

## TITLE

**Orforglipron, an oral small molecule GLP-1 receptor agonist, for the treatment of obesity in people with type 2 diabetes (ATTAIN-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial**

## *RUNNING TITLE*

Orforglipron for the treatment of obesity in people with type 2 diabetes (ATTAIN-2)

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## Research in context

### Evidence before this study

Strong and consistent evidence demonstrates the benefit of managing obesity in people with type 2 diabetes (T2D). Weight reduction improves glycaemia, functional status, and quality of life, and reduces the need for glucose-lowering medications in people with obesity and T2D. Additionally, greater weight reduction may promote sustained diabetes remission.

On June 18<sup>th</sup>, 2025, the authors searched PubMed using the search terms “glucagon-like peptide-1 receptor agonist” (GLP-1 RA), AND “obesity”, AND “overweight”, AND “type 2 diabetes” for any published articles with no date or language restrictions.

To date, two GLP-1 R monoagonists, liraglutide (3-mg once-daily) and semaglutide (2.4-mg once weekly), and tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 R agonist, all peptides in injectable formulations, have been approved for weight management. The oral formulation of semaglutide (7-mg and 14-mg once per day) is approved for T2D treatment; higher doses are being investigated to treat obesity but are not yet approved.

Orforglipron, a once-daily, oral, small molecule (non-peptide) GLP-1 RA was investigated for obesity treatment as an adjunct to lifestyle modification in two global, placebo-controlled Phase 3 trials in people with obesity without diabetes (ATTAIN-1) and with T2D (ATTAIN-2). Results of the ATTAIN-2 trial are reported herein.

### **Added value of this study**

In adults with body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup> and T2D, treatment with once-daily oral orforglipron 6-mg, 12-mg, and 36-mg as an adjunct to lifestyle intervention resulted in clinically meaningful mean percent reductions in body weight at 72 weeks of 5.1% (95% CI 4.2 to 6.0), 7.0% (6.2 to 7.8) and 9.6% (8.7 to 10.5), respectively, versus 2.5% (1.9 to 3.0) with placebo. Most participants (47.7-67.2%) treated with orforglipron reached the threshold for clinically meaningful effect ( $\geq 5\%$  weight reduction), with 45.6% of those on the orforglipron 36-mg dose reaching 10% or greater weight reduction, and 26.0% reaching 15% or greater weight reduction from baseline to Week 72. More than three out of four (75.5%) participants on orforglipron 36-mg achieved the glycated haemoglobin (HbA1c) target value of  $< 7\%$ ; 66.6% achieved the HbA1c target value of  $\leq 6.5\%$ , and approximately one-fourth (23.7%) achieved normoglycaemia (HbA1c  $< 5.7\%$ ) compared to 1.6% in the placebo group. HbA1c, fasting serum glucose, waist circumference, systolic blood pressure, non-HDL cholesterol, and triglycerides were significantly decreased with orforglipron versus placebo after 72 weeks of treatment.

### **Implications of all the available evidence**

In this Phase 3 trial in adults with obesity and T2D, orforglipron demonstrated clinically meaningful body weight reduction. Body weight reductions, and improvements in glucose control and other cardiometabolic risk markers observed in this study were consistent with previous orforglipron trials in people with obesity without diabetes (ATTAIN-1) and in people with early T2D with a BMI  $\geq 23$  kg/m<sup>2</sup> (ACHIEVE-1). As a non-peptide oral, orforglipron is simple to administer, with no restrictions on food and water intake or required refrigeration, potentially offering a more convenient option and broader global access to incretin therapy.

### **Summary (302/300 words)**

#### **Background**

Obesity is a chronic disease that significantly contributes to type 2 diabetes (T2D) and its complications. Orforglipron, an oral small molecule (non-peptide), glucagon-like peptide-1 receptor agonist (GLP-1 RA), was evaluated for obesity treatment in adults with T2D.

#### **Methods**

In this 72-week, Phase 3, double-blind, placebo-controlled trial, participants with BMI  $\geq 27$ kg/m<sup>2</sup> and HbA1c 7%-10% (53-86 mmol/mol) were randomly assigned (1:1:1:2) to once-daily orforglipron 6-mg,

12-mg, 36-mg, or placebo. The primary endpoint was the mean percent change in body weight from baseline to Week 72. Treatment regimen estimand was the primary estimand. (Registered at ClinicalTrials.gov, NCT05872620).

## Findings

From June 2023–February 2024, 2859 participants were screened, and 1613 (757 [46.9%] female) were randomised to orforglipron 6-mg (n=329), 12-mg (n=332), 36-mg (n=322), or placebo (n=630), as an adjunct to lifestyle intervention; 1444 (89.5%) completed the study. Baseline body weight was 101.4 kg (SD 22.5), BMI 35.6 kg/m<sup>2</sup> (SD 6.6), and HbA1c 8.05% (SD 0.75; 64.4 mmol/mol [SD 8.2]). Mean percent change in body weight from baseline to Week 72 was -5.1% (95% CI -6.0,-4.2) with 6-mg, -7.0% (-7.8,-6.2) with 12-mg, and -9.6% (-10.5,-8.7) with 36-mg orforglipron, versus -2.5% (-3.0,-1.9) with placebo (all p<.0001 compared with placebo). At Week 72, mean change in HbA1c was -1.2%, -1.5%, and -1.7% with orforglipron 6-mg, 12-mg, and 36-mg, respectively, versus -0.5% for placebo. 75.5% of participants achieved HbA1c <7% with orforglipron 36-mg versus 30.5% with placebo. All prespecified weight and cardiometabolic measures improved with orforglipron. Treatment discontinuations due to adverse events (mainly gastrointestinal-related) were higher for orforglipron (6.1-9.9%) versus placebo (4.1%). The most common adverse events with orforglipron were mild-to-moderate gastrointestinal events, predominantly occurring during dose escalation.

## Interpretation

In adults with obesity or overweight and T2D, once-daily orforglipron as an adjunct to lifestyle intervention led to clinically meaningful reductions in body weight and HbA1c.

## Funding

Eli Lilly and Company

## INTRODUCTION (4486/4500)

The global prevalence of obesity and overweight is expected to increase to three billion adults by 2030.<sup>1</sup> Obesity increases the risk of type 2 diabetes mellitus (T2D), metabolic dysfunction-associated steatotic liver disease (MASLD), hypertension, myocardial infarction, stroke, dementia, osteoarthritis, depression, obstructive sleep apnoea, and many cancers, thereby contributing to a decline in both quality of life and life expectancy.<sup>2</sup> Considering these increased risks, people with obesity and T2D need effective and safe therapies that lead to weight reduction and improved glycaemic control, which could ultimately translate into long-term health benefits.<sup>3-5</sup>

Current injectable glucagon-like peptide-1 (GLP-1)-based therapies demonstrated significant efficacy in weight reduction in people living with obesity and T2D<sup>6-8</sup> as well as improved glycemic control and reduced cardiovascular risks.<sup>9-11</sup> However, injectable therapies have several limitations including the need for cold chain distribution and storage, risk of injection site reactions, and needle-related discomfort, fear, and stigma. There is a need for orally administered GLP-1 receptor agonists (GLP-1 RAs) to address the continued unmet needs of people living with obesity and co-existing T2D.

Small-molecule GLP-1 RAs may offer the physiological benefits of peptide GLP-1-based therapies, including appetite suppression, clinically meaningful weight reduction, and stimulation of insulin secretion.<sup>12</sup> Compared with peptide oral GLP-1 RAs, small molecules have higher bioavailability and do not require food and water restrictions during administration, improving convenience.<sup>12-14</sup>

Additionally, an oral small molecule formulation could increase treatment adherence, and be manufactured at a greater scale thereby improving access.<sup>15</sup>

Orforglipron is a once-daily, orally administered, small molecule, GLP-1 RA currently being investigated for obesity, T2D, hypertension, obstructive sleep apnoea, and osteoarthritis.<sup>14,16,17</sup> In the ATTAIn-1 study, in adults with obesity and without T2D, orforglipron reduced body weight by up to 12.4% after 72 weeks of treatment, with associated improvements in cardiometabolic risk factors.<sup>18</sup> In addition, considering the importance of weight reduction for patients with T2D and the increasing prevalence of both diseases, it is of great interest to evaluate the effects of orforglipron in patients with obesity and co-existing T2D.

In this article, we present the results of the ATTAIn-2 study, which investigated orforglipron for weight management in adults with a BMI of  $\geq 27$  kg/m<sup>2</sup> and co-existing T2D.

## METHODS

### Study Design and Participants

ATTAIn-2 was a Phase 3, multicentre, randomised, parallel-arm, placebo-controlled, double-blind, 72-week study conducted across 136 sites in Argentina, Australia, Brazil, China, Czech Republic, Germany, Greece, India, Republic of Korea, and the USA. The study was comprised of the following periods: a 3-week screening, followed by 72-week treatment including 20-week dose escalation, and a 2-week post-treatment safety follow-up (**appendix figure S1**). The study protocol and statistical analysis plan can be found in the appendix.

Eligible participants were adults (aged  $\geq 18$  years) with a BMI of  $\geq 27$  kg/m<sup>2</sup>, diagnosed with T2D with an HbA1C  $\geq 7\%$  ( $\geq 53$  mmol/mol) to  $\leq 10\%$  ( $86$  mmol/mol), who had stable treatment for T2D for at least 90 days prior to Visit 1, with either diet/exercise alone or up to three oral antihyperglycemic medications (AHMs) (excluding DPP-4 inhibitors or GLP-1 RAs). They must have had a history of at least one self-reported unsuccessful dietary effort to lose body weight. Key exclusion criteria included any other type of diabetes except T2D, one or more episodes of severe hypoglycaemia and/or one or more episodes of hypoglycaemia unawareness within the 180 days prior to screening visit, self-reported change in body weight  $>5$  kg within 90 days before screening, receiving or planning to receive treatment for diabetic retinopathy and/or macular oedema, and an estimated glomerular filtration rate (eGFR) of  $<15$  ml per minute per 1.73 m<sup>2</sup> of body-surface area. Full inclusion and exclusion criteria are provided in the appendix (**appendix inclusion and exclusion criteria**).

The study was conducted in accordance with local regulations, the Declaration of Helsinki, the International Ethical Guidelines of the Council for International Organizations of Medical Sciences, and the Good Clinical Practice guidelines of the International Conference for Harmonisation and was approved by an independent ethics committee or institutional review board at each trial site. All participants provided written informed consent. This trial is registered at ClinicalTrials.gov (NCT05872620) and is completed.

### Randomisation and Blinding

Participants were randomised in a 1:1:1:2 ratio to receive daily doses of orforglipron (6-mg, 12-mg, or 36-mg) or placebo, using an interactive web-response system. Randomisation was stratified by

country, sex, and background oral AHMs classified according to their potential effect on body weight. Participant enrolment included an upper limit of 70% female and 30% treated with a sulfonylurea. Investigators, site staff, clinical monitors, sponsor, and participants remained blinded to the study intervention until the study was completed.

## Procedures

Following randomisation, all interventions were administered orally once-daily. Randomised participants received either 1 mg blinded orforglipron or matching placebo, followed by dose escalation every 4 weeks until the randomly assigned dose was reached (**appendix figure S1**). During the study, participants received lifestyle intervention consisting of individualised counselling regarding a healthy diet with the goal of achieving weight reduction. Participants were encouraged to focus on mindful eating throughout the day, portion control, fibre-rich foods, and choices individualised to personal, cultural, and budgetary needs/preferences. Additionally, participants were counselled on a healthy physical activity level of at least 150 minutes per week, as tolerated.

To minimise the risk for hypoglycaemia, participants taking sulfonylureas had their doses halved or stopped (if on the lowest dose) at randomisation. All other AHMs were to be continued at the current dose. Initiation of new AHMs (excluding GLP-1 RAs, DPP-4 inhibitors, or amylin analogues or agonists) was allowed according to specific rescue criteria for severe persistent hyperglycaemia, as described in the protocol. Glucometers were provided to self-monitor blood glucose and participants were encouraged to record values.

Mitigation strategies were implemented in case of intolerable gastrointestinal (GI) symptoms, as described in the protocol including counselling on quantity and frequency of food intake, support with antiemetic or antidiarrheal medication, and dose de-escalation if needed. If the GI symptoms became tolerable, re-escalation was recommended to achieve the randomised dose. However, if the re-escalation attempt was not tolerated or intolerable GI symptoms returned at any subsequent time point, then the participant underwent a final dose de-escalation to the next lower dose.

## Outcomes

The primary endpoint was the mean percent change in body weight at Week 72 from baseline. Key secondary endpoints at Week 72 included the percentage of participants who achieve body weight reduction of  $\geq 5\%$  and  $\geq 10\%$  on 6-mg, and  $\geq 5\%$ ,  $\geq 10\%$  and  $\geq 15\%$  on 12-mg or 36-mg, mean change in waist circumference on 36-mg; mean change in fasting serum glucose, mean change in HbA1c, percentage of participants achieving HbA1c target value of  $< 7\%$  and  $\leq 6.5\%$ , on all doses (6-mg, 12-mg, and 36-mg); mean change in systolic blood pressure, and mean percent change in non-HDL cholesterol and triglycerides, on pooled doses. All key secondary endpoints were prespecified and controlled for multiplicity.

Additional secondary endpoints included at Week 72 from baseline (not controlled for multiplicity): (1) mean change in absolute body weight, (2) mean change in BMI, (3) percentage of participants achieving HbA1c target value of  $< 5.7\%$ , (4) mean percent change in fasting insulin, (5) mean change in waist circumference for orforglipron 6-mg and 12-mg, (6) mean change in diastolic blood pressure, and (7) mean percent change in total, LDL-, and HDL-cholesterol.

Safety endpoints included the frequency of treatment-emergent adverse events and serious adverse events assessed through the safety follow-up period. Clinical laboratory assessments, physical examinations, vital sign measurements, and electrocardiograms were done as outlined in the protocol. Hepatic safety was thoroughly evaluated during the study, with liver function tests every 4

weeks during dose escalation, and every 3 months thereafter. Hypoglycaemic episodes were recorded in the study e-Diary. If the event met the criteria for severe (Level 3) hypoglycaemia (involving severe cognitive impairment requiring assistance from another person to administer carbohydrates, glucagon, or other resuscitation measures), it was also reported as an SAE. Additionally, deaths, major adverse cardiovascular events (such as myocardial infarction, hospitalization due to unstable angina or heart failure, coronary revascularization, and cerebrovascular events), pancreatitis and cases of severe or serious abdominal pain of unknown aetiology were reviewed by an independent external adjudication committee.

### **Statistical analysis**

A sample size of 1613 participants (initial power calculation assumed 1500 participants) provided a power of greater than 90% to demonstrate superiority of orforglipron 6-mg, 12-mg, and/or 36-mg to placebo with regards to mean percent change in body weight at Week 72 from baseline. The sample size determination assumes that evaluation of superiority of 6-mg, 12-mg, and 36-mg orforglipron to placebo will be conducted in parallel, under a family-wise two-sided type 1 error rate of 0.05 using a 2-sample t-test for the treatment regimen estimand. A difference of at least 5% mean body weight reduction at 72 weeks for orforglipron doses compared to placebo, and a common standard deviation (SD) of 10% was assumed for statistical power calculations. A graphical approach for multiple comparisons was used for testing primary and multiplicity-adjusted secondary objectives. Model-based estimates (MBE) and confidence intervals (CIs) are reported. CIs were not adjusted for multiplicity and should not be used for hypothesis testing.

Two estimands were utilized: the treatment regimen estimand and the efficacy estimand, each accounting for intercurrent events in distinct ways. Objectives related to the treatment regimen estimand were evaluated using data from all randomised participants regardless of adherence to study intervention or initiation of prohibited weight management medications (or glycaemic rescue therapy or prohibited glycaemic therapy for glycaemic endpoints only). For the treatment regimen estimand, the ANCOVA model was used to analyse continuous measurements at Week 72.<sup>19</sup> This analysis adjusted for baseline value, region, and other stratification factors, and interactions of treatment-by-baseline and treatment-by-stratification factors, incorporating imputed data for missing values at baseline and missing endpoints at Week 72. The details on imputation can be found in the statistical analysis plan. Achieving a certain threshold (5%, 10%, 15%) in body weight reduction at Week 72 from baseline was analysed using a logistic regression model, with treatment, region, other stratification factors, and continuous baseline value, and interactions of treatment-by-baseline and treatment-by-stratification factors as covariates.<sup>20</sup>

The efficacy estimand was analysed in all randomly assigned participants assuming intercurrent events, such as permanent discontinuation of the study drug or initiation of prohibited weight management medications (or glycaemic rescue therapy or prohibited glycaemic therapy for glycaemic endpoints only), did not occur. For the efficacy estimand, a maximum-likelihood-based mixed model for repeated measures (MMRMs) was used with adjustment for baseline value, region, and other stratification factors considering a 3-way interaction between treatments, visits and baseline value (or stratification factors).

Safety endpoints were evaluated using data from all participants who were randomly assigned to the study and had at least one dose of study intervention.

Additional details of the statistical methods can be found in the appendix (**appendix Statistical Analysis methods**).

## Role of the funding source

The sponsor (Eli Lilly) designed and oversaw the conduct of the trial, performed site monitoring, data collation, and analysis. The investigators were responsible for data collection and worked under confidentiality agreements with the sponsor. All authors had access to the data and analyses, interpreted the data, critically reviewed the manuscript, approved the decision to submit it for publication, and confirmed the accuracy and completeness of the data, and the fidelity of the trial to the protocol. The authors wrote the first draft of the manuscript with assistance from sponsor-funded medical writers.

## RESULTS

This trial was conducted from 5 June 2023 to 8 August 2025. Of the 2859 individuals screened for study eligibility, 1613 were randomly assigned (1:1:1:2) to orforglipron 6-mg (n=329), 12-mg (n=332), 36-mg (n=322), or placebo (n=630) in addition to a healthy diet and physical activity (**figure 1**). A total of 1444 (89.5%) participants completed the study (287 [87.2%], 303 [91.3%], 302 [93.8%] and 552 [87.6%] with orforglipron 6-mg, 12-mg, 36-mg, and placebo, respectively) and 1284 (79.6%) completed the study treatment (266 [80.9%], 258 [77.7%], 256 [79.5%] and 504 [80.0%] with orforglipron 6-mg, 12-mg, 36-mg, and placebo, respectively; **figure 1**). The proportion of participants who discontinued treatment due to adverse events was 6.1% for orforglipron 6-mg, 9.6% for 12-mg, 9.9% for 36-mg, and 4.1% for placebo (**figure 1**).

The baseline demographics and clinical characteristics were similar between orforglipron and placebo groups (**table 1**). The mean age of the participants was 56.8 years (SD 10.7), 757 (46.9%) were female, 1143 (70.9%) White, 279 (17.3%) Asian, 105 (6.5%) Black or African American, and 488 (30.3%) Hispanic or Latino. Baseline mean body weight was 101.4 kg (SD 22.5), BMI 35.6 kg/m<sup>2</sup> (6.6), mean duration of obesity 18.1 years (12.6), mean HbA1c 8.05% (0.75; 64.4 mmol/mol [8.2]), mean duration of diabetes 8.5 years, and 13.9% were treated with sulfonylureas (**table 1**).

For the treatment regimen estimand, the mean percent change from baseline in body weight to Week 72 was -5.1% (95% CI -6.0 to -4.2) or -5.3 kg with orforglipron 6-mg, -7.0% (-7.8 to -6.2) or -7.2 kg with orforglipron 12-mg, -9.6% (-10.5 to -8.7) or -9.6 kg with orforglipron 36-mg, and -2.5% (-3.0 to -1.9) or -2.7 kg with placebo (**figure 2, table 2**). All orforglipron doses were superior to placebo, with estimated treatment differences relative to placebo of -2.7% (95% CI -3.7 to -1.6) for the 6-mg dose, -4.5% (95% CI -5.5 to -3.6) for the 12-mg dose, and -7.1% (95% CI -8.2, -6.1) for the 36-mg dose (p<.0001 for all comparisons) (**table 2**).

For the efficacy estimand, the mean percent change from baseline in body weight to Week 72 was -5.5% (95% CI -6.2 to -4.8) or -5.5 kg with orforglipron 6-mg, -7.8% (-8.6 to -7.0) or -7.9 kg with orforglipron 12-mg, -10.5% (-11.5 to -9.6) or -10.4 kg with orforglipron 36-mg, and -2.2% (-2.6 to -1.8) or -2.3 kg with placebo (**figure 2, figure S2**). Estimated treatment differences were -3.3% (95% CI -4.1 to -2.5) for the 6-mg dose, -5.6% (95% CI -6.5 to -4.7) for the 12-mg dose, and -8.3% (95% CI -9.3 to -7.3) for the 36-mg dose versus placebo (p<.0001 for all comparisons) (**table 2**).

For both estimands, more participants in the orforglipron groups achieved weight reduction thresholds of ≥5%, ≥10%, or ≥15% from baseline than participants in the placebo group. At Week 72, body weight reduction of ≥10% for treatment regimen estimand was achieved in 22.6%, 31.2%, and 45.6% for orforglipron 6-mg, 12-mg, and 36-mg, respectively, compared with 9.0% of participants in placebo group (all p<.0001 for comparisons with placebo). The respective percentages for the

efficacy estimand were 23.9%, 35.5%, and 50.1% in the orforglipron groups compared with 7.0% in the placebo group. (**figure 2; table 2**). Figure appendix S5 shows the waterfall plots depicting each participant's percentage weight reduction from baseline for all treatment groups for the treatment regimen estimand.

At Week 72, HbA1c decreased significantly from baseline in the orforglipron groups by 1.22% with 6-mg, 1.50% with 12-mg, 1.66% with 36-mg, and 0.47% with placebo, for the treatment regimen estimand ( $p < .0001$  for all comparisons versus placebo; **table 2**). For the efficacy estimand, HbA1c decreased by 1.29% with 6-mg, 1.60% with 12-mg, 1.79% with 36-mg, and 0.14% with placebo (**appendix table s1**).

Proportion of participants reaching HbA1c levels  $<7\%$ , and  $\leq 6.5\%$  at Week 72 was significantly higher in all orforglipron groups compared to placebo (with orforglipron 36-mg: 75.5% vs 30.5%, and 66.6% vs 15.4%, respectively; **figure 3**). Decrease in fasting serum glucose was also significantly greater among participants in all orforglipron groups compared to placebo participants (ranging from -30.5 to -42.4 mg/dL vs -9.3 mg/dL) (**table 2; figure 3**).

Improvements with pooled orforglipron treatment (6-mg, 12-mg and 36-mg) were significantly greater versus placebo for key secondary endpoints: systolic blood pressure (-4.2 mmHg vs -1.6 mmHg; **figure 3E**), non-HDL cholesterol (-6.2% vs -2.5%), and fasting triglycerides (-16.0% vs -4.2%); and also for the additional secondary endpoint, HDL cholesterol (6.4% vs 1.0%; **figure 3F**). Mean reduction in waist circumference was significantly greater with orforglipron 36-mg compared with placebo (-8.3 cm vs -2.8 cm; **table 2; figure 3D**). There was a decrease from baseline in high-sensitivity C-reactive protein (hsCRP) with all orforglipron doses (ranging from -32.4% to -47.5% vs -10.0%) (**table 2; table s1, figure S6**). Results were consistent for the efficacy estimand, showing greater improvements with orforglipron treatment compared with placebo for all secondary endpoints (**appendix table S1**).

In the overall incidence of reported adverse events, there were no imbalances between the treatment groups. The most frequently reported adverse events were gastrointestinal (diarrhoea, nausea, vomiting, or constipation). They were more common in the orforglipron groups, were mostly mild-to-moderate in severity, and with higher incidence during the dose-escalation period (**table 3; appendix figure S4**). Serious adverse events were reported by 148 (9.2%) participants overall, with no significant differences in reporting across groups (**table 3**). A total of ten deaths were reported during the study: four in the 12-mg orforglipron group, two in the 36-mg orforglipron group, and four in the placebo group (**appendix table S2**).

There were three reported cases of adjudication-confirmed pancreatitis, one in the 12-mg orforglipron and two in the placebo groups (**table 3**). Mean ALT and AST levels decreased in orforglipron groups over 72 weeks (**appendix table S3**). The rates of postbaseline ALT or AST  $\geq 3$  or  $\geq 5$  times ULN were comparable across all treatment groups. Three orforglipron-treated participants and one in the placebo group had ALT and/or AST  $\geq 10X$  ULN (**appendix table S5**); one of which on orforglipron also showed total bilirubin  $>2X$  ULN. The causes of liver enzyme and bilirubin abnormalities were related to gallbladder disease and its complications in all three of the orforglipron-treated patients. No cases of medullary thyroid cancer (MTC) and one case of pancreatic neoplasm (in placebo group) were reported. Only one case of severe hypoglycaemia was reported with orforglipron 6-mg, which occurred in a patient who unintentionally missed the morning meal after taking study drug and metformin. There were 21 participants who reported Level 2 hypoglycaemia while on study treatment, with a higher incidence in the orforglipron groups, occurring mainly in the participants taking sulfonylureas at baseline (**appendix table S4**). There was a

mean increase in pulse rate up to 4.4 beats per minute in orforglipron groups compared to 0 beats per minute in the placebo group at Week 72 from baseline. Additional safety data is available in **appendix table S3**.

## DISCUSSION

In the ATTAIN-2 study, in adults with obesity and co-existing T2D, once-daily orforglipron at doses of 6-mg, 12-mg and 36-mg given as an adjunct to lifestyle intervention demonstrated mean body weight reductions of 5.1%, 7.0%, and 9.6% respectively, compared with 2.5% in the placebo group, after 72 weeks of treatment. Among participants assigned to the 36-mg orforglipron dose, 67.2%, 45.6%, and 26.0% achieved body weight reductions of  $\geq 5\%$ ,  $\geq 10\%$ , and  $\geq 15\%$ , respectively.

To provide a clinical perspective on the therapeutic landscape, GLP-1-based therapies for weight management are currently only available as injectable formulations, and include two GLP-1R monoagonists, daily liraglutide and weekly semaglutide, and a weekly dual GIP and GLP-1 R agonist, tirzepatide. These therapies have been evaluated in Phase 3 clinical trials in people with obesity and co-existing T2D. In the SCALE Diabetes study, treatment with once-daily 3-mg of liraglutide for 56 weeks was associated with 6.0% reduction in body weight, compared to 2.0% in the placebo group.<sup>7</sup> Once weekly semaglutide 2.4-mg improved upon this, with the STEP 2 study demonstrating 9.6% weight reduction from baseline versus 3.4% with placebo over 68 weeks.<sup>6</sup> Subsequently, once-weekly tirzepatide at a dose of 15-mg led to a 14.7% reduction in body weight versus 3.2% with placebo in the 72-week SURMOUNT-2 trial; the even larger weight reduction potentially due to the addition of GIPR agonism.<sup>8</sup> Although differences in trial design and population limit cross-trial comparisons, patients treated with orforglipron, an oral GLP-1 R monoagonist, in the current trial experienced weight reduction similar to injectable semaglutide in people with obesity and T2D. As such, orforglipron may have the potential to offer the clinical benefits of the well established GLP-1 RA class without the known limitations of injectable therapies.

In terms of oral GLP-1 RA therapies, oral semaglutide is approved at low doses (7-mg and 14-mg) for the treatment of T2D and has been investigated at higher doses (25-mg and 50-mg) for both T2D and obesity.<sup>21-23</sup> In PIONEER PLUS, a T2D trial, in patients with uncontrolled glycaemia and BMI > 25 kg/m<sup>2</sup>, 7.3% and 8.5% reductions in body weight were observed after 52 weeks of treatment with once-daily, oral semaglutide 25-mg and 50-mg, respectively, compared to 4.7% weight decrease with the 14-mg dose.<sup>24</sup> The potential of oral medicines to reduce body weight should be interpreted in the context of their use in clinical practice. Oral semaglutide as a peptide has low bioavailability of <2% and therefore has to be taken on an empty stomach in the morning with up to 120 ml of water, and at least 30 min before eating food, drinking beverages, and taking other oral medications.<sup>23</sup> As a small molecule, orforglipron has an improved bioavailability of 79.1%, which enables it to be taken without food and water restrictions.<sup>25</sup> This next advance in incretin therapies has the potential to simplify use in clinical practice and improve adherence, all of which may reduce barriers for patients.

ADA Standards of Care in Diabetes recommend weight management in patients with T2D, indicating that weight reduction of 3–7% improves glycemia and other cardiovascular risk factors, and that sustained weight loss of >10% usually confers greater benefits, including disease-modifying effects and possible remission of T2D, and may improve long-term cardiovascular outcomes and mortality.<sup>5</sup>

In the ATTAIN-2 trial, among participants assigned to the 36-mg orforglipron dose, 67·2%, 45·6%, and 26·0% achieved body weight reductions of  $\geq 5\%$ ,  $\geq 10\%$ , and  $\geq 15\%$ , respectively. Waterfall plots reveal the heterogeneity of response to treatment, showing that even at the 6-mg dose of orforglipron, some patients lose 15%-20% of their body weight or more. Clinical practice often requires personalised treatment, considering factors such as dosing flexibility based on treatment response and tolerability as well as patient preference. Availability of multiple doses of orforglipron may enable health care providers (HCPs) to individualise treatment plans to optimise efficacy and minimise side effects based on patient feedback and shared-decision making, resulting in improvements in HCP prescribing behaviour and patient time on treatment, the ultimate goal.

As previously observed in studies investigating lifestyle interventions and obesity management medications (OMMs), body weight reduction is more difficult to achieve for people with obesity and co-existing T2D compared to those without T2D.<sup>5,8</sup> Results of the ATTAIN-2 trial are consistent with this observation, showing less weight decrease than in the ATTAIN-1 trial, in participants with obesity without diabetes.<sup>18</sup> For the efficacy estimand, the placebo-adjusted body weight reduction for orforglipron 6-mg, 12-mg, and 36-mg was 7·0%, 8·4%, and 11·4% versus 3·3%, 5·6% and 8·3% for ATTAIN-1 versus ATTAIN-2, respectively. These results can help HCPs and patients understand the average expected response in different populations (i.e., with or without T2D) when the patient tolerates and stays on medication. In managing a diverse population, dosing flexibility allows treatment tailoring such that high response patients can remain on a lower dose at a safe and healthy weight while individuals who require higher doses can be dose-escalated to treat their disease.

Notably, both ATTAIN-2 and ATTAIN-1 trials included a more realistic approach to lifestyle modification. Participants followed a healthy balanced diet with a goal of weight reduction achieved through mindfulness and healthy choices, rather than enforced calorie restriction. This is novel compared to most previous obesity clinical trials which typically recommended a 500-kcal deficit diet.<sup>6,7,21</sup>

Dose-dependent clinically meaningful reductions in HbA1c were observed with all investigated orforglipron doses. Among participants assigned to the 36-mg dose, 75·5%, 66·6%, 23·7% reached an HbA1c target of less than 7%, less than or equal to 6·5%, and less than 5·7% (normoglycemia), respectively. These effects on glycaemic control are consistent with the results from the ACHIEVE-1 trial the Phase 3 trial investigating orforglipron in participants with early T2D and BMI  $\geq 23$  kg/m<sup>2</sup>.<sup>13</sup>

Additional findings in this trial included significant improvements in important cardiorenal metabolic (CKM) risk factors including waist circumference, systolic blood pressure, fasting triglycerides, HDL cholesterol, non-HDL cholesterol, and hsCRP. The 36-mg orforglipron dose resulted in an 8·3 cm mean decrease in waist circumference, which has been used as a surrogate for visceral adiposity and to evaluate cardiovascular risk associated with obesity.<sup>26</sup> These improvements in CKM risk factors, in addition to the benefits of weight reduction, have the potential to translate over time to risk reductions in cardiovascular disease, chronic kidney disease, and MASLD, among other outcomes. Multiple cardiovascular outcome trials in people with T2D with and without established

cardiovascular disease have shown that GLP-1 RAs reduce the risk of major adverse cardiovascular events (MACE); however it is unknown for orforglipron without confirmatory cardiovascular outcomes trials.<sup>10</sup> While there are other non-incretin oral OMMs (phentermine/ topiramate, bupropion/naltrexone, phentermine), they have generally shown less mean weight reduction and have not demonstrated the reduction in MACE seen with the GLP-1 RA class of medications, which further underscores the unmet need among patients who prefer oral therapy or do not have access to injectable incretin-based treatments.<sup>27,28</sup>

The safety profile of orforglipron in the present trial was consistent with the GLP-1 RA class and with previous findings from ATTAIN-1 in people with obesity, and ACHIEVE-1 in those with T2D.<sup>13,18</sup> As typically seen with other incretin-based therapies, the most commonly reported adverse events with orforglipron were mild-to-moderate gastrointestinal events, occurring mainly during dose escalation. Adverse events leading to treatment discontinuation were higher in orforglipron-treated participants, and most commonly due to gastrointestinal-related events. No cases of MTC were reported. No liver safety signal was detected. There were no imbalances in adjudication-confirmed pancreatitis between the treatment groups. Despite substantial reductions in HbA1c, the incidence of Level 2 hypoglycaemia was low (table S4). While acknowledging differences across studies and lack of head-to-head comparisons, the treatment discontinuation rate due to adverse events in ATTAIN-2 was greater than injectable semaglutide and tirzepatide, and less than oral semaglutide.<sup>6,8,24</sup>

Strengths of the trial include the large sample size, diversity of the trial population, the double-blind, randomised, placebo-controlled design, and the stratification at randomisation that included the classification of background AHMs based on their potential effect on body weight. ATTAIN-2 also reported both duration of obesity and diabetes which averaged 18.1 years and 8.5 years, respectively. Little has been reported in the literature thus far with respect to severity or progression of obesity based on duration of disease; future obesity trials should assess this further. Orforglipron may provide a highly efficacious option for initial and chronic treatment and is being investigated as a potential long-term maintenance treatment following successful injectable GLP-1-based therapy (ATTAIN-MAINTAIN trial [ClinicalTrials.gov, NCT06584916]).<sup>29</sup>

Limitations for this study are the absence of direct comparison with other approved medications for weight management; and that gastrointestinal adverse events were self-reported, which though standard practice, could contribute to reporting bias.

In conclusion, in the ATTAIN-2 study, the once-daily non-peptide GLP-1 RA, orforglipron demonstrated clinically meaningful body weight reductions across all three doses along with substantial improvements in glycaemic control and cardiorenal metabolic risk factors in patients with obesity and T2D.

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DBH, DHR, SGK, BA, YM, SGK, JA, SCB, SA, ES, QW, AS, and IJ participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. BA and SGK were investigators in the study. AS, SA, SGK and IJ were involved in the study design and data analyses. ES and QW conducted the statistical analysis. All authors were responsible for the decision to submit the manuscript.

## **Declaration of Interests**

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## **Data Sharing**

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at [www.vivli.org](http://www.vivli.org).

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## **Main tables and figures**

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Figure 2. Effect of once-daily orforglipron compared to placebo on body weight

Table 2. Primary and secondary endpoints by treatment group

Figure 3. Orlorglipron effects in HbA<sub>1c</sub>, FSG, waist circumference, SBP, and lipid levels.

Table 3. Adverse events