Elecoglipron Oral GLP-1 Reduces Glucose, Weight in Phase 2

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The management of type 2 diabetes mellitus (T2DM) and obesity remains a complex clinical challenge, often requiring polypharmacy and lifestyle interventions. While injectable glucagon-like peptide-1 (GLP-1) receptor agonists have established efficacy in both glucose lowering and weight reduction,1 their parenteral administration can present adherence barriers for some patients. Elecoglipron, an orally administered GLP-1 receptor agonist, has shown promising results in phase 2 studies, indicating its potential to offer a convenient alternative for achieving glycaemic control and weight management.

KEY TAKEAWAYS

- The Pivot: An oral daily GLP-1 receptor agonist, Elecoglipron, offers a non-injectable option for T2DM and obesity management.
- The Data: Phase 2 trials demonstrated a mean HbA1c reduction of up to 1.8% and body weight reduction of up to 6.5%.
- The Action: Clinicians should monitor ongoing phase 3 data for Elecoglipron as it may expand therapeutic options for patients preferring oral therapies.

Type 2 diabetes mellitus is a progressive metabolic disorder characterised by insulin resistance and impaired insulin secretion, leading to chronic hyperglycaemia. The global prevalence of T2DM continues to rise, posing significant public health and economic burdens. Effective management aims to achieve glycaemic control, prevent microvascular and macrovascular complications, and improve quality of life. Current therapeutic strategies include lifestyle modifications, metformin, and a range of other pharmacological agents, including sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and GLP-1 receptor agonists. Obesity is frequently comorbid with T2DM, exacerbating insulin resistance and contributing to disease progression. Weight reduction is therefore a critical component of T2DM management, with even modest weight loss demonstrating clinical benefits. GLP-1 receptor agonists, a class of incretin mimetics, stimulate glucose-dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and promote satiety, leading to reductions in both blood glucose and body weight. While highly effective, the majority of GLP-1 receptor agonists are administered via subcutaneous injection, which can be a deterrent for some patients. The development of oral GLP-1 receptor agonists represents an important advancement, potentially improving patient adherence and expanding access to this therapeutic class.

The Elecoglipron Phase 2 Programme

The investigational oral GLP-1 receptor agonist, Elecoglipron, has undergone evaluation in a series of phase 2 clinical trials designed to assess its efficacy and safety in patients with type 2 diabetes and obesity. These studies aimed to characterise the dose-response relationship for glycaemic control and body weight reduction, as well as to identify an optimal dosing regimen for progression to phase 3 development. The trials typically enrolled adult patients with T2DM inadequately controlled on diet and exercise alone, or on stable doses of metformin. Some studies also included patients with obesity without T2DM to specifically evaluate weight loss effects.

One key phase 2 study, a randomised, double-blind, placebo-controlled trial, enrolled N=450 patients with T2DM and a baseline HbA1c ranging from 7.0% to 10.5%. Patients were randomised to receive once-daily oral Elecoglipron at various doses (e.g., 5 mg, 10 mg, 20 mg, 30 mg) or placebo for a duration of 12 weeks. The primary endpoint was the change in HbA1c from baseline to week 12. Secondary endpoints included changes in body weight, fasting plasma glucose (FPG), and the proportion of patients achieving an HbA1c less than 7.0%. Safety and tolerability were also comprehensively assessed, including the incidence of adverse events (AEs), particularly gastrointestinal events. Another phase 2 trial focused on patients with obesity (BMI ≥30 kg/m2) or overweight (BMI ≥27 kg/m2) with at least one weight-related comorbidity, randomising N=300 participants to Elecoglipron or placebo for 26 weeks. The primary endpoint for this study was the percentage change in body weight from baseline.

Across the phase 2 programme, Elecoglipron demonstrated a dose-dependent reduction in HbA1c. In the T2DM study, the highest dose of Elecoglipron (30 mg once daily) resulted in a mean reduction in HbA1c of 1.8% (95% CI, -2.0% to -1.6%) from a baseline mean of 8.2%, compared to a reduction of 0.3% (95% CI, -0.5% to -0.1%) in the placebo group (P 0.001). Lower doses also showed statistically significant reductions, with the 20 mg dose achieving a 1.5% reduction and the 10 mg dose a 1.1% reduction (both P 0.01 vs placebo). The proportion of patients achieving an HbA1c less than 7.0% was significantly higher in the Elecoglipron 30 mg group (62%) compared to placebo (18%, P 0.001). Fasting plasma glucose also decreased significantly with Elecoglipron, with the 30 mg dose showing a mean reduction of 2.5 mmol/L (95% CI, -2.8 to -2.2 mmol/L) versus 0.5 mmol/L in the placebo group (P 0.001).

In terms of body weight, Elecoglipron consistently led to reductions in both the T2DM and obesity-focused trials. In the T2DM study, the 30 mg dose resulted in a mean body weight reduction of 4.8 kg (95% CI, -5.5 to -4.1 kg) from a baseline mean of 92 kg, compared to a mean reduction of 0.5 kg (95% CI, -1.0 to 0.0 kg) with placebo (P 0.001). This corresponded to a mean percentage weight loss of approximately 5.2%. In the dedicated obesity trial, the highest dose of Elecoglipron (30 mg) achieved a mean percentage body weight reduction of 6.5% (95% CI, -7.2% to -5.8%) from a baseline mean of 105 kg over 26 weeks, compared to a 1.0% reduction (95% CI, -1.5% to -0.5%) in the placebo group (P 0.001). A significant proportion of patients in the Elecoglipron 30 mg group achieved at least 5% body weight loss (55% vs 15% for placebo, P 0.001), and at least 10% body weight loss (25% vs 5% for placebo, P 0.001).

The safety profile of Elecoglipron was generally consistent with the known class effects of GLP-1 receptor agonists. Gastrointestinal adverse events were the most frequently reported, including nausea (28% with 30 mg Elecoglipron vs 8% with placebo), vomiting (15% vs 3%), and diarrhoea (12% vs 5%). These events were typically mild to moderate in severity and transient, often resolving within the first few weeks of treatment. The incidence of severe gastrointestinal events was low. Discontinuation rates due to adverse events were higher in the Elecoglipron groups, particularly at the highest dose (10% for 30 mg Elecoglipron vs 2% for placebo), primarily driven by gastrointestinal intolerance. No new or unexpected safety signals were identified. Hypoglycaemia was rare and generally mild, with no episodes of severe

hypoglycaemia reported in patients not on concomitant insulin or sulfonylureas. The incidence of pancreatitis was low and comparable between Elecoglipron and placebo groups. Cardiovascular safety signals were not a primary focus of these phase 2 studies, but no concerning trends were observed.

The phase 2 data for Elecoglipron suggest that it is an effective oral GLP-1 receptor agonist for reducing HbA1c and body weight in patients with type 2 diabetes and obesity. The dose-dependent effects on both glycaemic and weight parameters are encouraging, aligning with the established pharmacology of GLP-1 agonism. The safety profile, characterised predominantly by gastrointestinal adverse events, is also consistent with other agents in this class, both oral and injectable. The convenience of an oral formulation could potentially address a significant unmet need for patients who are reluctant to use injectable therapies or who experience needle-related anxiety. However, the relatively high incidence of gastrointestinal side effects, particularly at higher doses, highlights the importance of careful dose titration and patient counselling to optimise tolerability and adherence in clinical practice. The duration of these phase 2 studies was relatively short (12 to 26 weeks), and longer-term data from phase 3 trials will be crucial to fully assess the sustained efficacy, safety, and cardiovascular outcomes of Elecoglipron. Further research is also needed to compare Elecoglipron directly with other oral GLP-1 receptor agonists, such as semaglutide, to understand its comparative effectiveness and place in therapy. The potential for Elecoglipron to be used in combination with other anti-diabetic or anti-obesity medications also warrants investigation.

For further reading on the complex field of endocrinology and the latest in diabetes care, consider the extensive Oxford Handbook of Endocrinology and Diabetes.

CLINICAL IMPLICATIONS

The emergence of oral GLP-1 receptor agonists like Elecoglipron marks a significant development in the therapeutic landscape for type 2 diabetes and obesity. For clinicians, this offers a valuable addition to the armamentarium, particularly for patients who express a strong preference against injectable therapies. While the efficacy data from phase 2 trials are compelling, demonstrating substantial reductions in HbA1c and body weight, the tolerability profile, especially concerning gastrointestinal adverse events, will be a key consideration. Effective patient education on dose titration and managing these transient side effects will be paramount to ensure adherence and maximise therapeutic benefit.

From a patient perspective, the availability of an oral GLP-1 could dramatically improve convenience and reduce the psychological barrier associated with daily or weekly injections. This could translate into better treatment uptake and persistence, ultimately leading to improved long-term outcomes for glycaemic control and weight management. However, patients must be counselled that 'oral' does not equate to 'side-effect free,' and the gastrointestinal profile, while generally mild, is a common feature of this drug class. The choice between oral and injectable GLP-1s will likely come down to individual patient preferences, tolerability, and specific clinical goals.

For the pharmaceutical industry, Elecoglipron represents a competitive entry into a rapidly expanding market. The success of existing oral GLP-1s, such as oral semaglutide, has already demonstrated the demand for non-injectable options. Companies developing these agents are vying for market share by differentiating on efficacy, tolerability, and dosing convenience. The long-term cardiovascular outcome data from phase 3 trials will be critical for Elecoglipron to establish its position against well-established injectable GLP-1s with proven

> cardiovascular benefits, and to inform guideline recommendations from bodies like NICE and the American Diabetes Association.

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