41)	(N = 39)	(N = 40)	(N = 41)	(N = 8)	(N = 62)
Glycemic variables						
HbA1c, %						
Week 24	6.40 (0.63)	6.07 (0.88)	5.92 (0.59)	5.70 (0.59)	5.34 (0.37)	7.82 (1.42)
Change from baseline at week 24	-1.66(-1.88,-1.45)	-2.04(-2.26,-1.82)	-2.14(-2.36,-1.92)	-2.34(-2.56,-2.12)	-2.76(-3.25,-2.26)	-0.25(-0.43,-0.07)
Difference vs placebo	-1.41(-1.69,-1.14)	-1.79(-2.07,-1.51)	-1.89(-2.17,-1.61)	-2.09(-2.37,-1.81)	-2.51(-3.03,-1.98)	-
P-value vs. placebo	< .0001	< .0001	< .0001	< .0001	< .0001	-
Patients achieving HbA1c targets at week 24						
< 7%	32 (80)[c]	34 (89.47)[c]	34 (94.44)[c]	38 (95.00)[c]	7 (100)[b]	21 (36.21)
≤ 6.5%	24 (60)[c]	32 (84.21)[c]	32 (88.89)[c]	36 (90.00)[c]	7 (100)[c]	12 (20.69)
≤ 5.7%	3 (7.50)	12 (31.58)[c]	11 (30.56)[c]	22 (55.00)[c]	5 (71.43)[c]	1 (1.72)
< 7% and ≥ 5% weight loss	13 (32.50)	23 (60.53)[c]	21 (58.33)[c]	31 (77.50)[c]	7 (100)[c]	7 (12.07)
Fasting plasma glucose, mmol/L						
Week 24	6.93 (1.81)	6.12 (1.13)	5.85 (1.01)	5.67 (1.04)	4.90 (0.61)	9.06(2.94)
Change from baseline at week 24	-2.40(-2.94,-1.85)[c]	-3.13(-3.69,-2.57)[c]	-3.26(-3.83,-2.69)[c]	-3.65(-4.21,-3.10)[c]	-4.94(-6.28,-3.61)[c]	-0.19(-0.63,0.26)
Weight outcomes						
Body weight, kg						
Week 24	77.62 (16.23)	70.83 (15.51)	76.62 (18.64)	73.63 (17.06)	80.60 (20.10)	77.58 (14.56)
Change from baseline at week 24	-2.42(-3.75,-1.09)	-5.23(-6.58,-3.87)[c]	-5.24(-6.59,-3.88)[c]	-8.36(-9.69,-7.04)[c]	-12.87(-15.91,-9.83)[c]	-1.39(-2.47,-0.31)
Percent change from baseline at week 24	-3.17(-4.41,-1.93)	-7.08(-8.34,-5.82)[c]	-6.53(-7.80,-5.25)[c]	-10.46(-11.70,-9.22)[c]	-14.20(-17.08,-11.32)[c]	-1.69(-2.69,-0.68)
Patients achieving body weight targets at week 24						
≥ 5%, n(%)	15 (37.50)[a]	25 (65.79)[c]	21 (58.33)[c]	32 (80.00)[c]	7 (100)[c]	10 (16.95)
≥ 10%, n(%)	3 (7.50)	12 (31.58)[b]	10 (27.78)[b]	19 (47.50)[c]	6 (85.71)[c]	3 (5.08)
≥ 15%, n(%)	0 (0)	4 (10.53)	1 (2.78)	7 (17.5)[b]	3 (42.86)[c]	0 (0)
Waist circumference, cm						

Data are mean (SD), n (%), or least-squares mean (LSMean) (95% CI), unless otherwise indicated. LSMean (95% CI) for estimated treatment difference versus placebo, predicated from MMRM analysis, with multiple variables as fixed effects. N, number of patients who were randomized and received at least one dose of study drug. [a]p<0.05 versus placebo. [b]p<0.01 versus placebo. [c]p<0.001 versus placebo. Missing data at Week 24. HbA1c data were missing for 8 participants (placebo 4; 3 mg 1; 6 mg 1; 9 mg 4; 12 mg 1; 15 mg 1), and fasting plasma glucose, body weight, waist circumference, and BMI data were missing for 12 participants (placebo 3; 3 mg 1; 6 mg 1; 9 mg 4; 12 mg 1; 15 mg 2).

	Bilpatide 3mg	Bilpatide 6mg	Bilpatide 9mg	Bilpatide 12mg	Bilpatide 15mg	Placebo
	(N = 41)	(N = 39)	(N = 40)	(N = 41)	(N = 8)	(N = 62)
Week 24	95.33 (10.83)	90.41 (11.33)	95.83 (15.43)	92.65 (11.87)	93.56 (11.27)	95.61 (11.14)
Change from baseline at week 24	-3.52(-4.79,-2.25)[c]	-5.67(-6.96,-4.38)[c]	-5.14(-6.43,-3.85)[b]	-8.70(-9.96,-7.44)[c]	-11.12(-14.01,-8.23)[c]	-2.29(-3.32,-1.27)
Waist-to-hip ratio	0.96 (0.06)	0.93 (0.07)	0.96 (0.08)	0.96 (0.06)	0.94 (0.05)	0.96 (0.06)
BMI, kg/m^2						
Week 24	27.79 (4.14)	26.28 (4.26)	27.91 (5.50)	26.90 (4.59)	26.66 (4.12)	28.14 (4.41)
Change from baseline at week 24	-0.90(-1.27,-0.53)	-2.03(-2.41,-1.66)[c]	-1.88(-2.26,-1.50)[c]	-3.11(-3.48,-2.74)[c]	-4.40(-5.25,-3.54)[c]	-0.52(-0.82,-0.22)

Data are mean (SD), n (%), or least-squares mean (LSMean) (95% CI), unless otherwise indicated. LSMean (95% CI) for estimated treatment difference versus placebo, predicated from MMRM analysis, with multiple variables as fixed effects. N, number of patients who were randomized and received at least one dose of study drug. [a]p<0.05 versus placebo. [b]p<0.01 versus placebo. [c]p<0.001 versus placebo. Missing data at Week 24. HbA1c data were missing for 8 participants (placebo 4; 3 mg 1; 6 mg 1; 9 mg 4; 12 mg 1; 15 mg 1), and fasting plasma glucose, body weight, waist circumference, and BMI data were missing for 12 participants (placebo 3; 3 mg 1; 6 mg 1; 9 mg 4; 12 mg 1; 15 mg 2).

A significantly higher proportion of participants receiving any dose of bilpatide achieved HbA1c targets compared with those receiving placebo (Fig. 2C; Table 2). Strikingly, bilpatide demonstrated exceptional HbA1c target attainment: the proportions achieving HbA1c < 7% were 80.0–100.0% across bilpatide doses versus 36.2% with placebo ($p < 0.01$); for HbA1c ≤ 6.5%, rates were 60.0–100.0% versus 20.7% ($p < 0.0001$); and for HbA1c < 5.7%, rates in bilpatide groups (7.5–71.4%) were all significantly higher than placebo (1.7%) except for the 3 mg dose ($p < 0.0001$). The composite endpoint (weight loss ≥ 5% and HbA1c < 7%) was achieved by 32.5–100.0% of bilpatide-treated participants compared with 12.1% for placebo ($p < 0.05$).

At baseline, mean fasting plasma glucose (FPG) values were comparable across treatment groups. At week 24, FPG showed a statistically significant decrease from baseline in all bilpatide group, with least squares mean changes ranging from − 2.40 mmol/L (3 mg) to -4.94 mmol/L (15 mg), versus − 0.19 mmol/L for placebo (all $p < 0.001$; Fig. 2D, 2E; Table 2).

Significant reductions in body weight versus placebo were observed from week 8 onwards, with greater effects in 12 mg and 15 mg after dose escalation at week 12, continuing through week 24 (Fig. 3A; Table 2). At week 24, the least squares mean (LSMean) changes in body weight ranged from − 2.42 kg (-3.17%) with 3 mg to -12.87 kg (-14.20%) with 15 mg of bilpatide, compared with − 1.39 kg (-1.69%) in the placebo group (all $P < 0.001$ vs placebo, except for the 3 mg dose; Fig. 3B; Table 2). Higher-dose groups also showed greater proportions of participants achieving ≥ 5%,≥10%, and ≥ 15% weight loss (Fig. 3C; Table 2). Greater reductions in waist circumference were observed with bilpatide compared with placebo(Fig. 3D; Table 2). Systolic and diastolic blood pressure were reduced with all bilpatide doses, with the most pronounced reduction observed with 15 mg of bilpatide (Sup. Table 2).

All doses of bilpatide significantly reduced triglycerides, total cholesterol, and free fatty acid (FFA) compared with placebo (Fig. 3E; Sup. Table 3). HDL cholesterol remained stable from baseline, while LDL cholesterol and non-HDL cholesterol showed a declining trend, though differences were not statistically significant compared with placebo. Improvements in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), urinary albumin to creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) were also observed in all bilpatide groups (Sup. Table 4).

Safety

The proportion of participants reporting treatment-emergent adverse events (TEAEs) in the bilpatide groups (36 [87.8%] in the 3 mg group, 37 [92.5%] in the 6 mg group, 36 [90.0%] in the 9 mg group, 40 [97.6%] in the 12 mg group, and 8 [100%] in the 15 mg group) was slightly higher than in the placebo group (53 [84.1%]), which was largely driven by the increasing incidence of gastrointestinal adverse events (Table 3). Most TEAEs were mild or moderate in intensity across all treatment groups. The incidence of grade ≥ 3 TEAEs was similar between bilpatide groups and the placebo group (13.5% vs 11.1%). Treatment discontinuation due to TEAEs occurred in 8 participants: 2 (3.2%) in the placebo group, 4 (10.0%) in the bilpatide 9 mg group, and 2 (4.9%) in the bilpatide 12 mg group. 11 (4.8%) participants reported 14 serious adverse events (SAEs). The proportion of participants reporting a serious adverse event was similar between the placebo group (4 [6.3%] of 63) and the bilpatide groups (7 [4.1%] of 170). There were no deaths, no severe hypoglycemia, no pancreatitis, no injection-site reactions, and no thyroid malignancy. The low treatment discontinuation rate due to TEAEs (3.5% in bilpatide groups combined) and the high study completion rate of 94% further underscore the favorable tolerability of bi-weekly bilpatide.

Table 3
Adverse events

	Bilpatide 3mg	Bilpatide 6mg	Bilpatide 9mg	Bilpatide 12mg	Bilpatide 15mg	Placebo
	(N = 41)	(N = 39)	(N = 40)	(N = 41)	(N = 8)	(N = 62)
Summary of adverse events						
TEAE	36 (87.7)	37 (92.5)	36 (90.0)	40 (97.6)	8(100.0)	53 (84.1)
TEAE ≥ Grade 3	2 (4.9)	6 (15.0)	5 (12.1)	9 (22.0)	1(12.5)	7 (11.1)
ADR	24 (58.5)	30 (75.0)	25 (62.5)	29 (70.7)	8 (100.0)	21(33.3)
ADR ≥ Grade 3	1 (2.4)	4 (10.0)	3 (7.5)	4 (9.8)	0	0
SAE	1 (2.4)	0	2 (5.0)	4 (9.8)	0	4 (6.3)
SADR	0	0	1 (2.5)	1 (2.4)	0	0
Death	0	0	0	0	0	0
TEAEs leading to treatment discontinuation	0	0	4(10.0)	2 (4.9)	0	2 (3.2)
TEAEs occurring in ≥5% in any treatment group, by preferred term*						
Lipase increased	10 (24.4)	10 (25.0)	14 (35.0)	14 (34.1)	2 (25.0)	4 (6.3)
Diarrhea	8 (19.5)	14 (35.0)	14 (35.0)	8 (19.5)	4 (50.0)	3 (4.8)
Upper respiratory tract infection	7 (17.1)	7 (17.5)	10 (25.0)	7 (17.1)	1 (12.5)	7 (11.1)
Urinary tract infection	4 (9.8)	7 (17.5)	4 (10.0)	4 (9.8)	0	8 (12.7)
Nausea	3 (7.3)	6 (15.0)	1 (2.5)	8 (19.5)	0	0
Abdominal distension	3 (7.3)	5 (12.5)	5 (12.5)	5 (12.2)	2 (25.0)	1 (1.6)
Vomiting	1 (2.4)	4 (10.0)	3 (7.5)	4 (9.8)	2 (25.0)	1 (1.6)
Decreased appetite	1 (2.4)	4 (10.0)	6 (15.0)	3 (7.3)	0	4 (6.3)
Amylase increased	2 (4.9)	1 (2.5)	4 (10.0)	5 (12.5)	0	0
Sinus tachycardia	2 (4.9)	3 (7.5)	0	5 (12.5)	4 (50.0)	1 (1.6)
Dyspepsia	1 (2.4)	3 (7.5)	1 (2.5)	2 (4.9)	0	0
Upper abdominal pain	1 (2.4)	1 (2.5)	2 (5.0)	0	0	2 (3.2)
Dizziness	2 (4.9)	2 (5.0)	2 (5.0)	1 (2.4)	0	2 (3.2)
AESI						
Injection site reactions	0	0	0	0	0	0
Cholecystitis	0	0	0	0	0	0
Hypersensitivity	0	0	0	0	0	0
Thyroid malignancy	0	0	0	0	0	0
Pancreatitis	0	0	0	0	0	0
Hypoglycemia	2 (4.9)	1 (2.5)	1 (2.5)	4 (9.8)	1(12.5)	0
Grade 1 (plasma glucose ≤ 3.9 mmol/L)	1 (2.4)	1 (2.5)	1 (2.5)	4 (9.8)	1 (12.5)	0
Grade 2 (plasma glucose ≤ 3.0 mmol/L)	1 (2.4)	0	0	0	0	0
Grade 3	0	0	0	0	0	0

Data are n (%) and reflect the safety population. *By the Medical Dictionary for Regulatory Activities (MedDRA; version 28.0) preferred terms. N, number of patients who were randomized and received at least one dose of study drug. TEAE, treatment-emergent adverse event. ARD, adverse drug reaction. SAE, serious adverse event. SARD, serious adverse drug reaction. AESI, adverse events of special interest. Hypoglycemia definitions are provided in the Supplementary Information.

Gastrointestinal events (diarrhea, nausea, abdominal distension, and vomiting) were the most common adverse events, with no clear association with bilpatide dose. The gastrointestinal events generally occurred during dose escalation, were transient, and most were mild to moderate in intensity (Sup. Figure 3). Of the gastrointestinal adverse events reported by ≥ 5% of participants in any treatment group, the most common were diarrhea and nausea (Table 3). Collectively, the incidence of nausea (10.6%) and vomiting (7.7%) with bilpatide was notably lower than the 24–31% and 12–18%, respectively,

reported for once-weekly tirzepatide in the SURPASS programme, suggesting that bi-weekly dosing with lower peak-to-trough pharmacokinetic fluctuations may confer gastrointestinal tolerability advantages.

Overall, 9 participants (5.3%) in the bilpatide treatment group reported hypoglycemia, of which 6 were concurrently receiving metformin. Hypoglycemia episodes with glucose levels ≤ 3.0 mmol/L occurred in one participant in the bilpatide 3 mg group. There were no reports of severe hypoglycemia (Table 3). No hypersensitivity reactions, injection site reactions, pancreatitis, acute cholecystitis, or thyroid malignancy were reported in either treatment group during the study (Table 3). The mean levels of lipase and amylase increased in participants treated with bilpatide, but no pancreatitis was reported (Sup. Table 5). At week 24, participants in the bilpatide groups showed increases in pulse rate ranging from + 1.1 to + 14.0 beats per minute (bpm), while a slight decrease of 0.2 bpm was observed in the placebo group.(Sup. Table 2). Vital signs and additional safety laboratory measures are shown in the Supplementary Information.

The number of patients with anti-drug antibodies ranged from 0 (0%) to 10 (25.0%) across the bilpatide groups (Sup. Table 6). Treatment-emergent anti-drug antibody was observed in 21 participants (12.4%) in the bilpatide groups, with peak titers ranging from 1:10 to 1:320 and no clear dose-dependent trend observed. There was no evidence of diminished effect of bilpatide in HbA1c lowering, bodyweight reduction, incidence of adverse events, or bilpatide pharmacokinetics in participants with anti-drug antibodies.

Discussion

In this phase 2 trial involving Chinese patients with type 2 diabetes, bi-weekly administration of bilpatide over 24 weeks demonstrated clinically meaningful and dose-dependent glycemic control, and improvement in multiple cardiometabolic risk factors including weight loss, with a favorable safety and tolerability profile. The high study completion rate of 94%, substantially exceeding rates reported for once-weekly therapies in comparable trials, supports the feasibility and patient acceptability of bi-weekly dosing in clinical practice. These findings support the further development of this GIP/GLP-1 receptor agonist as a promising bi-weekly therapy for type 2 diabetes and associated metabolic disorders.

We tested a broad dose range of bilpatide with a relatively long 24-week treatment period to assess the effect on glycemic control and body weight. Administration of bilpatide every two weeks led to clinically meaningful, dose-dependent reductions in HbA1c. Statistically significant and clinically relevant improvements in glycemic efficacy were observed across bilpatide doses ranging from 3 mg to 15 mg, compared with placebo, with the greatest glycemic efficacy seen at the bilpatide 15 mg dosage. Notably, these HbA1c reductions translated into exceptional target attainment rates: HbA1c < 7.0% was achieved by up to 100% of participants, HbA1c ≤ 6.5% by up to 100%, and normoglycemia (HbA1c < 5.7%) by up to 71.4%, demonstrating robust glycemic normalization despite only 12 injections over 24 weeks. Approximately half of participants receiving bilpatide 12 mg and three-quarters of those receiving bilpatide 15 mg achieved normoglycemia (HbA1c < 5.7%). These target attainment rates, achieved with half the injection frequency of currently approved therapies, highlight the potential for bi-weekly dosing to deliver comparable or superior glycemic outcomes while substantially reducing treatment burden.

In the SURPASS-AP-Combo trial, once-weekly GIP/GLP-1 dual receptor agonist tirzepatide (5, 10, and 15 mg) reduced HbA1c by 2.24%, 2.44%, and 2.49%, respectively, after 40 weeks of treatment in participants[20]. In comparison, subgroup analyses in our study showed that bilpatide (3–15 mg) lowered HbA1c by 1.33–2.27% after adjusting for the placebo over 24 weeks in treated patients, and by 2.50–3.51% in those with baseline HbA1c ≥ 8.5%.

Bilpatide treatment also led to dose-dependent bodyweight reductions across the tested dose range, with clinically meaningful differences versus placebo. Notably, a substantial proportion of participants on bilpatide achieved clinically relevant weight loss across the 12 mg and 15 mg groups, with 47.5–85.7% losing > 10% and 17.5–42.9% losing > 15% of baseline body weight. Weight loss of 5–10% improves cardiovascular risk factors such as hypertension and dyslipidemia, while more pronounced loss (> 15%) is linked to reduced mortality and additional clinical benefits, including improvements in obstructive sleep apnea and metabolic dysfunction-associated fatty liver disease (MAFLD)[21–24]. In this trial, bilpatide treatment led to modest reductions in both diastolic and systolic blood pressure despite baseline values in the normotensive range, suggesting a favorable antihypertensive effect that might support long-term reductions in microvascular and macrovascular complications. Furthermore, decreases in waist circumference indicated a potential reduction in visceral adipose tissue[25], and bilpatide was also shown to improve multiple cardiometabolic risk factors, including blood lipids (triglycerides, total cholesterol, free fatty acids), liver enzymes (ALT, AST, GGT), and UACR. These findings indicate that bilpatide holds potential for improving long-term outcomes of diabetes-related comorbidities.

As expected, bilpatide was well tolerated at all doses in Chinese participants with T2D treated with or without metformin, including the extension target doses of 9 mg, 12 mg, and 15 mg. No deaths were reported during the trial, and TEAE-related discontinuations were infrequent and comparable between the bilpatide and placebo groups (3.5% [6/170] vs. 3.2% [2/63]). The safety profile of bilpatide was consistent with the GLP-1 receptor agonist class and with findings from the global SURPASS trials[10–13,19,26,27]. The most frequent adverse events were gastrointestinal, predominantly mild and moderate in severity, and occurred mainly during the dose-escalation period. Both the incidence and severity decreased significantly over time, suggesting that slower up-titration and smaller dose increments might improve tolerability.

The safety profile of bilpatide was consistent with the GLP-1 receptor agonist class and with findings from the global SURPASS trials. The most frequent adverse events were gastrointestinal, predominantly mild to moderate in severity, and occurred mainly during the dose-escalation period. When compared with historical external data from the SURPASS-AP-Combo trial (which comprised 83.4% Chinese participants), the incidences of gastrointestinal adverse events with bilpatide were numerically lower for several individual events. Notably, the frequencies of nausea (10.6%) and vomiting (7.7%) in the bilpatide groups were numerically lower than the historical ranges reported for tirzepatide (24–31% and 12–18%, respectively).

However, given the exploratory nature of this cross-trial comparison—which is subject to unmeasured confounding from differences in study populations, titration protocols, and trial conduct—these observations should be considered hypothesis-generating rather than evidence of superior gastrointestinal tolerability. The mechanistic hypothesis that bi-weekly dosing, with lower peak-to-trough fluctuations, may mitigate gastrointestinal symptoms warrants testing in a dedicated head-to-head trial. Both the incidence and severity of gastrointestinal events decreased significantly over time, suggesting that slower up-titration and smaller dose increments might further improve tolerability.

There were no reported cases of severe hypoglycemia. A total of 9 participants in the bilpatide group experienced mild to moderate hypoglycemic events during the 24 weeks, 6 of whom were concomitantly using metformin. These findings suggest that bilpatide does not appear to increase additional hypoglycemic risk in both treatment-naïve and previously treated patients with T2D; however, more data are needed in a phase 3 program to assess the risk of this event.

Elevations in serum lipase and amylase are recognized class effects of GLP-1 receptor agonists, including tirzepatide[28–30]. In this trial, treatment with bilpatide led to mean increases in both lipase and amylase concentrations; however, no cases of acute pancreatitis were reported, and the clinical relevance of these elevations remains unclear. Increases in pulse rate reported in this study were consistent with previous data for GLP-1 receptor agonists[31–33]. The clinical relevance of bilpatide-associated increases in pulse rate is not yet known. Treatment-emergent anti-drug antibodies were frequently observed in participants receiving bilpatide, but titers were mostly low, non-progressive, and not associated with clinical consequences.

Long-term adherence remains a cornerstone of effective type 2 diabetes management. Accumulating evidence indicates that escalating from daily to weekly GLP-1 dosing improves treatment persistence and glycemic control[34], suggesting that further extension to bi-weekly administration may offer incremental benefits. In this study, the treatment discontinuation rate was 7.6%, which is numerically lower than the 12.8% reported in the SURPASS-AP-Combo trial for once-weekly tirzepatide[20]. The absence of injection-site reactions and the low incidence of gastrointestinal events—two common reasons for discontinuation with injectable incretin-based therapies—suggest the hypothesis that bi-weekly dosing may improve long-term adherence. However, because this comparison is indirect and unadjusted, confirmation of a true adherence benefit requires longer-term studies with active comparators.

The study had several limitations.One limitation of this trial is its small sample size, and a large sample size may have provided further insights into the glycemic effects of bilpatide. Secondly, all participants were of Chinese ethnicity, limiting the generalizability of the results to patients of other races or ethnicities. Thirdly, the 24-week treatment duration might limit the ability to fully assess the long-term glycemic and weight-loss potential of bilpatide. Furthermore, the duration of maintenance at the target dose of bilpatide was limited, which resulted in insufficient differentiation between cumulative doses across treatment groups.

In summary, this phase 2 trial established a wide dose range of a bi-weekly GIP/GLP-1 receptor agonist, bilpatide, which showed clinically meaningful and superior HbA1c control with greater weight loss and an acceptable tolerability profile. As the first bi-weekly GIP/GLP-1 co-receptor agonist, bilpatide shows promise as a potential treatment option for patients with type 2 diabetes, addressing a critical unmet need for treatment burden. These results support further evaluation of its efficacy and safety in a larger, longer-term phase 3 program, ideally including direct comparative assessment against once-weekly therapies.

Methods

Study design and participants

SHINING-1 was a multi-center, randomized, double-blind, placebo-controlled phase 2 trial conducted from February 23, 2024 through September 8, 2025 at 31 sites in China. Eligible participants (aged 18-70 years) had type 2 diabetes for at least 12 weeks (HbA1c ≥7.0% and ≤11.0%) and a BMI of ≥20 kg/m² at screening, with stable body weight (change no more than 5%) during the previous 12 weeks before screening. The full list of inclusion and exclusion criteria is provided in the Supplementary Information.

The study was conducted in compliance with local laws, the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference for Harmonisation. The clinical study protocol, the protocol amendments, and the informed consent forms were approved by the ethics committee of each participating hospital. All participants provided written informed consent before study entry. This study is registered on ClinicalTrials.gov, NCT06254274.

Randomization and masking

Eligible participants in both Part A and Part B expansion studies were stratified and randomized by their diabetes treatment status (treatment-naive or treated). In the Part B dose escalation study, block randomization was applied instead. Participants were assigned in a 1:1:1 ratio to two dose groups of bilpatide (3 mg and 6 mg) or a placebo group in Part A, whereas in Part B, they were assigned in a 4:1 ratio across three dose groups of bilpatide (9 mg, 12 mg, and 15 mg) or a placebo group.

The randomization schedule was generated by an unblinded statistician who was not involved in the clinical operations of the study. This was a double-blind study in which participants and investigators were masked to study product allocation. All study products (bilpatide and placebo) were similar in appearance to ensure individuals were masked to the actual treatment. Further details are provided in the Supplementary Information.

Procedures

The study consisted of a 2-week screening period, a 24-week treatment period, and a follow-up period of 4 or 6 weeks after the last dose (Supplementary Information). From the screening period until the end of the study, participants received guidance on a healthy lifestyle. Bilpatide or volume-matched (0.5 mL)placebo was administered subcutaneously once every two weeks, with the dose titrated stepwise from a low starting dose at 4-week intervals until the target maintenance dose was reached. Part A included the bilpatide3 mg, 6 mg, and the placebo group. Part B was a dose-escalation and expansion study using a sequential cohort design in which dosages of 9 mg, 12 mg, and 15 mg were administered sequentially. Each dose cohort of Part B was observed 14 days after dosing, and escalation to the next dose cohort was determined based on tolerability, and followed by a dose-expansion at the established target dosage.

Outcomes

The primary efficacy outcome was the change in HbA1c from baseline to 24 weeks in the (FAS, defined as all participants who received at least one dose of study drug and had both baseline and at least one post-baseline measurement of any outcome.

The secondary efficacy endpoints were: proportion of patients reaching the HbA1c target (≤5.7%, ≤6.5%, and <7.0%) from baseline to 24 weeks; proportion of patients achieving a composite endpoint of HbA1c <7.0% and bodyweight reduction ≥5% at week 24; and change in mean FPG, bodyweight, BMI, waist circumference, waist-to-hip ratio, blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and FFA) and blood pressure (diastolic and systolic) from baseline to 12 and 24 weeks.

Safety and tolerability outcomes included adverse events (AEs), physical examinations, vital signs, laboratory tests, 12-lead ECG, and fundus examination in the safety set (SS), consisting of all participants who received at least one dose of study drug (Supplementary Information). Treatment-emergent adverse events were monitored from day 1 to the safety follow-up period. Adverse events of special interest (AESIs) included hypoglycemia, hypersensitivity reactions, injection site reactions, pancreatitis, acute gallbladder disease, and thyroid malignancy. Immunogenicity was monitored by titers of antidrug antibodies(ADA) and neutralizing antibodies (Nab).

Statistical analysis

As a dose-, no formal hypothesis was established and the sample size was not determined by statistical estimation. However, a preliminary power calculation was performed based on the planned sample size, indicating that 40 participants per group would provide nearly 80% power to detect a difference between the study drug and placebo, assuming a between-group difference in HbA1c reduction of 0.8% and a common standard deviation (SD) of 1.2.

The primary efficacy outcome and other efficacy endpoints were analyzed based on the FAS data. The primary estimand was the change from baseline in HbA1c at week 24, which was analyzed using a mixed model for repeated measures (MMRM). The model included treatment group, visit, treatment-by-visit interaction, and diabetes treatment status (treatment-naive or treated) as fixed effects, with baseline HbA1c included as a continuous covariate. It estimated the least squares mean (LSMean) difference versus placebo along with the two-sided 95% confidence interval (CI) at Week 24. Descriptive statistics for HbA1c at each scheduled visit and change from baseline were summarized using all observed data.

Sensitivity analyses in the FAS included analysis of covariates (ANCOVA) with last observation carried forward (LOCF), multiple imputation (MI), jump-to-reference (J2R) imputation, and the primary MMRM. ANCOVA models included change from baseline in HbA1c as the dependent variable, treatment group and diabetes treatment status as fixed effects, and baseline HbA1c as a covariate; J2R-based results were pooled using Rubin's rule. In prespecified analyses, data after intercurrent events were set to missing and analyzed using MI+ANCOVA or the primary MMRM approach.

For secondary endpoints, categorical variables were summarized by the number and percentage of participants in each category. Continuous secondary parameters (fasting plasma glucose, lipids, body weight, blood pressure, etc.) were analyzed using a method consistent with the primary efficacy analysis. All statistical analyses were performed using SAS (version 9.4).

Role of the funding source

The funder of the study had a role in study design and management, data collection, data analysis, data interpretation, writing of the report, and the decision to submit the manuscript for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declarations

Data availability

The clinical study protocol and statistical analysis plan are provided in the Clinical Protocol and in the Supplementary Information, respectively. Anonymized participant data will be made available after publication on reasonable request directed to li_haijun@raynovent.com. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit.

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Contributors

L.J. conceptualised the study, provided medical insights prior to trial initiation, and contributed to the study design. L.G., N.M., Y.Z., X.H., X.Z., L.Y., C.W., and Y.Z. conducted the clinical trial and participated in data acquisition. H.L. contributed to protocol development and provided medical oversight throughout the trial. H.L. contributed to data analysis and manuscript drafting. L.G. and L.J. participated in data interpretation, manuscript review, and revision. L.J. and H.L. participated in study supervision, final approval of the manuscript, had full access to all study data, and took responsibility for data integrity and analytical accuracy. All authors approved the final version for submission.

Declaration of interests

H.L. is employed by Guangdong Raynovent Biotech Co., Ltd. The remaining authors declare no competing interests.

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Figures

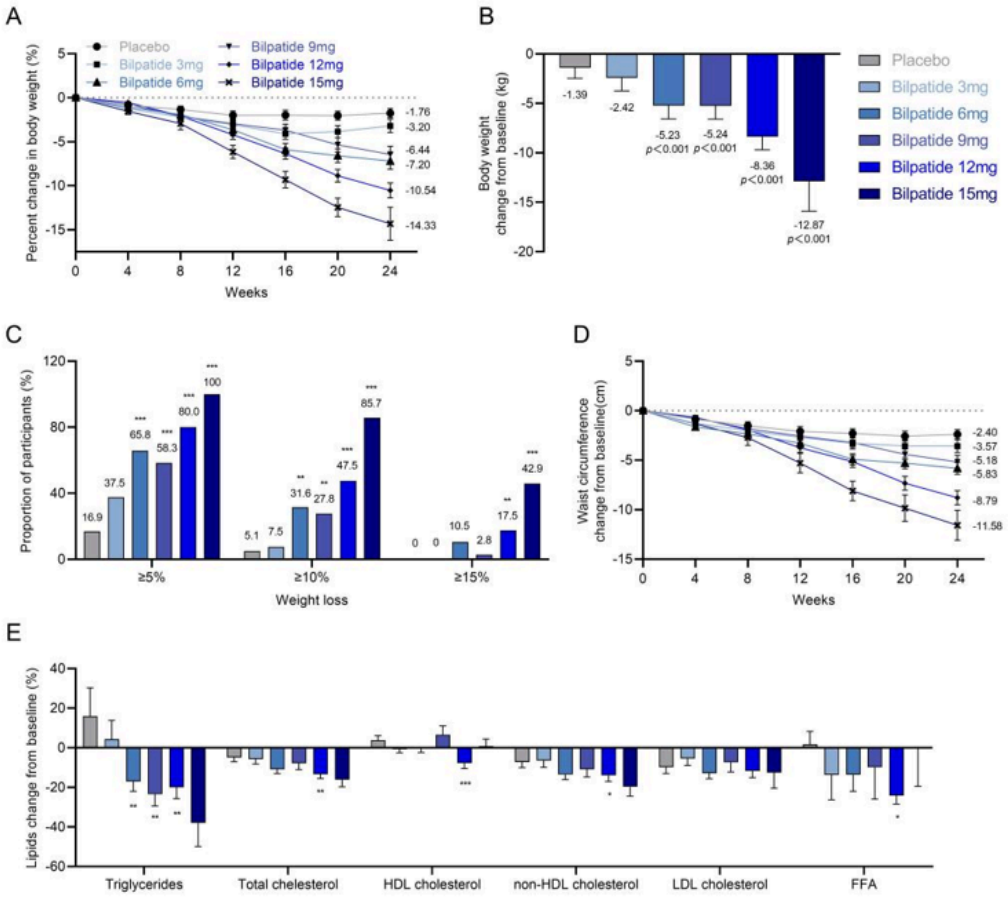


Figure 3

Effect of bilpatide on body weight, weight loss target attainment, waist circumference, and lipid profile

A. LSMean body weight over time. B. LSMean changes in body weight from baseline at 24 week. C. Proportion of participants reaching body weight targets (<7.0%, ≤6.5%, and <5.7%) at week 24. D. LSMean waist circumference values over time. E. Percentage changes in lipid profile from baseline at 24 week. Error bars indicate SE. *p<0.05, **p<0.01, ***p<0.001 vs placebo. Participant numbers were as follows: bilpatide 3mg *n*=41, bilpatide 6mg *n*=39, bilpatide 9mg *n*=40, bilpatide 12mg *n*=41, bilpatide 15mg *n*=8, and placebo *n*=62.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORTchecklist.docx
- Protocol.docx