Oral GLP-1 Analogues Show A1c Reduction, Weight Loss at ADA 2026

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Managing type 2 diabetes mellitus (T2DM) effectively requires therapies that not only control glycaemia but also address associated comorbidities such as obesity. While injectable glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated efficacy in both areas, their administration route can be a barrier for some patients. New phase 3 data presented at the American Diabetes Association (ADA) 2026 Scientific Sessions highlights the potential of novel oral GLP-1 receptor agonists to provide comparable benefits in HbA1c reduction and weight loss, offering a non-injectable option for T2DM management.

KEY TAKEAWAYS

- The Pivot: Oral GLP-1 receptor agonists are demonstrating efficacy comparable to injectable forms, potentially expanding access and adherence.
- The Data: Mean HbA1c reduction of -1.5% (95% CI, -1.6 to -1.4; p<0.001) and mean body weight reduction of -6.8 kg (95% CI, -7.2 to -6.4; p<0.001) were observed.
- The Action: Clinicians should anticipate the availability of oral GLP-1 receptor agonists as a viable alternative for patients requiring glycaemic control and weight management, particularly those averse to injections.

The clinical landscape for type 2 diabetes management has evolved to prioritise therapies that offer cardiovascular and renal protection in addition to glycaemic control. GLP-1 receptor agonists, initially available as injectables, have established themselves as a cornerstone of treatment due to their pleiotropic effects, including glucose-dependent insulin secretion, glucagon suppression, delayed gastric emptying, and central appetite suppression.1 However, the necessity for subcutaneous injection can impact patient preference and adherence, limiting their broader application. The development of oral formulations aims to mitigate this barrier, potentially broadening the utility of this therapeutic class.2

The Trial

A multinational, randomised, double-blind, placebo-controlled Phase 3 trial evaluated the efficacy and safety of a novel once-daily oral GLP-1 receptor agonist in adults with type 2 diabetes inadequately controlled on diet and exercise alone or on stable doses of metformin. The trial enrolled 1,850 patients across 18 countries.3 Participants were randomised in a 2:1 ratio to receive either the oral GLP-1 receptor agonist (titrated over 8 weeks to a target dose of 25 mg daily) or placebo for 52 weeks. Key inclusion criteria included an HbA1c between 7.0% and 10.5% and a body mass index (BMI) of at least 27 kg/m2. The primary endpoints were the change from baseline in HbA1c and body weight at week 52. Secondary endpoints included the proportion of patients achieving HbA1c less than 7.0% and changes in fasting

plasma glucose (FPG) and lipid profiles.3

The trial design incorporated a robust titration schedule to optimize tolerability, a common challenge with GLP-1 receptor agonists. Patients initiated treatment at a lower dose, gradually increasing to the target 25 mg daily dose over the initial 8 weeks. This approach aimed to minimize the incidence and severity of gastrointestinal adverse events, allowing patients to adapt to the medication's effects. Adherence to the study protocol was closely monitored, with regular patient visits and medication accountability to ensure data integrity. The broad geographic reach across 18 countries aimed to capture a diverse patient population, enhancing the generalizability of the results to various clinical settings and ethnic backgrounds.3

At week 52, patients receiving the oral GLP-1 receptor agonist demonstrated a mean reduction in HbA1c of -1.5% (95% CI, -1.6 to -1.4) from a baseline mean of 8.1%, compared to a mean reduction of -0.3% (95% CI, -0.4 to -0.2) in the placebo group ($p<0.001$).4 A significantly greater proportion of patients in the active treatment arm achieved an HbA1c of less than 7.0% (68% versus 22% for placebo; odds ratio, 7.2; 95% CI, 6.1 to 8.5; $p<0.001$).4

Regarding weight management, the oral GLP-1 receptor agonist group experienced a mean body weight reduction of -6.8 kg (95% CI, -7.2 to -6.4) from a baseline mean of 92.5 kg, compared to -1.0 kg (95% CI, -1.3 to -0.7) in the placebo group ($p<0.001$).4 A reduction of at least 5% of body weight was achieved by 55% of patients on active treatment, versus 18% on placebo.4

The safety profile was consistent with the known class effects of GLP-1 receptor agonists. Gastrointestinal adverse events were the most common, with nausea reported in 28% of patients in the active arm (versus 9% in placebo), vomiting in 15% (versus 4%), and diarrhoea in 19% (versus 8%). These events were predominantly mild to moderate in severity and transient, decreasing in frequency after the initial titration phase. Discontinuation due to adverse events occurred in 9% of patients receiving the oral GLP-1 receptor agonist, compared to 3% in the placebo group. No new safety signals were identified.5

While these results are promising, the trial's duration of 52 weeks limits the assessment of long-term cardiovascular outcomes, which have been established for some injectable GLP-1 receptor agonists. Future studies will need to address these longer-term benefits and safety profiles. The patient population, predominantly individuals with a BMI over 27 kg/m2, may also limit generalisability to patients with lower BMI. Further research is warranted to compare the efficacy and safety of oral GLP-1 receptor agonists directly against established injectable formulations and other oral antidiabetic agents in head-to-head trials.6

CLINICAL IMPLICATIONS

The emergence of highly effective oral GLP-1 receptor agonists represents a significant step forward for patients with type 2 diabetes. For years, the undeniable benefits of GLP-1 agonism, particularly for weight management and cardiovascular risk reduction, have been constrained by the need for injections. This new data, showing substantial reductions in HbA1c and body weight with an oral formulation, directly addresses a major barrier to adherence and patient preference. It is not merely a convenience; it is a potential expansion of access to a critical therapeutic class for a broader patient population, including those who may have previously declined injectable options.

Clinicians should prepare for a shift in prescribing patterns. While the established injectable GLP-1 receptor

agonists have robust long-term cardiovascular outcome data, the initial efficacy and safety profile of this oral agent suggest it will quickly become a preferred first-line GLP-1 option for many. The challenge will be to integrate this new option into existing treatment algorithms, balancing its benefits against the cost implications and the need for careful titration to manage gastrointestinal side effects. Pharmaceutical companies developing these oral agents will need to provide clear guidance and support for clinicians and patients during the initial adoption phase.

The impact on the pharmaceutical market will be considerable. Companies with established injectable GLP-1 franchises will face increased competition, while those bringing oral formulations to market stand to capture a significant share. This innovation underscores the ongoing drive to make highly effective therapies more accessible and patient-friendly. The next few years will likely see further refinements in oral GLP-1 formulations and head-to-head trials that will solidify their position in the diabetes treatment paradigm.

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