International Journal of Basic & Clinical Pharmacology
Kumar R et al. Int J Basic Clin Pharmacol. 2025 Jul;14(4):565-582
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20251843

Systematic Review

Addressing cardio-metabolic risks in type 2 diabetes: evidence-based insights on efpeglenatide

Rajesh Kumar, Sunil Kumar Singh*, Shruti Singh, Alok Kumar

Department of Pharmacology, All India Institute of Medical Sciences, Patna, Bihar, India

Received: 15 January 2025
Revised: 17 March 2025
Accepted: 18 June 2025

***Correspondence:**
Dr. Sunil Kumar Singh,
Email: drsunilks@aiimspatna.org

ABSTRACT

Type 2 diabetes (T2D) is a chronic metabolic disorder linked to significant complications, including cardiovascular disease (CVD) and chronic kidney disease (CKD). Efpeglenatide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), has emerged as a promising therapy for addressing glycemic control, weight management, and cardio metabolic risks. A systematic review of randomized controlled trials (RCTs) was conducted using PRISMA guidelines. Searches in PubMed, Google Scholar, and Science Direct identified studies on efpeglenatide impact on T2D outcomes. Data on efficacy, safety, dose-response, and combination with sodium-glucose cotransporter-2 (SGLT2) inhibitors were extracted and analyzed. Out of 843 studies screened, 10 were included. The AMPLITUDE-O trial showed a 27% reduction in major adverse cardiovascular events (MACEs) (hazard ratio [HR]: 0.73, p=0.007) and significant renal benefits (HR: 0.68, p<0.001). Phase 2 trials demonstrated HbA1c reductions (0.6%-1.2%) and weight loss (up to 7.5%). Gastrointestinal side effects were common but mild to moderate, with no major safety concerns. Sub-analyses indicated that combining efpeglenatide with SGLT2 inhibitors did not diminish its efficacy, suggesting potential synergy in reducing cardio metabolic risks. Efpeglenatide demonstrates robust efficacy in glycemic control, weight loss, and reducing cardiovascular and renal risks, with a tolerable safety profile. Its long-acting properties and compatibility with SGLT2 inhibitors support its use in comprehensive, individualized T2D management. Further research is warranted to refine dosing strategies and evaluate long-term outcomes in diverse patient populations.

Keywords: Type 2 diabetes, Efpeglenatide, Glucagon-like peptide-1 receptor agonist, Cardio-metabolic risks

INTRODUCTION

Type 2 diabetes (T2D) is a chronic, multifaceted metabolic disorder characterized by persistent hyperglycaemia due to insulin resistance, impaired insulin secretion or both. The global prevalence of T2D has risen substantially, driven by aging populations, sedentary lifestyles and increasing rates of obesity. Beyond hyperglycemia, T2D is associated with severe complications, including cardiovascular disease (CVD) and chronic kidney disease (CKD), which represent the leading causes of morbidity and mortality in this population. These complications underscore the importance of therapeutic strategies that extend beyond glycemic control to address cardiometabolic and renal risk factors.[1,2] In recent years, two classes of glucose-lowering therapies glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors have gained prominence for their ability to mitigate cardiovascular and renal risks independently of their glucose-lowering effects. GLP-1 RAs, such as efpeglenatide, exert their effects through multiple pathways, including enhancing glucose-dependent insulin secretion, suppressing glucagon release, slowing gastric emptying and promoting satiety. Additionally, these agents have demonstrated significant reductions in major adverse cardiovascular events (MACEs) and modest renal protective effects. SGLT2 inhibitors, by contrast, primarily reduce heart failure and CKD progression,

offering complementary benefits when combined with GLP-1 RAs.[3-5] Efpeglenatide, a long-acting exendin-based GLP-1 RA, has shown substantial promise in addressing the diverse therapeutic needs of patients with T2D. The AMPLITUDE-O trial, a landmark cardiovascular outcomes study, provided robust evidence of the efficacy of efpeglenatide in reducing MACEs, renal composite outcomes and body weight in high-risk T2D patients. The trial also explored the effects of concurrent SGLT2 inhibitor use, revealing no significant interactions that would diminish efpeglenatide's benefits, thereby supporting its use as part of a combination therapy approach. Moreover, efpeglenatide's long half-life facilitates flexible dosing regimens, enhancing adherence and patient convenience, particularly in populations with complex therapeutic needs.[6-11]

Despite these advances, several questions remain unanswered regarding efpeglenatide's role within the broader T2D treatment landscape. Dose-response relationships, long-term safety and efficacy in diverse populations are critical areas requiring further investigation. This systematic review aims to synthesize existing evidence on the clinical efficacy, safety and mechanistic insights of efpeglenatide in T2D. Specifically, it seeks to address the following objectives.

To evaluate the impact of efpeglenatide on cardiovascular, renal and metabolic outcomes in patients with T2D. To analyse the dose-dependent effects of efpeglenatide and identify optimal therapeutic regimens. To examine the safety profile of efpeglenatide, with a focus on gastrointestinal adverse events, pancreatitis and other long-term risks. To explore the potential synergy between efpeglenatide and SGLT2 inhibitors and their combined efficacy in managing T2D.

This review aims to provide a comprehensive understanding of efpeglenatide's therapeutic potential. Additionally, it seeks to identify gaps in the current evidence base and propose directions for future research. Given the increasing complexity of T2D management, insights from this review will inform clinical decision-making and guideline development, ultimately improving patient outcomes.

METHODS

Study setting and design

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

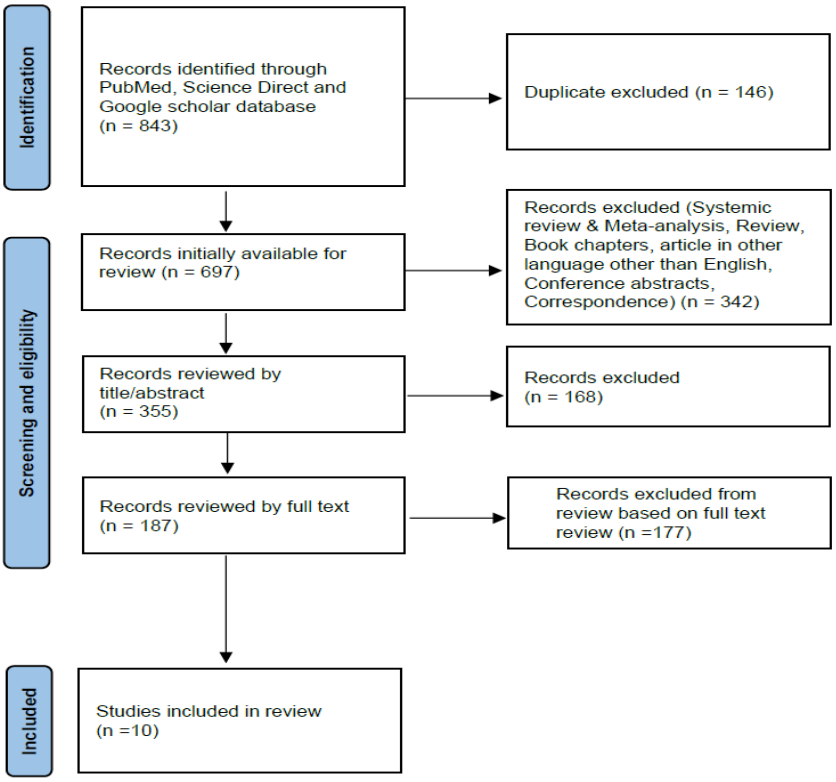

Figure 1: PRISMA flow chart of study selection for systematic review.

Search strategy and study selection

Search strings were developed and run across the electronic databases PubMed, Google Scholar and Science Direct from inception to November 30, 2024. Studies were searched using the keywords "efpeglenatide" OR "GLP-1 Agonist " and "Diabetes".

Table 1: Characteristics of all the included studies.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
1.	Hertzel C. Gerstein et al. 2023 6	NCT03496298; Sub analysis of the AMPLITUDE-O Trial; Randomized, Placebo-controlled, Double-blind trial	People with type 2 diabetes ≥18 years of age with previous coronary artery disease, stroke, or peripheral artery disease, or who were ≥50 years of age (if male) and 55 years of age (if female) with chronic kidney disease and at least one additional cardiovascular risk factor.	Mean baseline glycated haemoglobin was 8.9% (1.5), 31.6% had an eGFR <60 ml/min/1.73 m2, 89.5% had previous CV disease and 15.0% were on an SGLT2 inhibitor.	4 mg (n= 1359) or 6 mg (n= 1358) of efpeglenatide	Placebo (n=1359)	Primary outcome: First occurrence of a MACE Prespecified secondary outcomes: Expanded MACE composite Kidney composite outcome MACE or any death, Composite kidney function outcome	During a median follow-up of 1.8 years, major adverse cardiovascular events (MACE) occurred in 9.2% of placebo recipients, 6.2% of those receiving 6 mg of efpeglenatide (HR 0.65, 95% CI 0.5–0.86; P=0.0027), and 7.7% of those receiving 4 mg (HR 0.82, 95% CI 0.63–1.06; P=0.14). Higher efpeglenatide doses also reduced secondary outcomes, including MACE, coronary revascularization, or unstable angina hospitalization (HR 0.73 for 6 mg, P=0.011). A significant dose-response relationship was observed (P for trend ≤0.018).	Study drug discontinuation due to adverse events occurred in 3.6% of placebo recipients, 5.8% of those receiving 6 mg of efpeglenatide (P=0.0081), and 5.0% receiving 4 mg (P=0.087). Severe gastrointestinal events were more frequent with efpeglenatide (P<0.05), without other significant differences.	Efpeglenatide exhibited dose-dependent cardioprotective effects, improved glycemic control, and reduced body weight, with mild, transient gastrointestinal events and no safety concerns across patient subgroups, including those on SGLT2 inhibitors.
2.	Richard E Pratley el al. 2022 7	NCT02075281; Sub analysis of the BALANCE 205 study; Randomized, placebo-controlled, double-blind, parallel group trial	Patients were required to have a BMI ≥30kg/m2 or a BMI ≥27kg/m2 with comorbidities and fasting plasma glucose (FPG) <126mg/dL.	140 patients pre-diabetes at baseline; Median BMI was 34.9kg/m2; median age was 44 years.	4 mg QW (n=28); 6 mg QW (n=26); 6 mg Q2W (n=32); 8 mg Q2W (n=24)	Placebo (n=30)	Exploratory subgroup analysis: Efficacy and safety of efpeglenatide in patients with pre-diabetes; Changes from baseline to week 21 versus placebo in body weight and waist circumference; Treatment-emergent Adverse events (TEAEs)	In patients with baseline prediabetes, efpeglenatide significantly increased normoglycemia rates (40.6%–64.3%) compared to placebo (10.0%). HbA1c reductions ranged from –0.30% (4 mg QW) to –0.38% (6 mg Q2W) (P<0.0001). Fasting plasma glucose reductions were –7.72 mg/dL (P=0.0221) to –14.06 mg/dL (P=0.0001). Weight loss ranged from –5.61 kg to –7.32 kg (P<0.0001). Significant reductions in waist circumference, total cholesterol, and weight were	efpeglenatide increased treatment-emergent adverse events (TEAEs) (85.7%–96.9%) versus placebo (80.0%), particularly gastrointestinal TEAEs (64.3%–76.9% vs. 40.0%). Serious TEAEs were rare, with none in the placebo or 6 mg Q2W	Efpeglenatide exhibited dose-dependent cardioprotective effects, improved glycemic control, and reduced body weight, with mild, transient gastrointestinal events and no safety concerns across

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
								observed across subgroups (P<0.05).	groups. One non-severe hypoglycemia case occurred (6 mg QW). Common TEAEs included nausea (38.7%–73.3%), vomiting (12.9%–40.0%), and diarrhea (5.6%–43.5%). No pancreatitis was observed, and amylase/lipase elevations were infrequent.	patient subgroups, including those on SGLT2 inhibitors.
3.	Carolyn S.P. Lam et al.2022 8	NCT03496298 Exploratory analysis of the AMPLITUDE-O trial	Prespecified primary analysis pooled the 2 efpeglenatide dose groups (4 and 6 mg) for comparison with placebo of AMPLITUDE-O trial.	618/4076 (15.2%) reported SGLT2 inhibitor use at baseline in AMPLITUDE-O trial	Baseline SGLT2 inhibitors : Efpeglenatide (4 mg or 6 mg)-(412); Placebo-(206)	No baseline SGLT2 inhibitors Efpeglenatide (4 mg or 6 mg)-(2305); Placebo-(1153)	major adverse cardiovascular events (MACEs), expanded MACEs; a renal composite outcome and the composite of MACEs or noncardiovascular death.	The effects of efpeglenatide versus placebo on MACE (HR 0.74 [0.58–0.94] without vs. 0.70 [0.37–1.30] with SGLT2 inhibitors), expanded MACE (0.77 [0.62–0.96] vs. 0.87 [0.51–1.48]), renal outcomes (0.70 [0.59–0.83] vs. 0.52 [0.33–0.83]), and MACE or death (0.74 [0.59–0.93] vs. 0.65 [0.36–1.19]) were unaffected by baseline SGLT2 inhibitor use (P>0.2). Reductions in blood pressure, heart rate, body weight, LDL cholesterol, eGFR, and urinary albumin-to-creatinine ratio were also independent of SGLT2 inhibitor use (P≥0.08). However, HbA1c reduction with efpeglenatide was greater in patients not receiving SGLT2 inhibitors (interaction P=0.014).	The rates of discontinuation due to adverse events, severe gastrointestinal events, and acute renal failure were similarly low regardless of baseline SGLT2 inhibitor use. Efpeglenatide recipients experienced more severe gastrointestinal events than placebo, with event frequency unaffected by concurrent SGLT2 inhibitor use.	Efpeglenatide exhibited dose-dependent cardioprotective effects, improved glycemic control, and reduced body weight, with mild, transient gastrointestinal events and no safety concerns across patient subgroups, including those on SGLT2 inhibitors.

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
4.	Juan Pablo Frias et al. 2029	NCT03353350; AMPLITUDE-M Trial; Multicentre (54 sites in five countries); 56- week, randomized, double-blind, placebo controlled phase 3 trial	Inadequately controlled type 2 diabetes (HbA1c ≥7 and ≤10% [53–86 mmol/mol]) at screening	78.6% and 72.2% of patients completed the 30-week and 56-week treatment periods respectively, on treatment.	Once-weekly efpeglenatide 2mg (n=100) 4mg (n=101) 6 mg (n=103)	Placebo (n=102)	Primary objective: Demonstrate the superiority of efpeglenatide versus placebo for HbA1c reduction at week 30. Safety assessments	At week 30, HbA1c was reduced from 8.1% to 6.9%, 6.6%, and 6.4% with efpeglenatide 2 mg, 4 mg, and 6 mg, respectively. Least squares (LS) mean HbA1c reductions were significantly greater versus placebo for all doses (P<0.0001). At week 56, significant reductions persisted for efpeglenatide 4 mg and 6 mg (P<0.0001). A greater proportion achieved HbA1c <7% at week 30 (P<0.0001), and this effect remained at week 56. Fasting plasma glucose reductions were significantly greater with efpeglenatide 4 mg (-27 mg/dL, P=0.0003) and 6 mg (-35 mg/dL, P<0.0001). Body weight reductions were significant at week 30 for 4 mg (-2.3 kg, P<0.005) and 6 mg (-2.2 kg, P=0.001), with a sustained effect at week 56 for 4 mg (-3.6 kg, P=0.03). Hypoglycemia rates were low across all groups, with severe hypoglycemia reported in one patient (4 mg group). Adverse events of special interest were reported in up to 2.9% of patients, and <9% required specific monitoring.	Gastrointestinal adverse events, primarily diarrhea, nausea, and constipation, were the most frequently reported but were generally transient and mild to moderate. Nausea, vomiting, and diarrhea incidence increased with higher efpeglenatide doses. Hypoglycemia rates remained low across all groups. During the 56-week treatment period, TEAEs occurred in 78.4%–83.8% of efpeglenatide-treated patients versus 77.5% in the placebo group. Serious TEAEs were reported in 9–11% of patients, with no deaths. TEAEs leading to treatment discontinuation were more	Efpeglenatide exhibited dose-dependent cardioprotective effects, improved glycemic control, and reduced body weight, with mild, transient gastrointestinal events and no safety concerns across patient subgroups, including those on SGLT2 inhibitors.

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
									frequent with efpeglenatide (8.8–17.2%) versus placebo (4.9%), primarily due to gastrointestinal events (3.9–13.1% vs. 2.0%). Anti-drug antibody incidence was dose-dependent, ranging from 4.1% (2 mg) to 16.3% (6 mg).	
5.	Marcus Hompesch et al. 2021 10	NCT02059564 Phase Ib study Single center in the USA Randomized, parallel-group, exploratory study	Men and women ≥18and ≤70 years of age who had T2D treated with a stable dose of metformin for≥3 months, alone or in combination with a sulfonylurea	Across groups, mean age ranged from 50.1 to 56.8 years, weight ranged from 77.45 to 98.58 kg, and BMI ranged from 28.93 to 34.28 kg/m2	Cohort A: efpeglenatide 6mg QW (13) on days 1, 8, 15 and 22. Cohorts B: efpeglenatide 16mg QM (13) efpeglenatide dose was escalated from 4 mg on day 1 to 8 mg on day 15 and up to 16 mg on days 29, 57 and 85	Cohort A: Placebo (4) on days 1, 8, 15 and 22. Cohorts B: Placebo (4) with placebo injections on the same study days as efpeglenatide	Gastric emptying was assessed through the pharmacokinetic (PK) profile of acetaminophen at baseline and steady state. Glucose metabolism and beta-cell function were assessed based on mixed-meal tolerance testing and a graded glucose infusion procedure. Safety assessments included incidence and severity of AEs, assessment of injection site, physical examination, vital signs, 12-lead ECG and clinical	At peak concentrations, efpeglenatide 6 mg QW was non-inferior to liraglutide 1.8 mg QD in delaying gastric emptying, as assessed by acetaminophen pharmacokinetics. However, efpeglenatide 16 mg QM did not achieve non-inferiority. Both efpeglenatide regimens demonstrated comparable or superior glucometabolic effects and improved beta-cell function versus liraglutide. Efpeglenatide 6 mg QW and 16 mg QM significantly reduced fasting blood glucose, postprandial glucose, and HbA1c compared to placebo (P<0.05).	In the weekly cohort, adverse events (AEs) occurred in 84.6% (11/13) of participants receiving efpeglenatide 6 mg QW and 50% (2/4) with placebo. In the monthly cohort, AEs were reported in 92.3% (12/13) with efpeglenatide 16 mg QM and 100% (4/4) with placebo. Liraglutide-treated participants reported AEs at a rate of 61.5% (8/13). No serious AEs	Efpeglenatide exhibited dose-dependent cardioprotective effects, improved glycemic control, and reduced body weight, with mild, transient gastrointestinal events and no safety concerns across patient subgroups, including those on SGLT2 inhibitors.

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
						Cohort C: Liraglutide QD on days 1–26.	laboratory abnormalities.		occurred, and only one AE (increased eructation with 16 mg QM) led to discontinuation. Gastrointestinal AEs were mild (6 mg QW) or mild-to-moderate (16 mg QM, liraglutide), transient, and intermittent. Injection site reactions were reported in six participants. No clinically significant changes in vital signs, ECG, or physical examinations were observed.	
6.	Hertzel C. Gerstein et al. 2021 11	NCT03496298 AMPLITUDE-O trial Randomized, placebo-controlled trial Conducted at 344 sites across 28 countries	Persons with type 2 diabetes mellitus and a glycated hemoglobin level greater than 7% were enrolled if they were at least 18 years of age and had a history of cardiovascular disease	Mean (±SD) age of the participants was 64.5±8.2 years; 1344 (33.0%) were female	efpeglenatide 4 mg (n=1359) or 6 mg (n=1358)	Placebo (n=1359)	Primary outcome: First occurrence of a major adverse cardiovascular event Secondary outcomes: Expanded MACE composite outcome A composite renal outcome	During a median follow-up of 1.81 years, MACE occurred in 7.0% of efpeglenatide-treated participants versus 9.2% in the placebo group (HR, 0.73; P=0.007 for superiority). The 4 mg group had an HR of 0.82, while the 6 mg group had an HR of 0.65. Efpeglenatide significantly reduced expanded MACE (HR, 0.79; P=0.02), renal composite outcomes (HR, 0.68; P<0.001), and MACE or noncardiovascular death (HR, 0.73; P=0.004). It lowered	Severe gastrointestinal adverse events were more frequent in efpeglenatide-treated participants than in the placebo group (P=0.009). Reports of constipation, diarrhea, nausea, vomiting, and bloating were	Efpeglenatide lowers the risk of major cardiovascular and renal events in individuals with type 2 diabetes and established cardiovascular or kidney disease.

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
			or if they were at least 50 (if male) or 55 (if female) years of age and had kidney disease and at least one additional cardiovascular risk factor					HbA1c (-1.24%), BMI (-0.9), weight (-2.6 kg), systolic/diastolic BP (-1.5/-0.6 mmHg), pulse pressure (-2.1 mmHg), LDL (-2.7 mg/dL), and urinary albumin-to-creatinine ratio (-21%), while increasing heart rate (+3.9 bpm) and eGFR (+0.9 mL/min/1.73 m²).	also significantly higher with efpeglenatide (P=0.03).	
7.	Stefano Del Prato et al.2020 12	NCT02081118; LIBERATE 204; Phase 2, double-blind, randomized, placebo-controlled, parallel-group, multicentre trial	Eligible patients were aged ≥18 and <75 years, diagnosed with T2D	209 patients were randomized	efpeglenatide 8(n=52), 12(n=52) or 16 (n=53)mg once monthly s.c. prefilled injection .	placebo (n = 50) s.c. prefilled injection	Primary efficacy endpoint: Change in HbA1c from baseline to week 17 (16 weeks of treatment) for efpeglenatide versus placebo. Secondary efficacy endpoints: Percentage of patients with HbA1c <53 mmol/mol (<7%), Change from baseline to week 17 in FPG, mean daily glucose and body weight.; Pharmacokinetic assessments Safety endpoints	Efpeglenatide significantly reduced HbA1c at all doses versus placebo at week 17 (P≤0.0001). More efpeglenatide-treated patients achieved HbA1c <7% (48.7% vs. 30.6%; P=0.0320). Fasting plasma glucose reductions were not statistically significant, but mean daily blood glucose decreased with all doses (P=0.0419–0.0022). Postprandial glucose was significantly reduced with efpeglenatide 12 mg (P<0.05). Efpeglenatide significantly decreased body weight versus placebo (P=0.0312–0.0003). LDL cholesterol increases were smaller with 12 mg and overall groups, while HDL cholesterol, triglycerides, fasting insulin, and C-peptide remained unchanged. Glycated albumin significantly decreased with all doses. Plasma concentrations aligned with drug administration schedules, supporting its expected pharmacokinetic profil	Gastrointestinal disorders were the most common TEAEs, occurring in 77.8% of patients. Treatment-related AEs were reported in 57.3% of efpeglenatide-treated patients and 16.0% of placebo recipients. At least one TEAE occurred in 82.2% of efpeglenatide-treated patients and 64.0% of placebo recipients. Serious TEAEs occurred in 5.1% of efpeglenatide-treated patients and 4.0% of placebo recipients, with	Monthly efpeglenatide, following weekly titration, significantly improves HbA1c and reduces weight compared to placebo in patients with type 2 diabetes.

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
									no deaths reported. Discontinuation rates during the 16-week treatment period were 21%–30% with efpeglenatide and 18% with placebo, primarily due to AEs. No hypoglycemia TEAEs occurred. Injection-site reactions were reported in 3.8%–7.7% of efpeglenatide-treated patients and 4.0% of placebo recipients. Treatment-emergent antibody incidence was low, with no neutralizing antibodies detected in any group	
8.	Kun-Ho Yoon et al. 2020 13	NCT01452451 Two randomized, double-blind, placebo-controlled phase 2 trials	Single-dose study Men and women aged 18 to 75 years, with T2D, (FPG <13.3 mmol/L, HbA1c: 6%–10%) for ≥3	Baseline demographics and characteristics were largely comparable between treatment groups within each study	Single-dose study Eight cohorts Efpeglenatide (n=40) Placebo (n = 8) Repeated-dose study	Single-dose study Placebo (n = 8) Repeated-	Single-dose study Primary objective: Evaluate the safety and tolerability of single, escalating s.c. doses of efpeglenatide in patients with T2D.	Efpeglenatide showed dose-proportional serum concentration increases, with a half-life of 135–180 hours. Peak-to-trough ratios were 1.3–1.4 (weekly) and 5.9–12.9 (monthly). In the single-dose study, glucose reductions lasted ≥3 weeks. In the repeated-dose study,	In the single-dose study, TEAEs occurred in 83% of patients, with GI events most common (56%). Nausea (17%) and vomiting (6%) were	Efpeglenatide demonstrated efficacy and tolerability across dosing regimens, with a stable pharmacokinetic profile

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
			months, and a body mass index ≥25 and ≤40 kg/m2 Repeated-dose study Patients were men and women aged 18 to 65 years with T2D, who were required to be receiving a stable dose of metformin for ≥3 months and have an HbA1c: 7–10%		Six cohorts; Weekly: Efpeglenatide (n=27) Placebo (n = 9) Monthly: Efpeglenatide (n=24) Placebo (n = 8)	dose study Placebo weekly (n=9) Placebo monthly (n=8)	Repeated-dose study Primary objective: Evaluate the safety and tolerability of repeated doses of s.c. efpeglenatide once weekly or once monthly in patients on stable metformin.	HbA1c significantly decreased at day 29 (P≤0.003) and day 57 (P≤0.021) with weekly doses, and at day 57 with 8 mg and 12 mg monthly (P=0.006, P=0.015). More efpeglenatide-treated patients achieved HbA1c <7.0% than placebo. Fasting plasma glucose reductions were significant with 1 mg and 4 mg weekly and 8 mg monthly doses. No significant changes in MMTT glucose AUC0–2h were observed. Body weight significantly decreased at day 57 with 4 mg weekly (-2.63 kg, P=0.029) and at day 78 with 16 mg monthly (-2.82 kg, P=0.031).	reported only with efpeglenatide. Most TEAEs were mild, with no severe events, serious AEs, or study discontinuations. No significant changes in vital signs, labs, ECGs, hypoglycemia, or pancreatitis were observed. In the repeated-dose study, TEAEs were lower with efpeglenatide (68.6%) than placebo (83.3%), primarily GI-related. Nausea (33.3%) and vomiting (17.6%) increased with higher efpeglenatide doses. Most TEAEs were mild to moderate. Severe AEs were rare and unrelated to treatment. No significant changes in lab parameters or vital signs were	enabling flexible dosing. Weekly administration may enhance tolerability, and titration with lower introductory doses could further improve glycemic control in type 2 diabetes.

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
									noted. No treatment-emergent antibodies, hypoglycemia (except one case), or pancreatic injury occurred	
9.	Julio Rosenstock et al. 2019 14	NCT02057172 EXCEED 203 trial Multi center in multi country;	Eligible patients were ≥18 and <75 years of age and had been diagnosed with T2D ≥3 months before screening. .	Total of 254 patients were enrolled and randomized to efpeglenatide (n = 181), placebo (n = 37), and liraglutide (n = 36).	Efpeglenatide 0.3 mg (n = 37) 1 mg (n = 37) 2 mg (n = 33) 3 mg (n = 36) 4 mg (n = 36)	Placebo (n = 37), or Liraglutide (1.8 mg daily; n = 36)	Primary efficacy end point: Change in HbA1c from baseline to week 13 ; Secondary efficacy end points: Percentage of patients achieving HbA1c <7% or ≤6.5% at week 13; Change from baseline to week 13 in FPG Safety assessments	Efpeglenatide significantly reduced HbA1c at doses ≥1 mg from baseline (7.7–8.0%) to week 13 (6.3–6.8%), with greater reductions versus placebo (P<0.05). More efpeglenatide-treated patients achieved HbA1c <7% (70–81%) than placebo (24%), similar to liraglutide (61%). Fasting plasma glucose and postprandial glucose significantly decreased with efpeglenatide 1 mg, 3 mg, and 4 mg (P<0.05). Body weight reductions were significantly greater with efpeglenatide 3 mg (-2.7 kg) and 4 mg (-3.3 kg) versus placebo (-1.3 kg, P<0.05), comparable to liraglutide. LS mean percent weight change was greater with efpeglenatide 4 mg (-3.5%) versus placebo (-1.2%, P<0.05). More efpeglenatide-treated patients (1 mg and 4 mg, 22%) lost >5% body weight versus placebo (5%). Reductions >10% were similar across groups	TEAEs occurred in 51–76% of efpeglenatide-treated patients, 62% with placebo, and 81% with liraglutide. Nausea (20.1%), vomiting (9.5%), and headache (8.9%) were most common with efpeglenatide, peaking at week 1 and subsiding. Injection-site reactions ranged from 0–17% (efpeglenatide), 28% (liraglutide), and 11% (placebo). Three serious AEs and three severe TEAEs were reported, leading to five efpeglenatide and four	Weekly efpeglenatide significantly reduced HbA1c and weight, demonstrating a safety profile consistent with GLP-1 RAs in patients with early type 2 diabetes primarily on metformin monotherapy .

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
									liraglutide discontinuations. No significant changes in vital signs, labs, or ECGs were observed. Mild hypoglycemia occurred in two patients, resolving with carbohydrates. Self-reported hypoglycemia was lower with efpeglenatide (4.5%) versus placebo (8.1%), with no cases in the liraglutide group. Treatment-emergent antibodies were found in 8.4% of efpeglenatide-treated patients, but no neutralizing antibodies were detected.	
10.	Richard E. Pratley et al. 2019 15	NCT02075281; BALANCE Trial; Phase II trial multinational, double-blind, randomized, placebo controlled, parallel-group study	Eligible participants were aged ≥18 y and <65 y at screening and in stable health, with a fasting plasma glucose (FPG) of <7 mmol/L (<126 mg/dL)	A total of 295 participants received the study drug (efpeglenatide overall, n = 235; placebo, n = 60)	Efpeglenatide 4 mg once weekly (59), 6 mg once weekly (59), 6 mg once every 2 wk (59), or 8 mg once every 2 wk (58)	Placebo (60)	Primary endpoint: Body weight change from baseline after 20 wk of treatment Additional endpoints: Percentage of participants with ≥5% or ≥10% of body weight	Efpeglenatide significantly reduced body weight from baseline to week 21 across all doses versus placebo (P<0.0001), with LS mean changes of -6.5 to -7.2 kg and percent reductions of -6.8% to -7.5%. More participants lost ≥5% (45.8%–53.4%) or ≥10% (18.6%–27.1%) of baseline weight than placebo (P<0.0001, P<0.01).	A total of 86.4% of participants experienced at least one TEAE, occurring more frequently with efpeglenatide (88.1%) than placebo (80.0%). Most TEAEs were mild or	Weekly and biweekly efpeglenatide significantly reduced body weight, improved glycemic and lipid profiles, and was well tolerated for weight

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
			and a BMI of ≥30 kg/m2.				reduction from baseline to week 21; Change from baseline in waist circumference; Change in BMI from baseline; Safety assessments	Waist circumference and BMI reductions were significant (P<0.01). Efpeglenatide improved fasting plasma glucose and HbA1c at every visit (P<0.0001). At week 21, total cholesterol, LDL, and VLDL were significantly reduced (P<0.05). Higher doses also significantly lowered HDL (P<0.05). Triglyceride reductions were significant across all doses.	moderate, with gastrointestinal events being the most common (64.4%–83.1% vs. 46.7% placebo), primarily nausea. Severe GI AEs were reported in eight participants. Ten serious TEAEs occurred in six efpeglenatide-treated participants, with four discontinuing treatment. Only severe dehydration and acute renal failure were considered drug-related. No serious TEAEs occurred with placebo. Study discontinuation rates ranged from 5% to 19%. No cardiovascular TEAEs, acute pancreatitis, thyroid cancer, or cerebrovascular events were reported. Symptomatic hypoglycemia	management in adults without diabetes.

Continued.

S. no.	Author	Trial no. / design (duration)	Inclusion criteria	Participants/Study characteristics	Intervention	Control	Outcome/measures	Findings	Adverse effects	Conclusion
									was rare, with no severe cases. Heart rate increased (3.1–5.7 bpm), while significant systolic BP reduction (-6.0 mmHg) was observed in the 6 mg QW group. Elevated amylase and lipase levels occurred without pancreatitis signs. Treatment-emergent antibodies appeared in 21.7% of efpeglenatide-treated participants, but no neutralizing antibodies were detected. Injection-site reactions were reported in both efpeglenatide (8.5%–18.6%) and placebo (21.7%) groups.	

Inclusion criteria

All the studies (randomized controlled trials) published as full-text articles in indexed journals, involving all levels of evidence, which investigated the efpeglenatide intervention all over the world from inception, were included. Only articles published in English with available abstracts were included, with no restriction imposed in terms of the date of publication.

Exclusion criteria

Authors excluded systematic reviews and metanalysis, review articles, observational studies, commentaries and correspondences, expert opinions, letters to the editor, studies on animals, unpublished reports and book chapters.

Data extraction and analysis

Two authors (R.K. and S.K.S.) independently screened the data from the selected studies by reading the abstracts. After excluding non-eligible studies by duplicate studies and exclusion criteria, the full texts of the remaining articles were evaluated for eligibility. To minimize the risk of bias, the authors reviewed and discussed all the selected manuscripts, the references and the articles excluded from the study. Any disagreements were resolved by consensus after consulting with a third author (S.S.). At the end of the process, potentially missed studies were further manually searched for among the reference lists of the included papers.

For each study included in the present review, the following data were extracted: author name, year/period of the report, trial no. design, inclusion criteria, participants/study characteristics, intervention group, control group, outcome/measures, findings, adverse effects and conclusion.

Data synthesis

The study quality and characteristics of interest were tabulated and narratively described.

Ethics

As this is a systematic review using scientific articles available on public platforms, without providing any information related to patients' identities, the ethics committee's review and approval were not required.

RESULTS

Literature search

Based on the eligibility criteria, 843 studies were selected from three databases in the initial research. A total of 697 articles were initially available for review after removing duplicate studies. Of these, 355 articles were selected for review after applying the inclusion and exclusion criteria. Finally, 10 articles were chosen for this systematic review after removing papers based on the evaluation of title/abstract and full text. The PRISMA flow diagram shows the process of study selection (Figure 1). Characteristics of all the included studies are briefly described in Table 1.

Trials findings

Efpeglenatide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has been studied across multiple trials for its efficacy and safety in treating type 2 diabetes (T2D) and associated conditions. This summary covers various studies focusing on cardiovascular, glycemic and weight management outcomes, as well as adverse effects.

Cardiovascular and renal outcomes

AMPLITUDE-O trial

Study design

Randomized, placebo-controlled, double-blind trial involving 4076 participants with T2D, a history of cardiovascular disease or chronic kidney disease.

Findings

Efpeglenatide reduced major adverse cardiovascular events (MACEs) compared to placebo (HR: 0.73, p=0.007). Significant reductions in renal composite outcomes (HR: 0.68, p<0.001) and body weight (mean reduction: 2.6 kg). Adverse effects included gastrointestinal events, leading to higher discontinuation rates compared to placebo.

Conclusion

Efpeglenatide effectively reduced cardiovascular and renal risks, highlighting its potential in high-risk T2D populations.

Glycemic control and weight management

BALANCE and EXCEED trials

Design

Phase 2 trials comparing varying doses of efpeglenatide to placebo and liraglutide in patients with T2D.

Findings

Significant reductions in HbA1c from baseline (0.6% to 1.2%, p<0.05 across doses) and body weight (up to 7.5% reduction). Higher proportions of patients achieved HbA1c targets (<7% and ≤6.5%) compared to placebo. Weight loss effects were comparable to liraglutide. Gastrointestinal

adverse events were common but generally mild and transient.

Conclusion

Efpeglenatide demonstrated strong efficacy in glycemic control and weight reduction with a tolerable safety profile.

AMPLITUDE-M and BALANCE studies (weight loss focus)

Intervention

Weekly or biweekly doses of efpeglenatide.

Findings

Average weight reductions ranged from 6.5 to 7.2 kg, with significant reductions in waist circumference. A higher percentage of participants achieved≥5% and ≥10% weight loss compared to placebo. Improved lipid profiles and glucose metabolism were observed.

Conclusion

Efpeglenatide offers significant benefits in weight management, supporting its use in patients with obesity and T2D.

Exploratory pharmacokinetic and dose-response studies

Studies

Phase 1b and Phase 2 trials examined the pharmacokinetics, pharmacodynamics and safety of escalating doses of efpeglenatide.

Key observations

Dose-proportional increases in serum concentrations and a prolonged half-life, supporting weekly or monthly dosing. Enhanced beta-cell function and delayed gastric emptying. Adverse events were mostly gastrointestinal and dose-dependent but manageable.

Conclusion

Efpeglenatide's pharmacokinetics allow flexible dosing regimens, enhancing patient adherence and outcomes.

Safety and tolerability

Across studies, adverse events (AEs) included nausea, vomiting and diarrhoea, with higher incidence at higher doses. Serious adverse events were rare and no significant risks of hypoglycemia or pancreatitis were identified. Discontinuation rates due to AEs were dose-dependent but aligned with other GLP-1 RAs.

Combined therapy with SGLT2 inhibitors

AMPLITUDE-O sub-analysis

Concurrent use of SGLT2 inhibitors did not significantly alter efpeglenatide's efficacy in reducing MACEs and renal outcomes. Safety profiles were consistent, supporting the combined use of these agents for comprehensive diabetes management.

DISCUSSION

Efpeglenatide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), has emerged as a promising treatment for type 2 diabetes (T2D). Clinical trials have extensively evaluated its efficacy in improving glycemic control, reducing cardiovascular (CV) and renal risks and facilitating weight loss. This discussion synthesizes findings from key studies to explore its clinical utility and implications.

Efpeglenatide demonstrates significant efficacy in glycemic control. Across multiple trials, including the BALANCE and EXCEED studies, reductions in HbA1c ranged from 0.6% to 1.2% compared to placebo ($p<0.05$) and were comparable to liraglutide. Higher proportions of participants achieved HbA1c targets (≤7% and ≤6.5%) with efpeglenatide than with placebo, highlighting its potential in optimizing glycemic management in T2D patients. In addition to glycemic control, efpeglenatide offers considerable benefits in weight management.

Participants in the BALANCE study experienced weight reductions of 6.5 to 7.2 kg over 20 weeks, with significant improvements in waist circumference and body mass index (BMI) compared to placebo ($p<0.0001$). Similar findings were observed in the EXCEED trial, where reductions in body weight and percent change from baseline were significant at higher doses. Weight loss effects were attributed to efpeglenatide's impact on appetite suppression and delayed gastric emptying, making it a valuable option for overweight or obese individuals with T2D.[14,15]

Efpeglenatide's cardiovascular and renal outcomes, as demonstrated in the AMPLITUDE-O trial, are particularly noteworthy. Over a median follow-up of 1.8 years, the trial reported a 27% reduction in major adverse cardiovascular events (MACEs) compared to placebo (hazard ratio (HR): 0.73, $p=0.007$).

Similarly, renal composite outcomes including sustained decreases in estimated glomerular filtration rate (eGFR), renal replacement therapy and macroalbuminuria were significantly reduced (HR: 0.68, $p<0.001$). These benefits extend to broader outcomes, such as reductions in systolic and diastolic blood pressure, LDL cholesterol levels and urinary albumin-to-creatinine ratios. The dose-dependent relationship observed in AMPLITUDE-O underscores the

importance of titration to higher doses for maximizing cardiovascular and renal protection.[6,8]

Efpeglenatide's safety profile aligns with other GLP-1 RAs, with gastrointestinal (GI) adverse events being the most common. Nausea, vomiting and diarrhoea were dose-dependent but generally transient and mild to moderate in severity. Serious adverse events (AEs) were rare and no significant risks of hypoglycaemia or pancreatitis were identified across studies. Discontinuation rates due to AEs were higher in efpeglenatide groups than placebo but comparable to other GLP-1 RAs. Titration regimens and patient education on managing GI symptoms could enhance adherence. Importantly, no new safety signals, such as severe cardiovascular or renal adverse effects, emerged during the trials.[6-9]

Efpeglenatide's pharmacokinetics support flexible dosing regimens. Its prolonged half-life allows for weekly or monthly administration, enhancing patient adherence. The observed dose-proportional increases in serum concentrations and sustained effects on glycemic and weight parameters highlight its potential for individualized treatment strategies. The EXCEED and BALANCE trials demonstrated that efpeglenatide's efficacy and safety profiles remained consistent across different dosing frequencies. This flexibility is particularly beneficial for patients requiring tailored therapy due to lifestyle or comorbid conditions.[10,13-15]

The AMPLITUDE-O trial sub-analysis revealed that concurrent use of sodium-glucose cotransporter-2 (SGLT2) inhibitors did not alter efpeglenatide's efficacy in reducing MACEs and renal outcomes. This finding suggests that combining GLP-1 RAs with SGLT2 inhibitors could provide synergistic benefits, addressing both glycemic control and cardiovascular risks. Such combination therapy could be particularly advantageous in managing patients with complex comorbidities, such as T2D with established cardiovascular disease or chronic kidney disease. Efpeglenatide's independent effects on blood pressure, lipids and renal biomarkers further support its role in comprehensive diabetes care.[6]

Efpeglenatide offers a multi-faceted approach to T2D management, addressing glycemic control, weight reduction and cardiometabolic risks. Its dose-dependent benefits underscore the importance of individualized titration to balance efficacy and tolerability.

The potential for combination therapy with agents like SGLT2 inhibitors broadens its utility in complex cases. However, translating these trial findings into real-world practice requires addressing barriers such as GI side effects, cost and accessibility. Future research should explore strategies to mitigate adverse effects, optimize dosing regimens and assess long-term outcomes beyond the controlled trial setting.

CONCLUSION

Efpeglenatide robust efficacy and favourable safety profile position it as a valuable addition to the T2D treatment landscape. Its ability to address multiple therapeutic goals glycemic control, weight management and cardiometabolic risk reduction makes it a promising candidate for individualized, comprehensive care in T2D patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Pearson-Stuttard J, Bennett J, Cheng YJ, Vamos EP, Cross AJ, Ezzati M, et al. Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. Lancet Diabetes Endocrinol. 2021;9:165–73.
2. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, et al. Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med. 2014; 370:1514–23.
3. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394:121–30.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.
5. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–57.
6. Gerstein HC, Li Z, Ramasundarahettige C, Baek S, Branch KRH, Del Prato S, et al. Exploring the Relationship Between Efpeglenatide Dose and Cardiovascular Outcomes in Type 2 Diabetes: Insights From the AMPLITUDE-O Trial. Circulation. 2023;28(13):1004-13.
7. Pratley RE, Jacob S, Baek S, Trautmann ME, Hompesch M, Han O, et al. Efficacy and safety of efpeglenatide in key patient subgroups from the BALANCE randomized trial, stratified by pre-diabetes status, BMI and age at baseline. BMJ Open Diabetes Res Care. 2022;10(1):2207.
8. Lam CSP, Ramasundarahettige C, Branch KRH, Sattar N, Rosenstock J, Pratley R, et al. Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose cotransporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O Trial. Circulation. 2022;22(8):565-74.
9. Frias JP, Choi J, Rosenstock J, Popescu L, Niemoeller E, Muehlen-Bartmer I, et al. Efficacy and safety of once-weekly efpeglenatide monotherapy versus

placebo in type 2 diabetes: the AMPLITUDE-M randomized controlled trial. Diabetes Care. 2022;7;45(7):1592-600.
10. Hompesch M, Kang J, Han O, Trautmann ME, Sorli CH, Ogbaa I, et al. Effects of efpeglenatide versus liraglutide on gastric emptying, glucose metabolism and beta-cell function in people with type 2 diabetes: an exploratory, randomized phase Ib study. BMJ Open Diabetes Res Care. 2021;9(1):2208.
11. Gerstein HC, Sattar N, Rosenstock J, Ramasundarahettige C, Pratley R, Lopes RD, et al. AMPLITUDE-O trial investigators. cardiovascular and renal outcomes with efpeglenatide in type 2 Diabetes. N Engl J Med. 2021;2;385(10):896-907.
12. Del Prato S, Kang J, Trautmann ME, Stewart J, Sorli CH, Derwahl M, et al. Efficacy and safety of once-monthly efpeglenatide in patients with type 2 diabetes: Results of a phase 2 placebo-controlled, 16-week randomized dose-finding study. Diabetes Obes Metab. 2020;22(7):1176-86.
13. Yoon KH, Kang J, Kwon SC, Trautmann ME, Hompesch M, Stewart J, et al. Pharmacokinetic and dose-finding studies on efpeglenatide in patients with type 2 diabetes. Diabetes Obes Metab. 2020;22(8):1292-301.
14. Rosenstock J, Sorli CH, Trautmann ME, Morales C, Wendisch U, Dailey G, et al. Once-weekly efpeglenatide dose-range effects on glycemic control and body weight in patients with type 2 diabetes on metformin or drug naive, referenced to liraglutide. Diabetes Care. 2019;42(9):1733-41.
15. Pratley RE, Kang J, Trautmann ME, Hompesch M, Han O, Stewart J, et al. Body weight management and safety with efpeglenatide in adults without diabetes: A phase II randomized study. Diabetes Obes Metab. 2019;21(11):2429-39.

Cite this article as: Kumar R, Singh SK, Singh S, Kumar A. Addressing cardio-metabolic risks in type 2 diabetes: evidence-based insights on efpeglenatide. Int J Basic Clin Pharmacol 2025;14:565-82.