ORAL GLP-1 RECEPTOR AGONIST (ORFORGLIPRON) IN THE MANAGEMENT OF OBESITY AND TYPE 2 DIABETES

AGONISTA ORAL DE GLP-1 (ORFORGLIPRON) NO MANEJO DA OBESIDADE E DO DIABETES TIPO 2

AGONISTA ORAL DE GLP-1 (ORFORGLIPRON) EN EL TRATAMIENTO DE LA OBESIDAD Y LA DIABETES TIPO 2

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Valéria Goulart Viana[1], Enzo Goulart Viana[2], Viviane Lara Leal[3], Gustavo Ceccatto Andrade[4], Adrieli Tavares Polate[5], Luan Caimar Fuchs[6], Maurício Cavalcante Paixão[7], André Falcão Silva[8], Edermeson Roque Malheiro Brandão[9], Luiz Eduardo Xavier Queiroz[10], Juliano Correia Portela[11], Nayeli Eliana Valles Romani[12], Angelo Coutinho Mazolini[13], Guilherme Diniz Marcelino[14], Isadora Francisco Medeiros[15], Bruno Borges Porto Garcia[16], Sérgio Santos Sell[17], Lívia Francino Oliveira[18], Lia Amaral de Sousa[19], Valmari Felix de Souza[20], Isabela Said Araújo[21], Alancaster Silvério de Assis André[22], Allan Jacques Garcia[23], Felipe Dias Gonçalves[24]

[1] Medical Doctor. Faculdade de Medicina de Itajubá . E-mail: dravaleriagoulart@yahoo.com.br
[2] Medical Doctor. Universidade Paulista. E-mail: enzogoulartviana@outlook.com
[3] Medical Doctor. Universidade Estácio de Sá. E-mail: vivileal360@gmail.com
[4] Medical Doctor. Faculdade Evangélica Mackenzie do Paraná (FEMPAR).
E-mail: gustavoceccatto0@gmail.com
[5] Medical Doctor. FAMINAS. E-mail: atavarespolate@gmail.com
[6] Medical Doctor. Pontifícia Universidade Católica do Paraná (PUCPR). E-mail: drluanfuchs@gmail.com
[7] Medical Doctor. Universidade do Estado do Amazonas. E-mail: mpaixao210720@gmail.com
[8] Postgraduate in Family and Community Medicine. Universidade Federal de Mato Grosso (UFMT).
Universidade Federal do Ceará (UFC). E-mail: andre.f.silva@hotmail.com
[9] Medical Doctor. Universidade Estadual do Sudoeste da Bahia. E-mail: edermesonbrandao@gmail.com
[10] Medical Doctor. Faculdade Pernambucana de Saúde. E-mail: eduardoqueiroz-@hotmail.com
[11] Medical Doctor. Universidad del Valle (UNIVALLE). Universidade Estadual do Maranhão (UEMA).
E-mail: juliano.portela@hotmail.com
[12] Medical Doctor. Universidade do Estado do Amazonas. E-mail: nayeliromani17@gmail.com
[13] Medical Doctor. Centro Universitário do Espírito Santo (UNESC). E-mail: acmazolini@hotmail.com
[14] Medical Doctor. Universidad María Auxiliadora (UMAX). E-mail: guidiiniz12@gmail.com
[15] Medical Doctor. Universidade Internacional Três Fronteiras. E-mail: isadorafmed@gmail.com
[16] Medical Doctor. Centro Universitário IMEPAC. E-mail: brunoborges_pso@hotmail.com
[17] Medical Doctor. Universidade do Oeste de Santa Catarina (UNOESC). E-mail: sergiosellmed@gmail.com
[18] Medical Doctor. Pontifícia Universidade Católica de Minas Gerais (PUC Minas).
E-mail: liviafrancino07@gmail.com
[19] Medical Doctor. Universidade Federal do Pará (UFPA). E-mail: lia.amaralsousa@gmail.com
[20] Physician in Family Health Strategy. Faculdade Morgana Potrich (FAMP). E-mail: felixfarmed@gmail.com
[21] Medical Doctor. Universidade de Uberaba (UNIUBE). E-mail: contato.isabelasaid@gmail.com
[22] Medical Doctor. Universidade Municipal de São Caetano do Sul (USCS).
E-mail: dralancastersilverio@gmail.com
[23] Medical Doctor. Afya. UNIGRANRIO. E-mail: allanjacquesmedico@gmail.com
[24] Medical student. Universidade Federal do Ceará (UFC). E-mail: felipe_dias96@hotmail.com

ABSTRACT
Orforglipron (LY3502970) is the first small-molecule, non-peptidic oral agonist of the glucagon-like peptide-1 (GLP-1) receptor, developed for the treatment of obesity and type 2 diabetes mellitus (T2DM). This study conducted a narrative literature review, of a descriptive and qualitative nature, aiming to compile and critically analyze scientific evidence published between 2015 and 2025 regarding the pharmacology, clinical efficacy, safety, and therapeutic applicability of this agent. The literature search was performed in PubMed, SciELO, ScienceDirect, and ClinicalTrials.gov, using controlled descriptors from the DeCS and MeSH vocabularies. A total of 19 studies, including randomized clinical trials, systematic reviews, and meta-analyses, were included. Findings demonstrated mean reductions in glycated hemoglobin (HbA1c) of 1.3–1.6% and body weight loss of 10–15%, with a favorable safety profile and mild to moderate gastrointestinal effects. Additionally, improvements were observed in cardiometabolic parameters, such as blood pressure, LDL cholesterol, and high-sensitivity C-reactive protein, suggesting a possible indirect cardioprotective effect. In conclusion, Orforglipron represents a significant innovation in metabolic therapy, combining clinical efficacy, dosing convenience, and potential cardiovascular benefit. However, its clinical consolidation will depend on the completion of ongoing phase 3 multicenter trials, which are expected to confirm its effects on long-term clinical outcomes.

Keywords: Orforglipron. GLP-1. Type 2 Diabetes Mellitus. Obesity. Metabolic Therapy.

RESUMO
O Orforglipron (LY3502970) é o primeiro agonista oral do receptor do peptídeo semelhante ao glucagon tipo 1 (GLP-1) desenvolvido na forma não peptídica de molécula pequena, destinado ao tratamento da obesidade e do diabetes mellitus tipo 2 (DM2). Este estudo consistiu em uma revisão narrativa da literatura, de caráter descritivo e qualitativo, com o objetivo de reunir e analisar criticamente as evidências científicas publicadas entre 2015 e 2025 sobre a farmacologia, eficácia clínica, segurança e aplicabilidade terapêutica do fármaco. A busca bibliográfica foi realizada nas bases PubMed, SciELO, ScienceDirect e ClinicalTrials.gov, utilizando descritores controlados dos vocabulários DeCS e MeSH. Foram incluídos 19 estudos, entre ensaios clínicos randomizados, revisões sistemáticas e meta-análises, que demonstraram reduções médias de hemoglobina glicada (HbA1c) entre 1,3% e 1,6% e perda ponderal de 10% a 15%, com perfil de segurança favorável e efeitos gastrointestinais leves a moderados. Além disso, observou-se melhora de parâmetros cardiometabólicos, como pressão arterial, colesterol LDL e proteína C-reativa ultrassensível, indicando possível efeito cardioprotetor indireto. Conclui-se que o Orforglipron representa uma inovação relevante na terapêutica metabólica, ao combinar eficácia clínica, conveniência posológica e potencial benefício cardiovascular. No entanto, sua consolidação clínica dependerá da conclusão dos ensaios multicêntricos de fase 3, que deverão confirmar seus efeitos em desfechos clínicos de longo prazo.

Palavras-chave: Orforglipron. GLP-1. Diabetes Mellitus Tipo 2. Obesidade. Terapêutica Metabólica.

RESUMEN
Orforglipron (LY3502970) es el primer agonista oral del receptor del péptido similar al glucagón-1 (GLP-1) desarrollado en forma de molécula pequeña no peptídica, indicado para el tratamiento de la obesidad y la diabetes mellitus tipo 2 (DM2). Este estudio consistió en una revisión bibliográfica narrativa, descriptiva y cualitativa, cuyo objetivo fue recopilar y analizar críticamente la evidencia científica publicada entre 2015 y 2025 sobre la farmacología, la eficacia clínica, la seguridad y la aplicabilidad terapéutica del fármaco. La búsqueda bibliográfica se realizó en las bases de datos PubMed, SciELO, ScienceDirect y ClinicalTrials.gov, utilizando descriptores controlados de los vocabularios DeCS y MeSH. Se

incluyeron diecinueve estudios, que abarcaban ensayos clínicos aleatorizados, revisiones sistemáticas y metaanálisis, que demostraron reducciones medias de la hemoglobina glucosilada (HbA1c) de entre el 1,3 % y el 1,6 % y una pérdida de peso del 10 % al 15 %, con un perfil de seguridad favorable y efectos gastrointestinales de leves a moderados. Además, se observaron mejoras en parámetros cardiometabólicos como la presión arterial, el colesterol LDL y la proteína C reactiva de alta sensibilidad, lo que indica un posible efecto cardioprotector indirecto. Se concluye que Orforglipron representa una innovación relevante en la terapia metabólica, que combina eficacia clínica, conveniencia de dosificación y un posible beneficio cardiovascular. Sin embargo, su consolidación clínica dependerá de la finalización de ensayos multicéntricos de fase 3, que deberían confirmar sus efectos en los resultados clínicos a largo plazo.

Palabras clave: Orforglipron. GLP-1. Diabetes Mellitus Tipo 2. Obesidad. Terapia Metabólica.

1 INTRODUCTION

Obesity is a chronic, multifactorial condition with a high prevalence worldwide, characterized by the excessive accumulation of adipose tissue and associated with significant metabolic and inflammatory changes. This condition is one of the main risk factors for the development of type 2 diabetes mellitus (DM2), dyslipidemia, high blood pressure, and cardiovascular diseases (CVD). The scientific literature recognizes that excess body fat, especially visceral, contributes to a chronic low-grade inflammatory state, insulin resistance, and increased vascular stiffness, factors directly implicated in the genesis and progression of cardiometabolic complications (ALFARIS et al., 2024; NACHAWI; RAO; MAKIN, 2022).

In recent decades, the pharmacological management of obesity and T2DM has evolved with the development of incretin-based therapies, particularly glucagon-like peptide receptor agonists These agents have demonstrated significant efficacy in improving glycemic control, reducing body weight, and cardiovascular protection, becoming pillars of modern treatment of these diseases (MAHAPATRA; KARUPPASAMY; SAHOO, 2022; GOGINENI et al., 2024). However, most GLP-1RAs formulations available until recently require subcutaneous administration, which can negatively impact treatment adherence and acceptability among patients (MA et al., 2024).

Faced with this limitation, innovative oral formulations have emerged, such as **Orforglipron**, a non-peptide GLP-1 receptor agonist developed for once-daily oral administration. The drug has high bioavailability (about 79%) and does not require fasting or dietary restrictions, differing from peptide formulations such as oral semaglutide (MORSE et al., 2025; MA et al., 2024). Phase 2 and 3 clinical trials have shown that orforglipron promotes average reductions of 1.3 to 1.6% in HbA1c levels and weight loss of up to 15% at 36 weeks, with a safety profile comparable to injectable agonists and predominantly mild gastrointestinal adverse effects (IDRIS, 2023; DUTTA et al., 2024).

In addition to glycemic and weight benefits, recent studies indicate that orforglypron may exert indirect cardioprotective effects, with significant improvement in cardiovascular risk markers, including blood pressure, LDL cholesterol, triglycerides, and high-sensitivity C-reactive protein (WHARTON et al., 2025). These results reinforce the potential of orforglypron as an effective and convenient alternative for the integrated management of metabolic syndrome, combining metabolic, cardiovascular and therapeutic adherence benefits. Even so, the current literature on the clinical use of orforglipron remains limited, and there are few reviews that gather and critically analyze the evidence on its efficacy and safety compared to other GLP-1 agonists (GOGINENI et al., 2024).

Thus, the present study is justified by the need to systematize and critically discuss the available scientific knowledge on the **oral GLP-1 agonist Orforglipron** in the management of obesity and type 2 diabetes, identifying convergences, divergences and gaps in the contemporary literature. The objective of this work is **to analyze, describe and synthesize the scientific evidence published between 2015 and 2025** on the efficacy, safety and clinical applicability of orforglipron, contributing to the improvement of clinical practice and the development of evidence-based therapeutic protocols.

2 METHODOLOGY

The present study is a narrative literature review, of a descriptive and analytical nature, which aimed to gather, analyze and critically discuss the available scientific evidence on the use of the oral glucagon-like peptide receptor agonist type 1 (Orforglipron) in the management of obesity and type 2 diabetes mellitus (DM2).

The narrative review is characterized by allowing a broad and interpretative analysis of the current state of knowledge on a given topic, enabling the identification of gaps, advances and future perspectives in the field of study (ROTHER, 2007). This type of review was chosen due to the emerging nature of the topic, since Orforglipron is a drug in recent clinical development, with publications concentrated in recent years.

The bibliographic search was carried out between November and December 2025, in the following recognized scientific databases: PubMed (National Library of Medicine), SciELO (Scientific Electronic Library Online), ScienceDirect, and ClinicalTrials.gov. The last search was completed on December 20, 2025. Controlled descriptors from the DeCS (Health Sciences Descriptors) and MeSH (Medical Subject Headings) vocabularies were used, combined using Boolean operators AND and OR, with the following search expressions: ("Orforglipron" OR "LY3502970") AND ("GLP-1 receptor agonist" OR "glucagon-like peptide-1") AND ("obesity" OR "type 2 diabetes" OR "T2DM") AND ("oral" OR "small molecule").

The inclusion criteria included: articles published between 2015 and 2025, available in full text, written in English, Portuguese, or Spanish, and that directly addressed the pharmacology, clinical efficacy, safety, pharmacokinetics, or cardiovascular outcomes related to Orforglipron. Randomized clinical trials, systematic reviews, meta-analyses, and narrative reviews of proven scientific relevance were considered.

Studies with animal models, *in vitro research*, case reports, congress abstracts without complete publication, and duplicate articles between databases were excluded. The study selection process was conducted in three stages: (1) reading of titles and abstracts for initial

screening; (2) full reading of the selected texts; and (3) eligibility assessment according to the defined criteria.

Initially, 87 articles were identified in the searched databases. After screening the titles and abstracts, 49 articles were considered potentially relevant. Of these, 30 were excluded because they did not meet the inclusion criteria, resulting in 19 studies selected to compose the final sample analyzed in this review.

The data obtained were systematized in a spreadsheet prepared in Microsoft Excel® 365, covering the following variables: authors, year of publication, country of origin, methodological design, sample size and profile, interventions evaluated, main results and conclusions. The analysis was conducted in a critical and integrative manner, allowing the identification of patterns, divergences, and gaps between studies regarding the therapeutic efficacy, safety profile, and clinical applicability of Orforglipron in the management of obesity and type 2 diabetes mellitus.

The results were organized into comparative tables and tables, which summarize the main evidence found and facilitate the global understanding of the current scientific landscape. This approach allowed for a structured and interpretative discussion of the information, favoring the analysis of the trends and limitations observed in the included studies.

As this is a bibliographic-based documentary research, prepared from scientific studies already published in indexed databases, there was no need to submit it to the Research Ethics Committee, as established by Resolution No. 510/2016 of the National Health Council, which exempts this type of study from ethical appreciation.

Among the limitations of this study, the scarcity of available publications on Orforglipron stands out, since it is a drug in an advanced stage of clinical development. In addition, the methodological heterogeneity among the included studies, with different designs and sample populations, may limit the direct comparison of results. Such factors must be considered in the interpretation of the evidence presented.

3 RESULTS AND DISCUSSION

The analysis of the 19 studies included in this review demonstrated a growing scientific interest in the development of oral GLP-1 receptor agonists, especially after the advances made with Orforglipron, the first non-peptide compound of this class. Most of the publications were concentrated between 2023 and 2025, a period corresponding to phase 2 and 3 clinical trials conducted by Eli Lilly and Company. These studies comprehensively addressed the pharmacological aspects, clinical efficacy, safety, pharmacokinetics, and cardiometabolic

impact of Orforglipron, highlighting its potential as one of the main therapeutic innovations in the management of obesity and type 2 diabetes (DUTTA et al., 2024; MA et al., 2024; WHARTON et al., 2025).

The randomized controlled trials reviewed indicated that Orforglipron promoted a mean reduction in glycated hemoglobin (HbA1c) between 1.3% and 1.6% and a loss of body weight between 10% and 15% after 36 to 48 weeks of treatment. These results are comparable to or superior to those observed with oral semaglutide (10–12%) and subcutaneous liraglutide (8–10%), both of which are widely used in clinical practice (IDRIS, 2023; DUTTA et al., 2024; GOGINENI et al., 2024). Efficacy has been demonstrated in both individuals with type 2 diabetes and people with obesity without diabetes, reinforcing the pathophysiological role of GLP-1 in metabolic regulation and energy homeostasis.

From a pharmacological point of view, Orforglipron stands out for being the first small-molecule, non-peptide GLP-1 agonist developed for oral use, eliminating the need for subcutaneous injections. Pharmacokinetic studies have pointed to mean bioavailability of 79% and a half-life of 24 hours, which allows for once-daily administration without dietary restrictions, in contrast to oral semaglutide, which requires prolonged fasting (MA et al., 2024; MORSE et al., 2025). These characteristics represent an important advance in terms of adherence and therapeutic convenience, especially for patients with aversion to injectables or who have low adherence to complex regimens.

Regarding the safety profile, the most frequent adverse events were nausea, diarrhea, and reduced appetite, which were usually mild and self-limiting. The incidence of these effects was similar to that of other GLP-1 agonists, and there were no reports of serious events attributed to the use of Orforglypron (IDRIS, 2023; DUTTA et al., 2024). Intermediate cardiovascular safety studies have also not identified an increased risk of major cardiovascular events (MACE), such as myocardial infarction or stroke (WHARTON et al., 2025).

From the cardiometabolic point of view, a significant reduction in systolic blood pressure (mean of -5.6 mmHg), LDL cholesterol (-10.4%) and ultrasensitive C-reactive protein (-18%) was observed, suggesting an indirect cardioprotective effect (WHARTON et al., 2025). These findings are consistent with the already consolidated benefits for injectable GLP-1 agonists, such as liraglutide and semaglutide, reinforcing that Orforglypron can replicate such effects with greater practicality of use (DUTTA et al., 2024; GOGINENI et al., 2024).

Regarding tolerability and adherence, studies have indicated average adherence rates above 85%, a value significantly higher than that reported for injectable formulations (MA et

al., 2024). The convenience of the oral route associated with sustained efficacy contributes to the improvement of therapeutic engagement, an essential factor for long-term glycemic and weight control.

3.1 PHARMACOLOGICAL ADVANCES AND THERAPEUTIC RELEVANCE OF ORFORGLYPRON

The results of this review confirm Orforglipron as a milestone in modern metabolic pharmacotherapy, ushering in a new generation of oral, non-peptide, small-molecule GLP-1 agonists. Unlike injectable analogues, this formulation represents a significant advance in eliminating logistical and psychological barriers that often compromise therapeutic adherence, such as the need for refrigeration, syringe manipulation, and needle phobia (MA; MORSE, 2024; WHARTON et al., 2025).

The impact of this innovation transcends pharmacology: it expands global therapeutic access, especially in public health systems in developing countries, where infrastructure for injectable drugs is limited. Thus, Orforglipron not only represents a technological advance, but also a health equity response in the management of obesity and type 2 diabetes mellitus (T2DM).

3.2 CLINICAL EFFICACY AND PATHOPHYSIOLOGICAL MECHANISMS INVOLVED

The reviewed studies demonstrate that Orforglipron induces an average reduction of 1.3% to 1.6% in HbA1c and weight loss of between 10% and 15% after 36–48 weeks, results comparable to or superior to oral semaglutide (10–12%) and subcutaneous liraglutide (8–10%) (IDRIS, 2023; DUTTA et al., 2024). This magnitude of response reflects a multifactorial action, involving the suppression of gastric emptying, the delay of intestinal glucose absorption, the improvement of hepatic insulin sensitivity, and the reduction of spontaneous caloric intake (GOGINENI et al., 2024).

From a pathophysiological point of view, sustained activation of the GLP-1 receptor by Orforglipron stimulates the expression of lipolytic and anti-inflammatory genes in white adipose tissue and reduces hypothalamic inflammation by modulating neural appetite control centers. This combined central and peripheral action explains the dual efficacy of glycemic and weight, making the drug an integrative option for the management of metabolic syndrome (DUTTA et al., 2024).

3.3 PHARMACODYNAMIC COMPARISON WITH GLP-1 AND GIP AGONISTS

Compared with emerging molecules such as tirzepatide (dual agonist of GIP and GLP-1), Orforglipron has a more predictable pharmacokinetic profile, with a half-life of 24 hours, oral bioavailability of 79%, and no dietary dependence for absorption (MA; MORSE, 2024). These properties favor continuous and consistent use, reducing interindividual variations that compromise the clinical response of peptide agonists.

In addition, unlike compounds of a protein nature, Orforglipron does not undergo significant enzymatic degradation by gastrointestinal peptidases, which explains its oral stability. This consolidates the concept that small, non-peptide molecules can preserve incretinic efficacy and offer economically sustainable alternatives in the long term.

3.4 CARDIOMETABOLIC EFFECTS AND POTENTIAL CARDIOPROTECTIVE MECHANISMS

Short- and medium-term clinical studies point to significant reductions in systolic blood pressure (-5.6 mmHg), LDL cholesterol (-10.4%), triglycerides (-12%), and ultrasensitive C-reactive protein (-18%), suggesting indirect cardiovascular benefits (WHARTON et al., 2025). These effects are consistent with the cardioprotective profile observed in injectable GLP-1 agonists such as liraglutide and semaglutide, which demonstrated reductions in major cardiovascular events (MACE) in the LEADER and SUSTAIN-6 studies, respectively.

The physiological mechanisms underlying this effect include reduced endothelial inflammation, improved microvascular function, reduced arterial stiffness, and increased nitric oxide bioavailability, which culminates in improved myocardial perfusion and peripheral vascular resistance. Thus, Orforglipron emerges as a molecule with pleiotropic action potential, acting both in metabolic regulation and in cardiovascular protection, a highly desirable trait in therapies for T2DM and obesity.

3.5 METHODOLOGICAL LIMITATIONS AND INTERPRETATION CHALLENGES

Despite the promising results, the present review identified substantial methodological heterogeneity among the available studies. Most clinical trials are phase 2, with samples of less than 500 participants, duration of less than 52 weeks, and intermediate outcomes (HbA1c, weight, lipid profile), with no assessment of cardiovascular mortality or morbidity (DUTTA et al., 2024; WHARTON et al., 2025). In addition, there are no direct comparative trials between Orforglipron and the main oral and injectable GLP-1 agonists, such as semaglutide, which limits the definition of its hierarchical therapeutic position.

Another critical point is the scarcity of data on clinical subgroups, the elderly, patients with renal failure or established cardiovascular disease, which prevents generalizations. This gap reinforces the need for long-term, multicenter, randomized, heterogeneous population trials in order to confirm the cardiovascular and metabolic safety profile of the drug.

3.6 CLINICAL, ECONOMIC AND TRANSLATIONAL IMPLICATIONS

The translational potential of Orforglipron is significant. Its oral formulation, thermal stability, and simple dosage can reduce storage and logistics costs, increase therapeutic adherence, and favor the expansion of access in public and private health systems.

From a clinical point of view, the drug may represent a strategic resource in the early stages of DM2, preventing the need for early insulin therapy and reducing the risk of micro- and macrovascular complications.

In the field of translational pharmacology, Orforglipron serves as a proof-of-concept molecule for the development of double and triple oral agonists, associating GLP-1, GIP, and glucagon, as demonstrated by recent research pipelines in incretin GOGINENI et al., 2024).

3.7 CRITICAL SYNTHESIS AND FUTURE PERSPECTIVES

The findings of this review fully meet the proposed objectives by systematizing, comparing, and critically interpreting the evidence on Orforglipron. It is concluded that the drug represents a substantial advance in the interface between molecular pharmacology and clinical endocrinology, with the potential to redefine the therapeutic paradigm of obesity and DM2.

However, the consolidation of orforglypron as the first oral option in the class of GLP-1 agonists will depend on the conclusion of phase 3 trials (ACHIEVE and ATTAIN) and independent multicenter meta-analyses that validate its effects on mortality, cardiovascular function, and quality of life. The continuation of investigations in this line may not only confirm its efficacy, but also inspire the development of new generations of intelligent oral molecules, marking a new cycle in incretin-based metabolic therapeutics.

4 CONCLUSION

The present review shows that Orforglipron is one of the most relevant advances in the last decade in the pharmacological treatment of obesity and type 2 diabetes mellitus (DM2). Its non-peptide and orally administered structure overcomes logistical and adherence limitations associated with injectable GLP-1 agonists, demonstrating robust clinical efficacy, favorable safety profile, and potential cardiometabolic benefit.

The results of the reviewed clinical trials point to consistent reductions in glycated hemoglobin (HbA1c) and body mass, as well as improvement in lipid and inflammatory parameters, reinforcing the role of Orforglipron as a multifunctional agent in systemic metabolic modulation. These findings indicate that the drug may represent an effective therapeutic alternative with greater adherence, especially in populations with difficult access to or tolerance to injectable analogues.

However, critical analysis of the evidence reveals important methodological limitations, including small sample sizes, short follow-up time, and lack of direct comparisons with other oral incretinal therapies. These constraints reinforce the need for multicenter, randomized, long-term clinical trials capable of confirming cardiovascular safety, sustained efficacy, and impact on real-world clinical outcomes.

From a scientific and translational point of view, the development of Orforglipron represents a new paradigm in metabolic pharmacology, by demonstrating that small-molecule GLP-1 agonists can maintain the therapeutic potency of peptide formulations, with advantages of use and cost. This breakthrough could drive new generations of oral incretin agents by combining multiple mechanisms of action into a personalized and more accessible approach.

Therefore, it is concluded that Orforglypron has the potential to consolidate itself as the first oral option within the class of GLP-1 agonists, integrating efficacy, convenience and safety in the same therapeutic strategy. However, its definitive incorporation into clinical practice will depend on the confirmation of results in phase 3 studies, especially the ACHIEVE and ATTAIN trials, and on independent comparative analyses that determine its long-term impact on mortality and cardiovascular complications associated with T2DM and obesity.

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