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Research progress and future prospects of small-molecule glucagon-like peptide-1 receptor agonists (GLP-1RAs)

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are key agents in the treatment of type 2 diabetes mellitus (T2DM) and obesity. Small-molecule GLP-1RAs offer the advantage of oral administration while demonstrating efficacy comparable to that of peptide drugs. Despite synthetic challenges and solubility issues, compounds such as Pfizer's PF-06882961 (Danuglipron), Eli Lilly's LY3502970 (Orforglipron), and Hengrui Pharma's HRS-7535 have shown potential to reduce glycosylated hemoglobin A1c (HbA1c) levels and body weight in Phase I-II trials, with mild to moderate gastrointestinal adverse effects, suggesting that they may be promising therapeutic options in the future.

Keywords: Type 2 diabetes mellitus, obesity, small-molecule glucagon-like peptide-1 receptor agonists, efficacy, safety

In 2021, the global diabetes prevalence in 20-79-year-olds was estimated to be 10.5% (536.6 million people), projected to rise to 12.2% (783.2 million) by 2045[1], highlighting the expanding market for glucagon-like peptide-1 receptor agonists (GLP-1RAs). Currently, peptide GLP-1RAs dominate the market, with oral semaglutide having completed Phase 3 trials. Additionally, 14 Phase 3 trials are underway, exploring various

monotherapies and combination therapies involving GLP-1RAs. These drugs significantly lower blood glucose, reduce body weight, and decrease cardiovascular risk, and are particularly beneficial for patients with type 2 diabetes mellitus (T2DM) and obesity[2,3].

Injectable GLP-1RAs are associated with gastrointestinal adverse effects and injection dependence, leading to poor patient compliance[4]. Oral semaglutide solves the injection problem, but has limited bioavailability, is not as efficacious or cost-effective as subcutaneous formulations, and may lead to supply shortages. In addition, patients should avoid drinking or eating for 30 min before and after the dose.

In the STEP 2 trial, a significant weight loss (6.2%) and reduction in A1c (1.2%) were achieved with 2.4 mg of semaglutide, compared to placebo, after 68 weeks. The SURMOUNT-2 trial demonstrated that 10 and 15 mg of tirzepatide were more effective than placebo in reducing body weight (9.6% and 11.6%) and A1c (1.55% and 1.57%) after 72 weeks of treatment, with similar adverse effects to those seen with GLP-1 RA analogs[5]. Small-molecule agonists can theoretically replicate all the therapeutic effects of GLP-1 drugs and have the advantages of oral administration without interval between drug intake and meal, high bioavailability, and good stability, but face problems such as synthesis difficulties and poor water solubility, which limit their clinical application[6].

Studies on small-molecule GLP-1RAs, including Pfizer's PF-06882961 (Danuglipron), Eli Lilly's LY3502970 (Orforglipron), and Hengrui's HRS-7535, may differ in efficacy and safety due to different binding modes and sites of action[7].

High-throughput screening (HTS) and structure-activity relationship (SAR) studies have been used to identify and optimize small-molecule GLP-1RAs, resulting in improved efficacy and selectivity, and reduced risk of off-target binding and cardiotoxicity. Danuglipron activates the receptor through specific amino acid interactions and improves the pharmacokinetic profile through optimization[8,9]. Chen *et al.* reported a novel class of 5,6-dihydro-1,2,4-triazine derivatives as potent GLP-1RAs with enhanced cAMP accumulation and drug-like properties, which significantly reduced blood glucose and food intake, providing a promising opportunity for the treatment of T2DM and obesity, providing durable efficacy[10,11].

Danuglipron demonstrated a favorable safety profile and preliminary efficacy in Phase I clinical trials[12], with gastrointestinal reactions being the most common adverse events. After 8 weeks of treatment, glycosylated hemoglobin A1c (HbA1c) decreased by 1.41% and body weight decreased by 1.87 kg[13]. A Phase II trial of Japanese adults with T2DM further confirmed its effectiveness in lowering blood glucose and reducing body weight. After 12 weeks of treatment (200 mg, twice daily), HbA1c decreased by 1.57%, and body weight decreased by 5.38 kg (5.7%)[14]. In patients with T2DM, after 16 weeks of treatment (120 mg, twice daily), HbA1c decreased by 1.16%, and body weight decreased by 4.17 kg[15]. Although small-molecule GLP-1 RAs are slightly less effective than injectable formulations, the development of Danuglipron will focus on a once-daily, extended-release formulation.

Orforglipron demonstrated a favorable safety profile in Phase Ia clinical trials, with gastrointestinal events being the primary adverse reactions. Pharmacokinetic studies showed a half-life of 48.1 to 67.5 h, significant weight loss after 4 weeks of treatment (mean 5.4 kg, $P < 0.05$), decreased fasting glucose, and delayed gastric emptying[16]. In Phase Ib trials involving patients with T2DM, gastrointestinal reactions were the most common adverse reactions, with half-lives ranging from 29 to 49 h at 12 weeks, a 1.5% to 1.8% reduction in HbA1c, and a weight loss of 0.24 to 5.8 kg[17]. A Phase II trial (NCT05048719) demonstrated a 2.10% reduction in HbA1c at 26 weeks and a weight loss of 10.1 kg, and adverse effects were mainly mild to

moderate gastrointestinal reactions[18]. Another Phase II trial (NCT05051579) showed significant weight loss of 9.4% to 14.7% in non-diabetic obese patients at 36 weeks[19]. In two Phase I trials, the half-life ($t_{1/2}$) and median time to maximum concentration (t_{max}) of orforglipron were similar in both fed and fasted conditions, suggesting that orforglipron could be a viable oral therapeutic alternative for individuals with T2DM or obesity[16,20].

HRS-7535 demonstrated favorable safety and pharmacokinetics in the Phase I study with a half-life of 6.48-8.42 h supporting once-daily dosing. A weight loss of 4.38 kg (6.63%) was observed after 4 weeks, leading to entry into the Phase II/III study[21]. In parallel, a trial of HRS-735 in T2DM diabetic nephropathy (NCT06415214) is ongoing.

A summary of clinical trial results of small-molecule GLP-1RAs is provided in Table 1.

There are no cardiovascular outcomes trials (CVOT) on danuglipron, Orforglipron, or others. Danuglipron showed a slight decrease[12] or increase in blood pressure[13] in different studies. A Phase 1b study of Orforglipron reported no cardiovascular events in patients with T2DM over a 4-week period[17], and possible cardiovascular benefits by improving blood pressure and lipid levels[19].

GLP-1RAs have been extensively studied and proven to be effective in ameliorating metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic kidney disease (CKD)[22-24]. For instance, semaglutide significantly reduced liver enzyme levels in MASLD patients and attenuated hepatic steatosis through anti-inflammatory and antioxidant mechanisms[22]. In terms of renal protection, peptide-based GLP-1RAs such as semaglutide have been shown to reduce the risk of major renal disease events [a composite of the onset of kidney failure, at least a 50% reduction in the estimated glomerular filtration rate (eGFR) from baseline, or death from kidney-related or cardiovascular causes] by 24%[23]. In addition, semaglutide reduced the incidence of cardiovascular death/myocardial infarction/stroke by 18% [HR: 0.82 (95%CI: 0.68-0.98); P = .03], with consistent efficacy across eGFR categories and urine albumin/creatinine ratio levels[24]. In addition, there has been much interest in the potential mental health benefits of GLP-1RAs. In a Phase 2, double-blind, randomized, placebo-controlled trial, lixisenatide reduced the progression of motor disability at 1 year in patients with Parkinson's disease compared with placebo[25]. However, larger trials conducted more recently have not confirmed that exenatide improves Parkinson's disease, so further research is needed. Recent studies have also shown that GLP-1RA may prevent cognitive impairment and neurodegenerative diseases such as Alzheimer's disease[26].

In contrast, small-molecule GLP-1RA has emerged as a new therapeutic option, showing similar efficacy to peptide GLP-1RA in early clinical trials[16-19]. Small-molecule GLP-1RAs have potential benefits in the treatment of MASLD, CKD, cardiovascular disease, and mental health. However, peptide GLP-1RAs are more clinically established and their long-term efficacy and safety are well documented. The long-term impact of small-molecule GLP-1RA remains to be confirmed by additional clinical trial data.

In addition, small-molecule GLP-1RAs are less expensive to develop and produce, which may reduce the consumption of healthcare resources in long-term treatment[8-11]. If priced appropriately and included in health insurance, these agents could alleviate the financial burden of patients and improve drug accessibility.

In the Phase 1b study of orforglipron, two participants experienced elevated levels of lipase and amylase on Day 91 (7 days after the last dose of the study drug); the severity was mild or moderate in both cases. Otherwise, no effects on pancreatic or hepatic enzymes were observed, indicating off-target effects of

Table 1. Summary of clinical trial results of small-molecule GLP-1RAs

Drugs	Affiliations	Phase of clinical trials	Subjects	Security results	Effectiveness results
PF-06882961 (Danuglipron)	Pfizer	Phase I[12]	98 patients with T2DM	The most common TEAEs were gastrointestinal (67.6%), including nausea (48.6%), vomiting (43.2%), abdominal discomfort (35.1%), diarrhea (10.8%), and headaches (10.8%), mostly mild to moderate	After 8 weeks, HbA1c was reduced by 1.41% and body weight by 1.87 kg *vs.* placebo
		Phase I[13]	37 patients with T2DM	TEAEs: nausea (49.0%), dyspepsia (32.7%), vomiting (26.5%), diarrhea (24.5%), headache (23.5%), constipation (20.4%)	After 28 days, HbA1c decreased by 0.9%-1.2% *vs.* 0.4%-0.7% in placebo, with weight loss of 2.2-7.2 kg *vs.* 1.7-5.5 kg in the placebo group
		Phase IIa[14]	123 patients with T2DM; 28 obesity without diabetes	TEAEs: nausea (20.0%-47.6%), vomiting (18.2%-40.9%) in patients with T2DM	After 12 weeks of treatment (200 mg, BID), HbA1c decreased by 1.57%, and weight loss was 5.37 kg
		Phase IIb[15]	316 patients with T2DM	TEAEs: nausea (7%-33%), vomiting (0%-25%), diarrhea (4%-18%), with higher rates observed in higher dose groups	After 16 weeks of treatment (120 mg, twice a day), HbA1c decreased by 1.16%, and weight loss was 4.17 kg
LY3502970 (Orforglipron)	Eli Lilly	Phase Ia[16]	12 healthy people	TEAEs: nausea (11% to 22%), constipation (11% to 33%), vomiting (4% to 18%), abdominal discomfort (6% to 13%), and headache (7% to 29%)	After 4 weeks of treatment, weight loss was 5.4 kg in subjects treated with orforglipron compared to the placebo group ($P < 0.05$)
		Phase Ib[17]	68 patients with T2DM	TEAEs: nausea (33.3%-77.8%), vomiting (14.3%-55.6%), diarrhea (0%-22.2%), abdominal discomfort (0%-22.2%)	After 26 weeks of treatment, HbA1c decreased by 1.5% to 1.8%, and weight loss was 0.24 to 5.8 kg
		Phase II[18]	383 patients with T2DM, BMI ≥ 23 kg/m^2	TEAEs: gastrointestinal adverse events of mild to moderate severity (44.1% to 70.4% in the orforglipron group, and 34.0% in the dulaglutide group)	After 26 weeks of treatment, HbA1c decreased by 2.1%, and weight loss was 10.1 kg
		Phase II[19]	272 obesity without T2DM	TEAEs: nausea (37%-58%), vomiting (14% to 32%)	After 36 weeks of treatment, weight loss was 9.4% ~ 14.7%
HRS-7535	Hengrui	Phase I[21]	58 healthy people	TEAEs: nausea (16.7% at 15 mg, 33.3% at 60 mg and 100.0% at 120 mg), vomiting [no participants at 15 or 60 mg, and in 6 (100.0%) at 120 mg]	HRS-7535 [120 mg (30/60/90/120-mg titration scheme)]: after 36 weeks of treatment, weight loss was 4.38 kg (6.63%)

GLP-1RAs: Glucagon-like peptide-1 receptor agonists; TEAEs: treatment emergent adverse events; HbA1c: glycosylated hemoglobin A1c; T2DM: type 2 diabetes mellitus.

orforglipron treatment are unlikely[17]. However, small-molecule GLP-1RAs must undergo a stringent regulatory approval process, including providing sufficient preclinical and clinical data to demonstrate the drug's safety and efficacy. The main constraints of the existing research included geographical imbalances and the limited number of participants in the trials. Small-molecule GLP-1RAs need to conduct head-to-head clinical research with existing GLP-1RAs (such as injectable peptide drugs) to prove their advantages in efficacy, safety, convenience, and cost-effectiveness.

Of the three small-molecule non-peptide GLP-1RAs, Orforglipron is closest to the market based on clinical efficacy and safety data. CVOT results for small-molecule GLP-1RAs are critical for premarket evaluation, and their structural insights and clinical advances may provide new oral therapeutic options without interval between drug intake and meal for T2DM and obesity in the future.

DECLARATIONS

Authors' contributions
Writing - original draft: Tu Y
Writing - revision and editing: Yu H

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Not applicable.

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All authors declared that there are no conflicts of interest.

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