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Orforglipron as a Small-Molecule GLP-1 Receptor Agonist: A New Era of Incretin-Based Oral Therapy?

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ABSTRACT

Introduction: Facing the increasing number of people suffering from obesity, overweight and weight-related comorbidities, the development of medications that support weight loss is crucial. The currently available therapies based on glucagon-like peptide receptor 1 agonists (GLP-1 RAs) and glucose-dependent insulinotropic polypeptide/GLP-1 RAs allow for weight loss of 8-21% [1]. However, a significant factor reducing treatment adherence is

subcutaneous route of administation by injection, as well ass - in the case of oral semaglutide – restrictive dosing requirements: the drug need to be taken at least 30 minutes before the first meal, beverage, or other oral medication in the morning and with no more than 120 ml of plain water [2].

Aim of the study: The purpose of this study is to review the safety and tolerance of orforglipron and to compare it with oral semaglutide based on ACHIEVE-3 clinical trail.

Material and Methods: Review and analysis of randomised clinical trials available on PubMed. We excluded phase 1 trials in analysis of patients with obesity without diabetes mellitus and patients with DM2. Notably, main clinical trials focusing on orforglipron were funded or supported by Eli Lilly and Company.

Conclusions: Orforglipron is definitely promising as a small-molecule GLP-1 receptor agonist. The therapy is effective in body weight reduction and results in a significant, dose-dependent reduction in HbA1c levels. With significant effect on weight loss, cardiometabolic parameters and improvement in glycemic profile, it can be used in combination with a reduced-calorie diet and increased physical activity in adults, as a weight-loss therapy or in patient with type 2 diabetes. However, all of the studies published so far on the innovative molecule of orforglipron were based on limited number of patients, therefore long-term safety, tolerance in a larger population and general long-term impact of orforglipron on health needs extensive studies.

Keywords: *orforglipron, nonpeptide GLP-1 receptor agonists, body weight loss, obesity treatment*

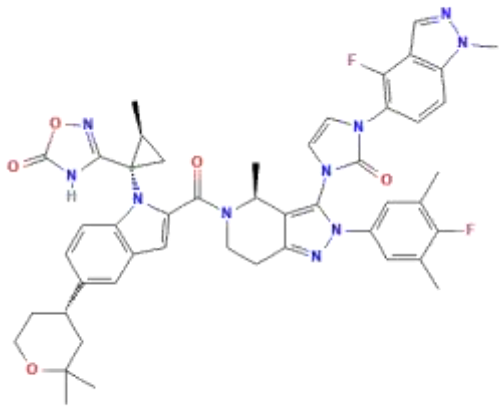
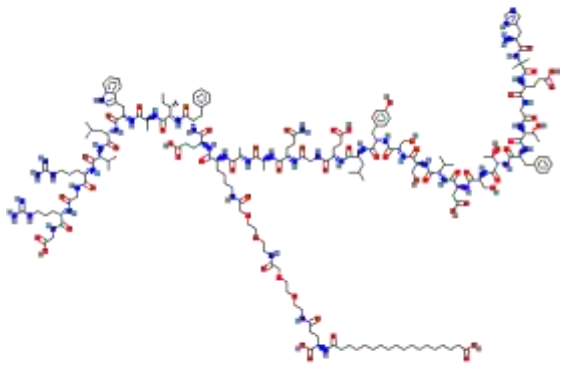
INTRODUCTION

Overweight (BMI ≥ 25 kg/m^2) is currently one of the most serious global health problems affecting 2.5 billion adults, of whom 890 million are obese (BMI ≥ 30 kg/m^2) [3]. It contributes to numerous medical complications, including cardiovascular disease, type 2 diabetes (DM2), osteoarthritis, depression, obstructive sleep apnea, hormonal disorders, and cancer [4,5]. Pharmacological treatment of obesity is currently under intensive development, and new drugs, especially GLP-1 receptor agonists, are showing promising results. However, a major limitation of them is the need to administer the drug by injection or - in the case of oral semaglutide - to take the drug on an empty stomach, with a 30-minute interval between taking the drug and a meal.

Orforglipron is a novel nonpeptide glucagon-like peptide-1 receptor agonist and is produced synthetically. Unlike peptide compounds, which require gastric absorption enhancers, orforglipron can be administered without them [6,7]. In GLP-1-based therapies, nonpeptide

compounds are characterized by improved bioavailability resulting from a significantly smaller molecule size and its distinct molecular structure (Table 1). Although an oral formulation of semaglutide is available, it requires strict dosing conditions and achieves a bioavailability of approximately 0.8% [8]. In contrast, orally administered orforglipron has demonstrated bioavailability ranging from approximately 40% in preclinical studies to up to 79.1% in the ATTAIN-2 study [9].

Orforglipron was approved by the FDA on April 1, 2026, as a drug for adults with obesity or overweight and at least one weight-related comorbid condition, supporting weight loss and long-term weight maintenance through diet and increased physical activity [10]. It is the first new molecular entity (NME) drug introduced to the US market under the Commissioner's National Priority Voucher (CNPV) pilot program, which allowed for its approval and authorization very quickly after submitting the application [11].

orforglipron	semaglutide
	

Tab. 1 Comparison of the molecular size and structure of orforglipron and semaglutide. *(National Center for Biotechnology Information (2026). PubChem Compound Summary for CID 137319706, Orforglipron. Retrieved April 10, 2026 from https://pubchem.ncbi.nlm.nih.gov/compound/Orforglipron & National Center for Biotechnology Information (2026). PubChem Compound Summary for CID 56843331, Semaglutide. Retrieved April 10, 2026 from https://pubchem.ncbi.nlm.nih.gov/compound/Semaglutide.*

REVIEW OF LITERATURE

In the recent literature, orforglipron has been studied for safety, efficacy, and pharmacokinetic and pharmacodynamic parameters. Studies have been conducted in both

animal models and, later, in adult patients. Below, we present the most important findings regarding the effects of orforglipron in both healthy patients and those with DM2 or obesity without DM2. We also detail the only fully completed head-to-head study comparing orforglipron and semaglutide – the ACHIEVE-3 trial.

Clinical trials in healthy volunteers

In 2023 Pratt E. et al. conducted a phase 1a clinical trial involving 92 healthy adults with HbA1c <6.5%. They were recruited to receive single- or multiple-ascending-doses of oral orforglipron. Tolerance, safety, pharmacokinetics, and pharmacodynamics of single and repeated doses of orforglipron were examined. This study demonstrated that both single and multiple doses of orforglipron have safety profile similar to injectable GLP-1 RAs in healthy patients. Due to its long half-life, it can be administered once daily, exhibits dose-dependent pharmacokinetics, and its blood concentrations are characterized by a constant absorption phase [7].

In healthy adults, the drug resulted in a duration- and dose-dependent reduction in body weight and a reduction in both fasting and OGTT glucose levels. The most frequently reported adverse events were gastrointestinal disturbances like nausea, vomiting and constipation.

Clinical trials in patients with obesity without diabetes mellitus

Both clinical trials presented in 2023 (phase 2) and 2025 (phase 3 - ATTAIN-1 study) on broader groups of patients showed that orforglipron therapy was associated with weight loss greater than placebo [12,13]. After 36 weeks of therapy (phase 2) and 72 weeks (phase 3), body weight loss was significantly greater than placebo and was dose-dependent. In addition to changes in body weight, other parameters were assessed, including body mass index, waist circumference, and metabolic risk factors such as blood pressure, non-HDL cholesterol, triglycerides, glycemic parameters, and high-sensitivity C-reactive protein levels. Improvements were noted in all of these parameters. Changes in heart rate were also identified: in ATTAIN-1 trial, mean pulse rate increased from +4.3 to +5.3 beats per minute, while in the phase 2 study, the increase in heart rate at the endpoint (week 36) was from +3.2 to +7.4 beats per minute. Increasing baseline pulse rate had been previously demonstrated with other GLP-1 RAs [14].

Orforglipron therapy was associated with a mean weight loss of -7.5% to -11%, compared with a placebo difference of -2.1%. A weight loss of 10% or more is often used as the

threshold for significant improvement in cardiovascular parameters [15,16,17], and in patients receiving orforglipron for 72 weeks, this target was achieved by 33.3% of patients (6 mg dose) and 54.6% of patients on the 36 mg dose [13]. Two endpoints were established for patients receiving orforglipron for 36 weeks: the first at 26 weeks and the second, at the end of the study after 36 weeks. After 26 weeks, participants were assessed for weight change, and it was estimated that among patients receiving orforglipron, a minimum weight loss of 10% was achieved in 39% of participants (6 mg dose) and 71% of patients (36 mg dose). After 36 weeks of therapy, weight reduction of at least 10% was observed in 46% of the participants who received orforglipron (dose 6 mg) and 75% of individuals on dose 36 mg. It should be noted that during this study, the majority of patients in the group receiving the 36 mg dose exceeded the threshold of at least 10% body weight reduction in both endpoints, and in the group of patients receiving the highest examined dose of the drug, which was 45 mg per day, this threshold was reached by 69% of the subjects at week 36. Although the 36-week study indicated that weight loss had not plateaued [12], the extent of weight reduction at 72 weeks was similar to that observed at 36 weeks. This observation may be partly explained by the greater ethnic diversity of this study population than in the phase II study and a larger percentage of men, who are characterized by a lower treatment response to incretin drug therapy than women [18,19].

In ATTAIN-1 trial no cases of medullary thyroid cancer were observed. In the orforglipron groups seven patients with aminotransferase levels of at least 10 times the upper limit of the normal range (ULN) were reported, compared to one in the placebo group. Additionally two patients with orforglipron had a total bilirubin level of more than two times the ULN and an alanine aminotransferase level of more than three times the ULN. For all mentioned, alternative causes were recognized and were considered not associated with drug-induced liver injury.

In the subgroup in one of the studies body composition was assessed and showed mean body mass reduction in patients on orforglipron therapy of −13.8% in total body fat mass at week 72. In the placebo group the change was –1.7%. Among patients receiving orforglipron, 73.1% of the reduction in body weight was due to fat mass loss, with the remaining 26.9% resulting from loss of lean mass. An, Xuedong et al. in an analysis of studies including 42 664 patients with BMI $\geq$ 25 kg/m^2 concluded that orforglipron demonstrated the most significant effect in the medication efficacy ranking in weight reduction [20].

Clinical trials in patients with type 2 diabetes

In ATTAIN-2 study Horn, Deborah B et al. assessed body weight in patients with DM2 during orforglipron therapy compared to placebo. During this 72-week trial, orforglipron demonstrated statistically significant weight loss and HbA1c reduction compared to placebo as an adjunct to lifestyle modification and had a safety profile similar to other GLP-1 receptor agonist medications [9].

Including criteria for this study were BMI ≥ 27 kg/m^2 in adult patients, HbA1c 7-10% and at least one failed dietery attempt to lose body weight in the past. Participants could have been using up to three oral antihyperglycemic medications, except GLP-1 RAs and DPP-4 inhibitors. The trial was conducted in 10 countries, and the patients were instructed to perform at least 150 minutes of physical activity per week and to maintain a healthy diet. In groups receiving orforglipron, the dose started at 1 mg and gradually increased to the dose assigned to a group of patients (6 mg, 12 mg or 36 mg). After 72 weeks significant reductions in body weight and in HbA1c values were observed. Each dose group achieved a better effect than the placebo group, with greater weight loss compared to baseline at higher doses. Significant changes in glycated hemoglobin were observed, with orforglipron 36 mg achieving HbA1c values below 7% in 75.5% of subjects. Furthermore, improvements were observed in waist circumference, systolic blood pressure, non-HDL cholesterol, and triglycerides. The most frequently reported adverse events were mild-to-moderate gastrointestinal events, especially during the dose-escalation phase. Serious adverse events were reported without significant difference between groups (different doses of orforglipron + placebo). Liver parameters were also assessed in the study, as the development of other small-molecule GLP-1 RAs, including danuglipron and lotiglipron, had been discontinued due to elevated liver enzyme levels [21]. However, no liver safety signals were observed in this study and the reason for hepatotoxicity with danuglipron and lotiglipron remains unclear.

In ACHIEVE-1 study Rosenstock, Julio et al. examined the impact of orforglipron on glycated hemoglobin level in patients with DM2 with no history of diabetic-related drug use in the last 3 months. At baseline, mean glycated hemoglobin level was 8.0%. In all groups of patients receiving orforglipron (3mg, 12mg or 36mg) for 40 weeks HbA1c reduction was superior to that in the placebo group, with a mean value of 6.5-6.7% compared to the change of -0.41 percentage points with placebo. Therapeutic aim of HbA1c < 7% was reached in 68-73% of patients receiving the drug, compared to 33% with placebo. No incidents of severe hypoglycemia were reported during this trial and most

popular side effect were mild-to-moderate gastrointestinals mainly occurring in the dose-escalation period [22].

In a separate study conducted by the same author [23], Rosenstock, Julio et al., analyzed the effect of orforglipron on β-cell function and insulin sensitivity biomarkers and compared it with dulaglutide and placebo. Dulaglutide 1.5 mg subcutaneously at the study endpoint demonstrated a decrease in fasting serum glucose (FSG), as did orforglipron at all doses. From week 4 of the study, FSG was significantly lower in all orforglipron groups compared with placebo, and at week 26, doses of 12 mg and higher resulted in significantly lower FSG values than dulaglutide. HOMA-B index was used to assess β-cell function. It was calculated using two approaches: based on C-peptide concentrations or insulin levels and on fasting serum glucose. HOMA-B increased in the first 4 weeks of the study and then reached a plateau with both orforglipron and dulaglutide. Although the increase in HOMA-B was statistically greater with orforglipron from the 12 mg dose at each time point. Other parameters were also examined, such as proinsulin, proinsulin/insulin, fasting glucagon, insulin-like growth factor binding protein 2 (IGFBP-2), and adipocentin. Statistically significant differences between orforglipron and dulaglutide (1.5 mg s.c.) were noted with superiority of orforglipron for the 45 mg dose in terms of proinsulin, proinsulin/insulin, and IGFBP-2 ratios, for the 36 mg dose in terms of proinsulin/insulin ratio, IGFBP-2, for the 24 mg dose only for IGFBP-2, and for the 12 mg dose in proinsulin/insulin ratio. The study shows that orforglipron in higher doses improves β-cell function greater than dulaglutide treatment at dose 1.5mg s.c. Improvements in insulin sensitivity markers with orforglipron were similar to those observed with dulaglutide. However, it should be noted that the study included only the 1.5 mg dose of dulaglutide, with the 3 mg and 4.5 mg doses not evaluated.

ACHIEVE-3 discussion

ACHIEVE-3 is the first completed phase III study comparing safety and efficacy of oral orforglipron and oral semaglutide in patients with DM2 insufficiently controlled with metformin. This study was perform on adults with type 2 diabetes and HbA1c ranging between 7.0% and 10.5% and included 1698 participants in 5 countries. Participants received either orforflipron or semaglutide once per day starting from lower doses and increasing up to 12mg or 36mg for orforlipron and 7mg or 14mg for semaglutide. The primary objective was to show non-inferiority of orforglipron versus semaglutide for doses 36mg to 14mg and 12mg to 7mg in HbA1c change from baseline. This objective was met and both orforglipron doses revealed superiority to both semaglutide doses, so does also

orforfglipron 12mg to semaglutide 14mg. Mean reduction in HbA1c for orfoglipron 12mg was -1.71%, for orforglipron 36mg -1.91%, for semaglutide 7mg -1.23% and for semaglutide 14mg -1.47%. Higher proportion of patients on orforglipron compared to semaglutide met all targets values of HbA1c at 52 week: less than 7.0%, less than 6.5% and less than 5.7%. Therapeutic target of HbA1c level less than 7.0% was met in 72-76% patients with orforflipron and 54-64% with semaglutide. For participants developing near normoglycemia (HbA1c < 5.7%), which is 21-31% in orforglipron patients and 7-12% in participants with semaglutide, 98-100% of orforglipron groups have not experienced level 2 or 3 hypoglycemia, comparing to 97-100% in semalgutide groups. The difference in the glycemia reduction between the drugs was observed in the fourth week of the study and remained to the end of the trial. Weight reduction was also assesed in this study and orforglipron therapy resulted in higher reduction than semaglutide. For patients with orforglipron 28-43% met therapeutic target of at least 10% body weight reduction and for semaglutide it was 13-21%.

Overall, there were more treatment-emergent adverse event in orforfglipron groups than in semaglutide. The frequency of gastrointestinal adverse events, increase of pulse rate and discontinuation of the study due to gastrointestinal events were higher in orforglipron groups. Gastrointestinal-related adverse events were the most frequent, reported by 58–59% of patients in the orforglipron groups compared with 37–45% in the semaglutide group. Most events were mild to moderate, however, the overall incidence of serious adverse events was higher in the orforglipron 36 mg group than in the other groups. Notably, about half of the patients in this group experienced serious events before escalation to the 36 mg dose [24].

CONCLUSIONS

Orforglipron appears to be a promising medication in the management of obesity, overweight and DM2. It can be considered as an alternative to peptide GLP-1RAs, especially in patients who fear injections or have low compliance. Based on this review we noted several important observations:

- Orforglipron therapy results in a significant, dose-dependent reduction in HbA1c levels and, compared with oral semaglutide, more frequently achieves glycemic targets
- Orforglipron significantly reduces body weight and BMI in patients with obesity, overweight, and/or type 2 diabetes, as well as in healthy subjects
- Orforglipron improves insulin sensitivity and β-cell function in patients with DM2

- Results demonstrated a positive effect on the lipid profile compared to placebo, however the therapy is associated with an increase in pulse rate
- The most common adverse events are gastrointestinal, the majority of which are mild to moderate in severity
- Orforglipron therapy can be effective in achieving ≥10% body weight reduction

The impact of orforglipron has not yet been fully explored. Further studies focusing on cardiovascular risk in patients with atherosclerosis and chronic kidney disease are currently underway and may be crucial for determining more detailed cardiovascular outcomes. Only a limited number of published studies include comparisons of orforglipron with other therapies. The effects of orforglipron therapy require further investigation and additional clinical trials are needed to assess long-term safety, rare adverse events and efficacy in a broader populations.

Disclosure

Author's contribution

Conceptualization, M. Blecharczyk; methodology, I. Zydlewski and A. Zielińska; software, A. Jakimowicz; check, A. Malcher and Z. Kamińska; formal analysis, M. Pacanowska-Trawnicka and M. Mrozek; investigation, M. Pacanowska-Trawnicka; resources, I. Zydlewski; data curation, A. Malcher and A. Jakimowicz; writing - rough preparation, Z. Kamińska; writing - review and editing, M. Mrozek; visualization, A. Zielińska; supervision, M.Blecharczyk; project administration, M. Blecharczyk;

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Conflict of interest

The authors deny any conflict of interest.

REFERENCES

1. Elmaleh-Sachs A, Schwartz JL, Bramante CT, Nicklas JM, Gudzune KA, Jay M. Obesity Management in Adults: A Review. *JAMA*. 2023;330(20):2000-2015. doi:10.1001/jama.2023.19897
2. Novo Nordisk Rybelsus (semaglutide) tablets [prescribing information]. Plainsboro, NJ, Novo Nordisk, 2019
3. World Health Organization. Obesity and Overweight. World Health Organization. Published May 7, 2025. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
4. Solsona-Vilarrasa E, Vousden KH. Obesity, white adipose tissue and cancer. *FEBS J*. 2025;292(9):2189-2207. doi:10.1111/febs.17312
5. Cefalu WT, Bray GA, Home PD, et al. Advances in the Science, Treatment, and Prevention of the Disease of Obesity: Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care*. 2015;38(8):1567-1582. doi:10.2337/dc15-1081
6. Pratt E, Ma X, Liu R, et al. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1b, multicentre, blinded, placebo-controlled, randomized, multiple-ascending-dose study in people with type 2 diabetes. Published online June 1, 2023. doi:https://doi.org/10.1111/dom.15150
7. Pratt E, Ma X, Liu R, et al. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study in healthy participants. Published online June 21, 2023. doi:https://doi.org/10.1111/dom.15184
8. Overgaard RV, Navarria A, Ingwersen SH, Bækdal TA, Kildemoes RJ. Clinical Pharmacokinetics of Oral Semaglutide: Analyses of Data from Clinical Pharmacology Trials. *Clinical Pharmacokinetics*. 2021;60(10):1335-1348. doi:https://doi.org/10.1007/s40262-021-01025-x
9. Horn DB, Ryan DH, Kis SG, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist, for the treatment of obesity in people with type 2 diabetes (ATTAIN-2): a phase 3, double-blind, randomised, multicentre, placebo-controlled trial. *The Lancet*. Published online November 2025. doi:https://doi.org/10.1016/s0140-6736(25)02165-8
10. FDA Approves First New Molecular Entity Under National Priority Voucher Program. U.S. Food and Drug Administration. Published 2026. https://www.fda.gov/news-events/press-announcements/fda-approves-first-new-molecular-entity-under-national-priority-voucher-program

11. Commissioner's National Priority Voucher (CNPV) Pilot Program. U.S. Food and Drug Administration. Published 2026. https://www.fda.gov/industry/commissioners-national-priority-voucher-cnpv-pilot-program
12. Wharton S, Blevins T, Connery L, et al. Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. *N Engl J Med*. 2023;389(10):877-888. doi:10.1056/NEJMoa2302392
13. Wharton S, Aronne LJ, Stefanski A, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment. *N Engl J Med*. 2025;393(18):1796-1806. doi:10.1056/NEJMoa2511774
14. Alkhezi OS, Alahmed AA, Alfayez OM, Alzuman OA, Almutairi AR, Almohammed OA. Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: A network meta-analysis of randomized clinical trials. *Obesity Reviews*. 2022;24(3). doi:https://doi.org/10.1111/obr.13543
15. Brown JD, Buscemi J, Milsom V, Malcolm R, O'Neil PM. Effects on cardiovascular risk factors of weight losses limited to 5–10 %. *Translational Behavioral Medicine*. 2015;6(3):339-346. doi:https://doi.org/10.1007/s13142-015-0353-9
16. Ryan DH, Yockey SR. Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and over. *Current Obesity Reports*. 2017;6(2):187-194. doi:https://doi.org/10.1007/s13679-017-0262-y
17. Look AHEAD Research Group, Gregg EW, Jakicic JM, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2016;4(11):913-921. doi:10.1016/S2213-8587(16)30162-0
18. Yang Y, He L, Han S, et al. Sex Differences in the Efficacy of Glucagon-Like Peptide-1 Receptor Agonists for Weight Reduction: A Systematic Review and Meta-Analysis. *Journal of Diabetes*. 2025;17(3). doi:https://doi.org/10.1111/1753-0407.70063
19. Gasoyan H, Pfoh ER, Schulte R, Le P, Butsch WS, Rothberg MB. One-Year Weight Reduction With Semaglutide or Liraglutide in Clinical Practice. *JAMA Netw Open*. 2024;7(9):e2433326. Published 2024 Sep 3. doi:10.1001/jamanetworkopen.2024.33326

20. An X, Sun W, Wen Z, et al. Comparison of the efficacy and safety of GLP-1 receptor agonists on cardiovascular events and risk factors: A review and network meta-analysis. *Diabetes Obes Metab*. 2025;27(4):1735-1751. doi:10.1111/dom.16228
21. Saldívar-Cerón HI, Vargas-Camacho JA, León-Cabrera S, et al. Oral Small-Molecule GLP-1 Receptor Agonists: Mechanistic Insights and Emerging Therapeutic Strategies. *Scientia Pharmaceutica*. 2025;93(2):26. doi:https://doi.org/10.3390/scipharm93020026
22. Rosenstock J, Hsia S, Nevarez Ruiz L, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes. *N Engl J Med*. 2025;393(11):1065-1076. doi:10.1056/NEJMoa2505669
23. Rosenstock J, Robins DA, Duffin KL, et al. Orforglipron, an oral non-peptide glucagon-like peptide-1 receptor agonist, improves markers of β-cell function and insulin sensitivity in type 2 diabetes. *Diabetes Obes Metab*. 2025;27(11):6314-6322. doi:10.1111/dom.70022
24. Rosenstock J, Yabe D, Cox D, et al. Efficacy and safety of once-daily oral orforglipron compared with oral semaglutide in adults with type 2 diabetes (ACHIEVE-3): a multinational, multicentre, non-inferiority, open-label, randomised, phase 3 trial. *Lancet*. 2026;407(10534):1147-1160. doi:10.1016/S0140-6736(26)00202-3