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

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Summary

Background Obesity is a chronic disease that significantly contributes to type 2 diabetes and its complications. We aimed to evaluate orforglipron, an oral small-molecule (non-peptide) GLP-1 receptor agonist, for obesity treatment in adults with type 2 diabetes.

Methods This 72-week, phase 3, double-blind, placebo-controlled trial was conducted across 136 sites in ten countries. Participants with a BMI of 27 kg/m² or higher and glycated haemoglobin (HbA_{1c}) of 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 bodyweight from baseline to week 72. The treatment regimen estimand (using data from all randomly assigned participants, regardless of intercurrent events) was the primary estimand, with the efficacy estimand considered supportive. Safety was assessed in all patients who received at least one dose of study drug. This trial was registered at ClinicalTrials.gov (NCT05872620) and is completed.

Findings From June 5, 2023, to Feb 15, 2024, 2859 participants were screened, and 1613 (757 [46·9%] female) were randomly assigned, following a dose-escalation phase, to receive orforglipron 6 mg (n=329), 12 mg (n=332), 36 mg (n=322), or placebo (n=630), as an adjunct to lifestyle modification; 1444 (89·5%) completed the study. Baseline bodyweight was 101·4 kg (SD 22·5), BMI 35·6 kg/m² (SD 6·6), and HbA_{1c} 8·05% (SD 0·75; 64·4 mmol/mol [SD 8·2]). For the treatment regimen estimand, the mean percent change in bodyweight from baseline to week 72 was –5·1% (95% CI –6·0 to –4·2) with 6 mg (estimated treatment difference [ETD] –2·7 [95% CI –3·7 to –1·6]; p<0·0001), –7·0% (–7·8 to –6·2) with 12 mg (ETD –4·5 [–5·5 to –3·6]; p<0·0001), and –9·6% (–10·5 to –8·7) with 36 mg orforglipron (ETD –7·1 [–8·2 to –6·1]; p<0·0001), versus –2·5% (–3·0 to –1·9) with placebo (all p<0·0001 compared with placebo). All prespecified weight and cardiometabolic measures including HbA_{1c} statistically significantly 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. Ten deaths were reported during the study: six with orforglipron and four with placebo. Investigators deemed all deaths unrelated to the study treatment, except for one case in the placebo group and one case in the 12 mg orforglipron group. For the case in the orforglipron group, no treatment-related association was reported.

Interpretation In adults with obesity or overweight and type 2 diabetes, statistically superior reduction in bodyweight compared with placebo was demonstrated by once-daily orforglipron as an adjunct to lifestyle modification, with a safety profile similar to other GLP-1 receptor agonists.

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See Online for appendix

Introduction

The global prevalence of obesity and overweight is expected to increase to 3 billion adults by 2030.[1] Obesity increases the risk of type 2 diabetes, 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.[2] Considering these increased risks, people with obesity and type 2 diabetes need effective and safe therapies that lead to weight reduction and improved glycaemic control, which could ultimately translate into long-term health benefits.[3–5]

Current injectable GLP-1-based therapies demonstrated substantial weight reduction in people living with obesity and type 2 diabetes,[6–8] as well as improved glycaemic control

Research in context

Evidence before this study

Strong and consistent evidence demonstrates the benefit of managing obesity in people with type 2 diabetes. Weight reduction improves glycaemia, functional status, and quality of life, and reduces the need for glucose-lowering medications in people with obesity and type 2 diabetes. Additionally, greater weight reduction can promote sustained diabetes remission. On June 18, 2025, we searched PubMed using the search terms "glucagon-like peptide-1 receptor agonist" (GLP-1 receptor agonist), AND "obesity", AND "overweight", AND "type 2 diabetes" for any published articles, with no date or language restrictions.

To date, two GLP-1 receptor monoagonists, liraglutide (3 mg once daily) and semaglutide (2·4 mg once weekly), and tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor 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 type 2 diabetes 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 receptor agonist 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 type 2 diabetes (ATTAIN-2). Results of the ATTAIN-2 trial are reported herein.

Added value of this study

ATTAIN-2 is the first completed long-term (72-week) trial with a once-daily, oral, small-molecule GLP-1 receptor agonist, as an adjunct to lifestyle modification, in adults with a BMI of 27 kg/m² or higher and type 2 diabetes with the primary objective focusing on bodyweight changes. In this trial, orforglipron demonstrated clinically meaningful reductions in bodyweight along with improvements in glycaemic control and cardiometabolic risk factors. The mean bodyweight reduction at week 72 was up to 9·6% at the highest orforglipron dose, and a substantial proportion of participants reached weight loss of 10% or greater or 15% or greater. The results exceed what is typically seen in this population with currently available oral medications for obesity management. Additionally, glycated haemoglobin (HbA_{1c}) reduction of up to 1·66%, and a substantial proportion of participants reaching HbA_{1c} levels less than 7% (75·5%) and less than or equal to 6·5% (66·6%) with orforglipron 36 mg, highlight the dual benefit of orforglipron for both weight reduction and glycaemic improvement, addressing the challenge of managing both obesity and diabetes simultaneously. Observed reductions in waist circumference, systolic blood pressure, non-HDL cholesterol, and triglycerides suggest that orforglipron could offer broad cardiometabolic benefits, which is particularly important given the elevated cardiovascular risk in this population. Overall, the findings indicate that orforglipron could address the unmet need for oral therapy by achieving outcomes similar to those of injectable GLP-1 receptor agonists, potentially shifting treatment paradigms.

Implications of all the available evidence

In this phase 3 trial in adults with obesity and type 2 diabetes, orforglipron demonstrated clinically meaningful bodyweight reduction. Bodyweight 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 type 2 diabetes with a BMI of 23 kg/m² or higher (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.

and reduced cardiovascular risks.[9–11] 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 to address the continued unmet needs of people living with obesity and co-existing type 2 diabetes.

Small-molecule GLP-1 receptor agonists could offer the physiological benefits of peptide GLP-1-based therapies, including appetite suppression, clinically meaningful weight reduction, and stimulation of insulin secretion.[12] Compared with peptide oral GLP-1 receptor agonists, small molecules have higher bioavailability and do not require food and water restrictions during administration, improving convenience.[12–14] Additionally, an oral small-molecule formulation could increase treatment adherence and be manufactured at a greater scale, thereby improving access.[15]

Orforglipron is a once-daily, orally administered, small-molecule, GLP-1 receptor agonist currently being investigated for treatment of obesity, type 2 diabetes, hypertension, obstructive sleep apnoea, and osteoarthritis.[14,16,17] In the ATTAIN-1 study, in adults with obesity and without type 2 diabetes, orforglipron 36 mg reduced bodyweight by up to 12·4% after 72 weeks of treatment, with associated improvements in cardiometabolic risk factors.[18] Considering the importance of weight reduction for patients with type 2 diabetes 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 type 2 diabetes.

Here, we present the results of the ATTAIN-2 study, which investigated orforglipron for weight management in adults with a BMI of 27 kg/m² or higher and co-existing type 2 diabetes.

Methods

Study design and participants

This phase 3, multicentre, randomised, parallel-arm, placebo-controlled, double-blind, 72-week study was conducted across 136 sites in Argentina, Australia, Brazil, China, Czech Republic, Germany, Greece, India, South Korea, and the USA. The study comprised a 3-week screening period, followed by a 72-week treatment period including up to 20-week dose escalation, and a 2-week post-treatment safety follow-up period (appendix p 24). The study protocol and statistical analysis plan can be found in the appendix. Changes to the initial study protocol are listed in the appendix (pp 42–45). Protocol deviations are listed in the appendix (pp 46–47); the trial conclusions were not affected by the protocol deviations.

Eligible participants were adults (aged ≥18 years) with a BMI of 27 kg/m² or higher, with pre-existing type 2 diabetes with a glycated haemoglobin (HbA_{1c}) of 7–10% (53–86 mmol/mol), who had stable treatment for type 2 diabetes for at least 90 days before visit 1, with either diet or exercise alone or up to three oral antihyperglycaemic medications (excluding DPP-4 inhibitors or GLP-1 receptor agonists). They must have had a history of at least one self-reported unsuccessful dietary effort to lose bodyweight. Key exclusion criteria included any other type of diabetes except type 2, one or more episodes of severe hypoglycaemia or one or more episodes of hypoglycaemia unawareness within the 180 days before the screening visit, self-reported change in bodyweight of more than 5 kg within 90 days before screening, receiving or planning to receive treatment for diabetic retinopathy or macular oedema, and an estimated glomerular filtration rate of less than 15 mL/min per 1·73 m² of body surface area. Full inclusion and exclusion criteria are provided in the appendix (pp 11–15).

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. An independent data safety monitoring board was not established for this study, as the associated risks, trial size, and complexity were adequately addressed by a sponsor-implemented safety monitoring plan. All participants provided written informed consent. This trial is registered at ClinicalTrials.gov (NCT05872620) and is completed. The trial was conducted from June 5, 2023, to Aug 8, 2025.

Randomisation and masking

Participants were randomly assigned in a 1:1:1:2 ratio (based on regulatory requirements to ensure enough participants in the placebo group for safety evaluation) 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 antihyperglycaemic medications 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, the sponsor, and participants remained masked to the study intervention until the study was completed.

Procedures

Following randomisation, all interventions were administered orally once daily. Participants received blinded orforglipron or matching placebo. The starting dose was 1 mg, and the dose increased every 4 weeks (to 3 mg, 6 mg, 12 mg, and 36 mg, as applicable) until the assigned dose (6 mg, 12 mg, or 36 mg) was reached (appendix p 24). Dose selection was based on the assessment of efficacy and safety in phase 2 studies and exposure–response modelling.[16,17] During the study, participants received lifestyle modification consisting of individualised counselling regarding a healthy diet with the goal of achieving weight reduction. Participants were counselled on portion control (eating smaller, more frequent meals or snacks), avoiding skipping meals, adding protein and fibre-rich foods (fruits, vegetables, whole grains), limiting foods high in solid fats, added sugar, and salt, and choices individualised to personal, cultural, and budgetary needs and preferences. Additionally, participants were counselled on a healthy physical activity level of at least 150 min 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 antihyperglycaemic medications were to be continued at the current dose. Initiation of new antihyperglycaemic medications (excluding GLP-1 receptor agonists, DPP-4 inhibitors, or amylin analogues or agonists) was allowed according to specific rescue criteria for severe persistent hyperglycaemia, as described in the protocol. Gluco-meters were provided to self-monitor blood glucose and participants were encouraged to record values.

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

Outcomes

The primary endpoint was the mean percent change in bodyweight at week 72 from baseline. Key secondary endpoints at week 72 included the percentage of

participants who had bodyweight reduction of 5% or greater and 10% or greater on orforglipron 6 mg, and 5% or greater, 10% or greater, and 15% or greater on 12 mg or 36 mg; mean change in waist circumference on 36 mg; mean change in fasting serum glucose on all orforglipron doses (6 mg, 12 mg, and 36 mg); mean change in HbA_{1c} on all doses; percentage of participants reaching HbA_{1c} target values of less than 7% and less than or equal to 6·5% on all doses; mean change in systolic blood pressure for pooled doses; and mean percent change in non-HDL cholesterol and triglycerides for 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 were mean change in absolute bodyweight on all orforglipron doses (6 mg, 12 mg, and 36 mg); mean change in BMI on all doses; percentage of participants reaching an HbA_{1c} target value of less than 5·7% on all doses; mean percent change in fasting insulin on all doses; mean change in waist circumference on 6 mg and 12 mg; mean change in diastolic blood pressure for pooled doses; mean percent change in total, LDL, and HDL cholesterol for pooled doses; mean change in Short Form-36 version 2 (SF-36v2) acute form domain scores for pooled doses; and mean change in the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) total score for pooled doses. Data on the other prespecified patient-reported outcomes (EuroQoL 5-Dimensions 5-Level [EQ-5D-5L], and Patient Global Impression of Severity and Patient Global Impression of Change (with regard to physical function due to weight) are unavailable at the time of this publication. High-sensitivity C-reactive protein (hsCRP) and self-monitoring blood glucose (SMBG) were included as prespecified exploratory objectives.

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 conducted 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 a serious adverse event. Additionally, deaths, major adverse cardiovascular events (MACE; such as myocardial infarction, hospitalisation due to unstable angina or heart failure, coronary revascularisation, 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: 300 participants per orforglipron treatment group and 600 participants in the placebo group) provided a power of greater than 90% to demonstrate superiority of orforglipron 6 mg, 12 mg, and/or 36 mg to placebo with regard to mean percent change in bodyweight 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 I error rate of 0·05 using a two-sample *t*-test for the treatment regimen estimand. A difference of at least 5% mean bodyweight reduction at 72 weeks for orforglipron doses compared with placebo, a common SD of 10%, and a dropout rate of 30% in the placebo group and 20% in the orforglipron groups were assumed for statistical power calculations. A graphical approach for multiple comparisons was used for testing primary and key secondary endpoints. Model-based estimates and 95% CIs are reported. 95% CIs were not adjusted for multiplicity and should not be used for hypothesis testing.

Two estimands were used: 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 randomly assigned 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.[19] 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. Reaching a certain threshold (5%, 10%, 15%) in bodyweight 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.[20]

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 (MMRM) was used with adjustment for baseline value, region, and other stratification factors considering a three-way interaction between treatments, visits, and baseline value (or stratification factors).[13,21]

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. Safety assessments included adverse events and serious adverse events reported during the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and assessed for severity and relationship to study treatment by investigators. The frequency and proportion of participants experiencing adverse events and serious adverse events were summarised descriptively. Categorical comparisons used Fisher's exact test and risk differences with 95% CIs were provided. Some prespecified continuous measures were analysed using MMRM with relevant covariates. Safety analyses were exploratory. No imputation was applied.

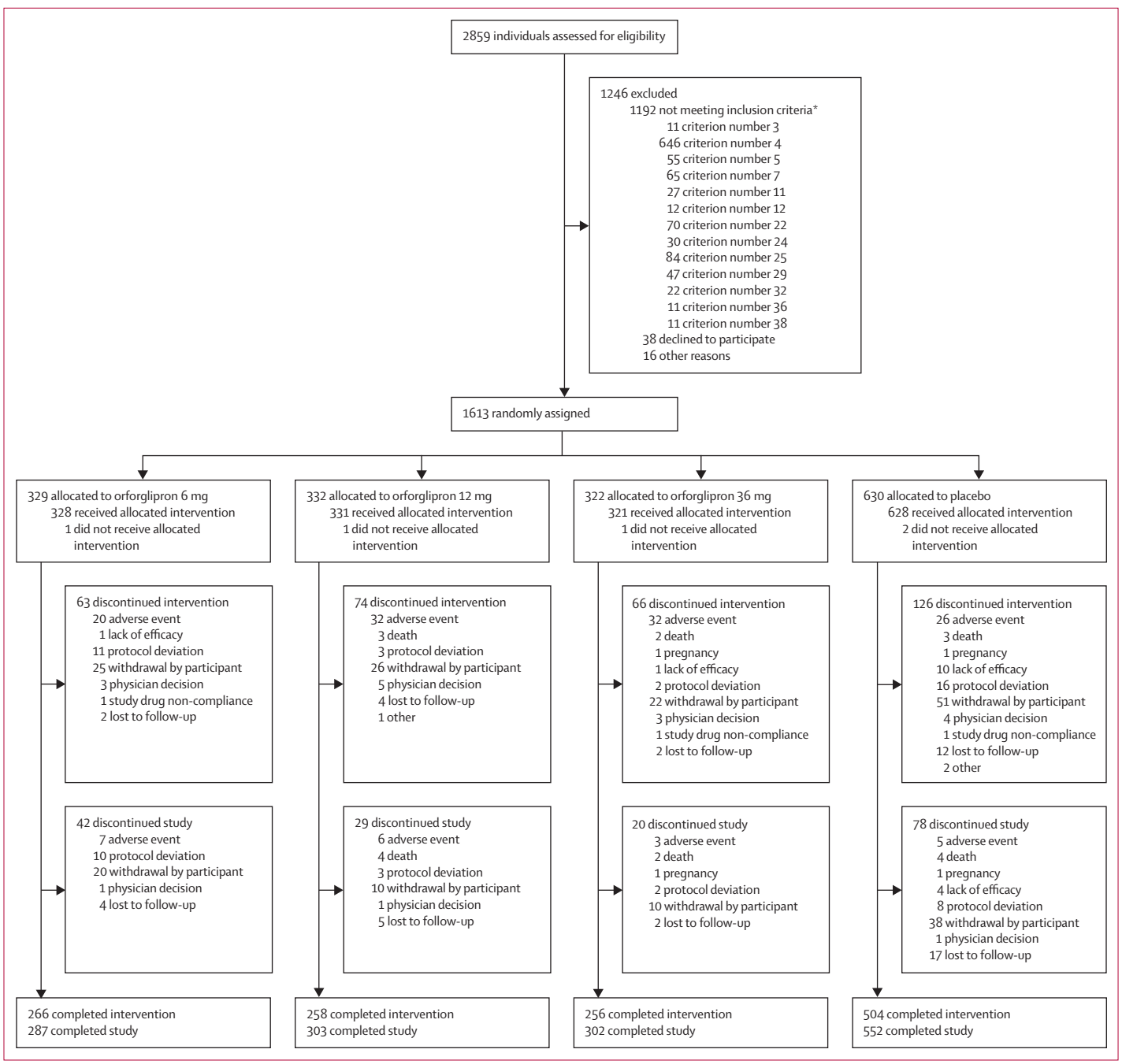


Figure 1: **Trial profile**

*Individual numbers are shown for inclusion criteria with n>10. For full details on the inclusion criteria and the complete list refer to the appendix (pp 11–15).

	Orforglipron 6 mg (n=329)	Orforglipron 12 mg (n=332)	Orforglipron 36 mg (n=322)	Placebo (n=630)	Total (n=1613)
Age, years	56·8 (10·4)	56·2 (10·5)	58·1 (10·8)	56·5 (10·9)	56·8 (10·7)
Age <65 years	251 (76·3%)	247 (74·4%)	221 (68·6%)	474 (75·2%)	1193 (74·0%)
Age ≥65 years	78 (23·7%)	85 (25·6%)	101 (31·4%)	156 (24·8%)	420 (26·0%)
Sex					
Female	150 (45·6%)	155 (46·7%)	154 (47·8%)	298 (47·3%)	757 (46·9%)
Male	179 (54·4%)	177 (53·3%)	168 (52·2%)	332 (52·7%)	856 (53·1%)
Race*					
American Indian or Alaska Native	0	2 (0·6%)	1 (0·3%)	2 (0·3%)	5 (0·3%)
Asian	58 (17·6%)	55 (16·6%)	54 (16·8%)	112 (17·8%)	279 (17·3%)
Black or African American	21 (6·4%)	19 (5·7%)	28 (8·7%)	37 (5·9%)	105 (6·5%)
White	238 (72·3%)	235 (70·8%)	228 (70·8%)	442 (70·2%)	1143 (70·9%)
Native Hawaiian or other Pacific Islander	2 (0·6%)	1 (0·3%)	0	3 (0·5%)	6 (0·4%)
Multiple	5 (1·5%)	12 (3·6%)	6 (1·9%)	22 (3·5%)	45 (2·8%)
Ethnicity*					
Hispanic or Latino	102 (31·0%)	95 (28·6%)	97 (30·1%)	194 (30·8%)	488 (30·3%)
Not Hispanic or Latino	221 (67·2%)	229 (69·0%)	218 (67·7%)	416 (66·0%)	1084 (67·2%)
Geographical region					
Asia	52 (15·8%)	50 (15·1%)	50 (15·5%)	102 (16·2%)	254 (15·7%)
Australia	18 (5·5%)	19 (5·7%)	20 (6·2%)	35 (5·6%)	92 (5·7%)
Central and South America	77 (23·4%)	80 (24·1%)	76 (23·6%)	150 (23·8%)	383 (23·7%)
Europe	92 (28·0%)	93 (28·0%)	87 (27·0%)	170 (27·0%)	442 (27·4%)
North America	90 (27·4%)	90 (27·1%)	89 (27·6%)	173 (27·5%)	442 (27·4%)
Duration of obesity, years	17·5 (7·6–26·1)	14·8 (7·8–23·8)	15·7 (8·5–24·1)	16·1 (8·0–24·8)	15·9 (8·0–24·6)
Duration of diabetes, years	7·6 (3·8–13·7)	6·4 (3·5–10·1)	7·0 (4·0–13·1)	6·8 (3·5–10·9)	6·9 (3·7–11·7)
Bodyweight, kg	102·3 (22·7)	102·7 (21·3)	99·8 (23·0)	101·2 (22·6)	101·4 (22·5)
BMI, kg/m²	35·9 (7·0)	36·1 (6·3)	35·1 (6·5)	35·5 (6·5)	35·6 (6·6)
BMI category					
<30 kg/m²	67 (20·4%)	52 (15·7%)	83 (25·8%)	124 (19·7%)	326 (20·2%)
≥30 to <35 kg/m²	108 (32·8%)	111 (33·4%)	97 (30·1%)	222 (35·2%)	538 (33·4%)
≥35 to <40 kg/m²	85 (25·8%)	90 (27·1%)	83 (25·8%)	151 (24·0%)	409 (25·4%)
≥40 kg/m²	69 (21·0%)	79 (23·8%)	59 (18·3%)	133 (21·1%)	340 (21·1%)
Waist circumference, cm	116·8 (15·1)	116·2 (13·4)	114·7 (15·1)	115·0 (14·6)	115·6 (14·6)
Blood pressure, mm Hg					
Systolic	131·3 (14·7)	132·1 (15·0)	132·5 (13·7)	130·6 (14·1)	131·4 (14·4)
Diastolic	81·6 (10·4)	82·1 (10·0)	81·8 (10·1)	81·0 (9·1)	81·5 (9·8)
Pulse, bpm	75·9 (11·4)	73·7 (10·7)	74·6 (10·5)	74·2 (10·5)	74·5 (10·8)
Lipid parameters, mg/dL					
Total cholesterol	167·9 (25·3)	167·1 (26·0)	167·6 (27·4)	167·5 (26·2)	167·5 (26·2)
Non-HDL cholesterol	120·7 (36·0)	121·4 (34·7)	121·2 (37·4)	122·3 (35·4)	121·6 (35·7)
HDL cholesterol	43·5 (25·7)	42·8 (23·8)	43·1 (25·1)	42·0 (25·8)	42·7 (25·3)
LDL cholesterol	84·3 (47·5)	83·8 (45·3)	85·5 (50·0)	84·6 (49·3)	84·5 (48·2)
Triglycerides	157·4 (57·2)	164·4 (53·3)	157·2 (52·1)	162·8 (53·5)	160·9 (53·9)
eGFR†, mL/min per 1·73 m²	82·3 (20·9)	83·9 (21·0)	82·2 (22·5)	82·7 (21·5)	82·8 (21·5)
HbA_{1c}, %	8·03 (0·73)	8·08 (0·76)	8·05 (0·73)	8·03 (0·75)	8·05 (0·75)
HbA_{1c}, mmol/mol	64·3 (8·0)	64·8 (8·4)	64·5 (8·0)	64·3 (8·2)	64·4 (8·2)
Fasting serum glucose, mg/dL	152·9 (41·6)	155·1 (43·0)	154·7 (40·1)	151·5 (39·5)	153·1 (40·8)
Fasting serum glucose, mmol/L	8·5 (2·3)	8·6 (2·4)	8·6 (2·2)	8·4 (2·2)	8·5 (2·3)
Fasting insulin, mIU/L	18·9 (75·6)	19·7 (65·9)	18·8 (76·0)	18·2 (71·7)	18·8 (72·2)
hsCRP, mg/L	2·7 (147·6)	2·8 (169·6)	2·4 (138·4)	3·0 (151·3)	2·8 (151·9)

(Table 1 continues on next page)

	Orforglipron 6 mg (n=329)	Orforglipron 12 mg (n=332)	Orforglipron 36 mg (n=322)	Placebo (n=630)	Total (n=1613)
(Continued from previous page)					
Antihyperglycaemic drug class					
Biguanides	282 (85·7%)	275 (82·8%)	270 (83·9%)	524 (83·2%)	1351 (83·8%)
Sulfonylureas	40 (12·2%)	51 (15·4%)	50 (15·5%)	83 (13·2%)	224 (13·9%)
SGLT2 inhibitor	105 (31·9%)	97 (29·2%)	109 (33·9%)	206 (32·7%)	517 (32·1%)
Thiazolidinediones	15 (4·6%)	14 (4·2%)	16 (5·0%)	32 (5·1%)	77 (4·8%)
α-glucosidase inhibitors	0	4 (1·2%)	2 (0·6%)	4 (0·6%)	10 (0·6%)
Other‡	0	0	1 (0·3%)	2 (0·3%)	3 (0·2%)
Number of oral antihyperglycaemic drugs					
0	31 (9·4%)	35 (10·5%)	35 (10·9%)	73 (11·6%)	174 (10·8%)
1	176 (53·5%)	172 (51·8%)	146 (45·3%)	311 (49·4%)	805 (49·9%)
2	103 (31·3%)	106 (31·9%)	121 (37·6%)	204 (32·4%)	534 (33·1%)
≥3	19 (5·8%)	19 (5·7%)	20 (6·2%)	42 (6·7%)	100 (6·2%)
Comorbidities§					
Hypertension	252 (76·6%)	233 (70·2%)	246 (76·4%)	470 (74·6%)	1201 (74·5%)
Dyslipidaemia	232 (70·5%)	242 (72·9%)	225 (69·9%)	441 (70·0%)	1140 (70·7%)
Coronary artery disease	19 (5·8%)	21 (6·3%)	27 (8·4%)	49 (7·8%)	116 (7·2%)
Cerebrovascular disease	14 (4·3%)	19 (5·7%)	17 (5·3%)	32 (5·1%)	82 (5·1%)
Obstructive sleep apnoea	49 (14·9%)	45 (13·6%)	34 (10·6%)	86 (13·7%)	214 (13·3%)
Osteoarthritis	71 (21·6%)	57 (17·2%)	78 (24·2%)	112 (17·8%)	318 (19·7%)
Anxiety or depression	45 (13·7%)	50 (15·1%)	42 (13·0%)	86 (13·7%)	223 (13·8%)
MASLD	96 (29·2%)	100 (30·1%)	96 (29·8%)	173 (27·5%)	465 (28·8%)
Asthma or COPD	28 (8·5%)	37 (11·1%)	23 (7·1%)	48 (7·6%)	136 (8·4%)
PCOS¶	3 (2·0%)	1 (0·6%)	4 (2·6%)	6 (2·0%)	14 (1·8%)
Gout or hyperuricaemia	36 (10·9%)	39 (11·7%)	45 (14·0%)	81 (12·9%)	201 (12·5%)
Renal disease	34 (10·3%)	37 (11·1%)	31 (9·6%)	78 (12·4%)	180 (11·2%)
Number of comorbidities in addition to type 2 diabetes					
None	16 (4·9%)	21 (6·3%)	17 (5·3%)	43 (6·8%)	97 (6·0%)
1–2	142 (43·2%)	143 (43·1%)	145 (45·0%)	272 (43·2%)	702 (43·5%)
3–4	124 (37·7%)	129 (38·9%)	111 (34·5%)	224 (35·6%)	588 (36·5%)
≥5	47 (14·3%)	39 (11·7%)	49 (15·2%)	91 (14·4%)	226 (14·0%)

Data are n (%); mean (SD); median (IQR), for duration of obesity and duration of diabetes; or geometric mean (coefficient of variation, %), for lipid parameters, fasting insulin, and hsCRP. bpm=beats per minute. COPD=chronic obstructive pulmonary disease. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin. hsCRP=high-sensitivity C-reactive protein. MASLD=metabolic dysfunction-associated steatotic liver disease. PCOS=polycystic ovarian syndrome. *Race or ethnicity was reported by the participants. †The value of the eGFR was calculated according to the cystatin C-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. ‡Other blood glucose-lowering drugs, excluding insulins. §Comorbidities were assessed through a review of medical history. ¶Percentage is based on the total number of female participants in the respective treatment group: n=150 (orforglipron 6 mg), n=155 (orforglipron 12 mg), n=154 (orforglipron 36 mg), n=298 (placebo), n=757 (total).

Table 1: **Demographic and baseline clinical characteristics of participants**

Additional details of the statistical methods can be found in the appendix (pp 16–23).

Role of the funding source

The sponsor (Eli Lilly) designed and oversaw the conduct of the trial, performed site monitoring, data collation, and data analysis, and was involved in data interpretation and writing of the report. The investigators were responsible for data collection and worked under confidentiality agreements with the sponsor.

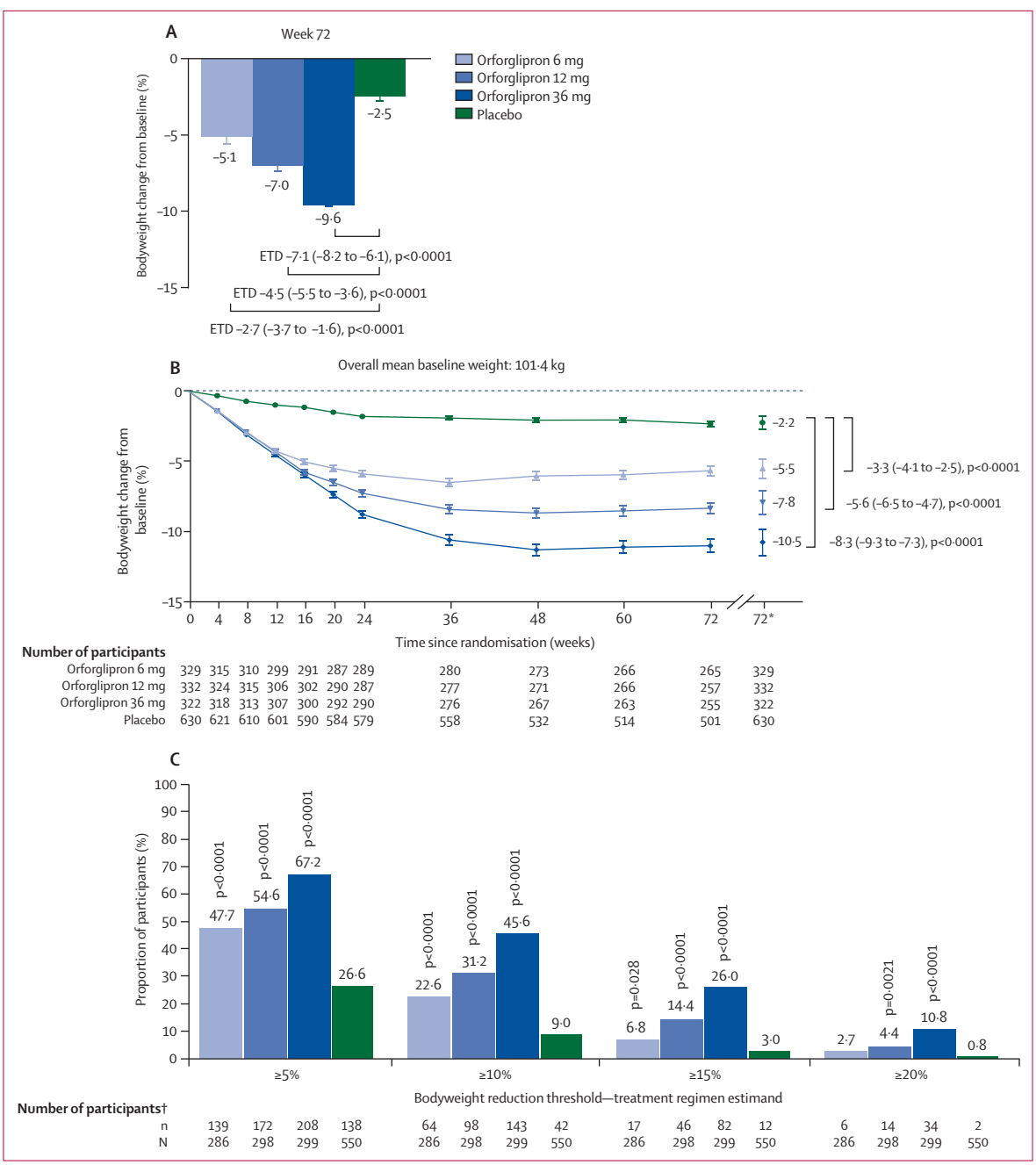
Results

From June 5, 2023, to Feb 15, 2024, 2859 participants were screened for study eligibility, of whom 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 most common reasons for treatment discontinuations were withdrawal by the patient (due to personal reasons not related to the trial, scheduling conflicts, or relocation to another part of the country) and adverse events. 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 bodyweight was 101·4 kg (SD 22·5), BMI 35·6 kg/m² (SD 6·6), median duration of obesity 15·9 years (IQR 8·0–24·6), mean HbA_{1c} 8·05% (SD 0·75; 64·4 mmol/mol [SD 8·2]), and median duration of diabetes 6·9 years (IQR 3·7–11·7); 13·9% were treated with sulfonylureas and 32·1% treated with SGLT2 inhibitors (table 1).

For the treatment regimen estimand, the mean percent change from baseline in bodyweight 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,



(Figure 2 continues on next page)

and –2·5% (–3·0 to –1·9) or –2·7 kg with placebo (figure 2A, 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% (–5·5 to –3·6) for the 12 mg dose, and –7·1% (–8·2 to –6·1) for the 36 mg dose (p<0·0001 for all comparisons; table 2). Results by subgroup can be found in the appendix (pp 25–27).

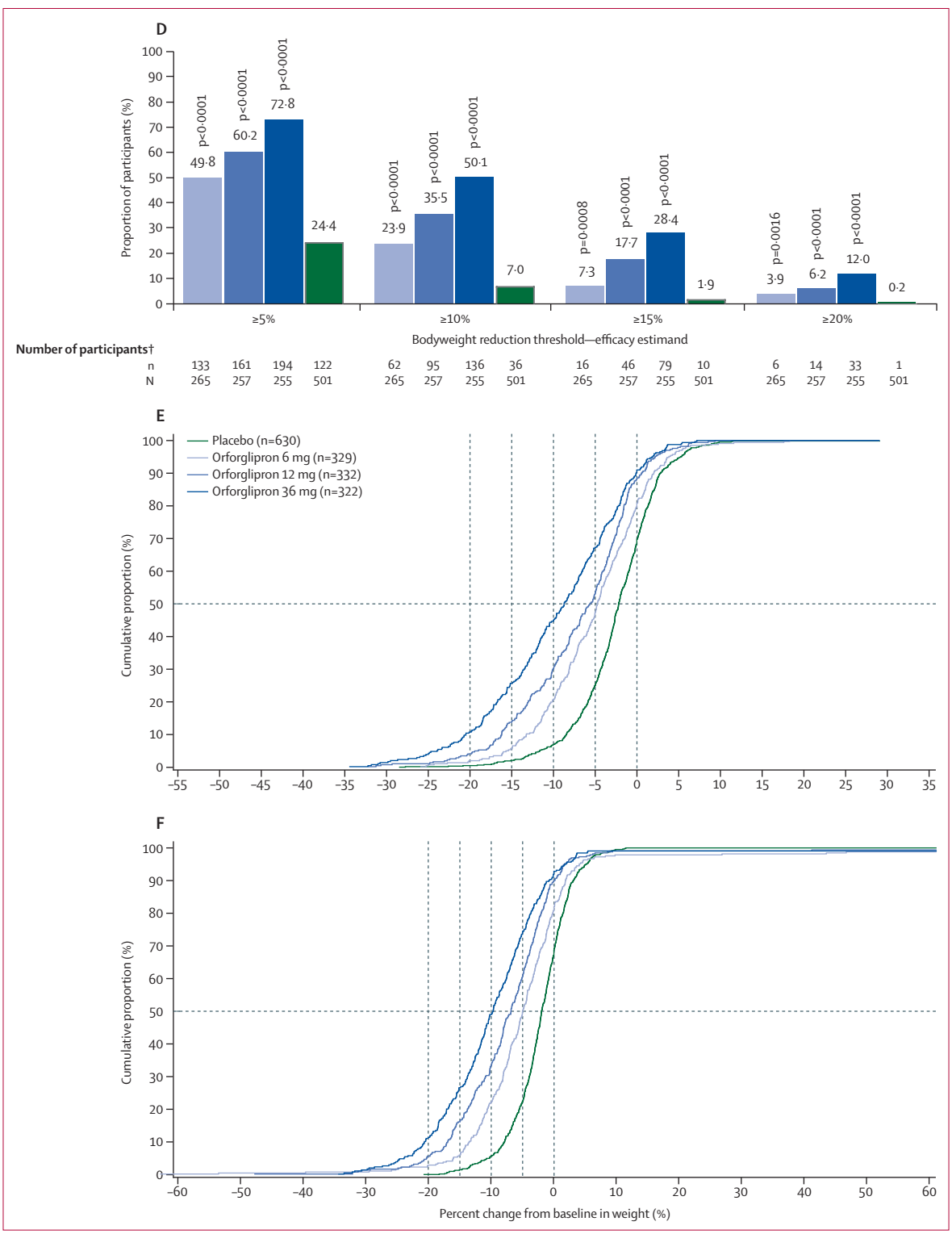


Figure 2: **Bodyweight and bodyweight reduction thresholds**

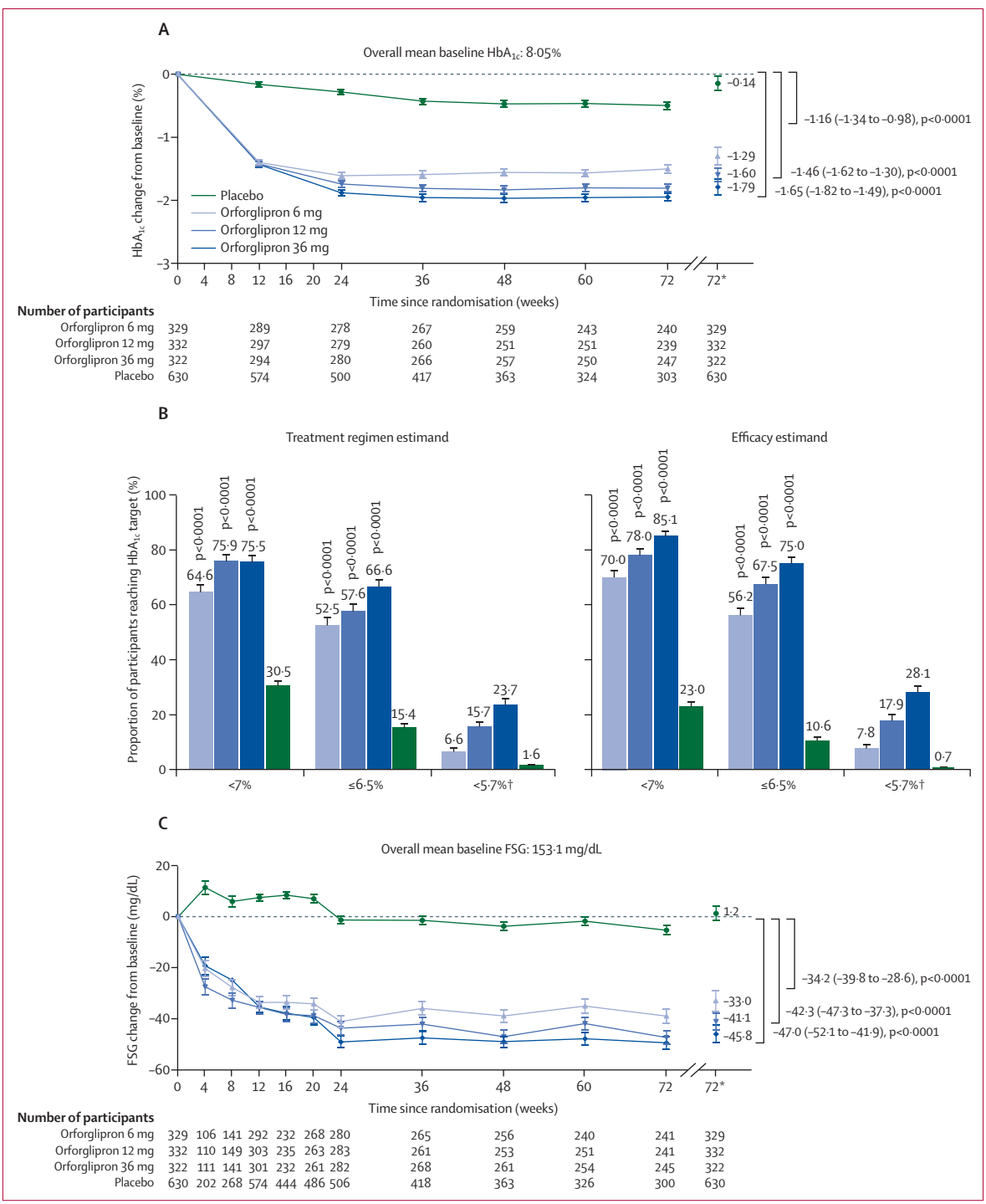
Data are model-based estimate (MBE) unless otherwise stated. (A) Percent change in bodyweight at week 72 from baseline (treatment regimen estimand). (B) Percent change in bodyweight from baseline to week 72. The curves shown from week 0 to week 72 are based on observed mean with standard errors using the efficacy estimand datapoints set, including all datapoints obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments. (C, D) Percentage of participants who reached bodyweight reduction thresholds (≥5%, ≥10%, ≥15%, and ≥20%) from logistic regression analysis for the treatment regimen estimand (C) and for the efficacy estimand (D). ≥15% threshold was an additional secondary endpoint for the orforglipron 6 mg dose and not controlled for multiplicity; ≥20% threshold was an exploratory objective and was not controlled for multiplicity. (E) Cumulative distribution of percent change in bodyweight for the treatment regimen estimand; missing data were imputed with primary multiple imputation method. (F) Cumulative distribution of percent change in bodyweight for the efficacy estimand; missing data were imputed using multiple imputation with missing at random assumption. p values refer to comparison with placebo. ETD=estimated treatment difference. *MBE (95% CI) for percent change in bodyweight from baseline to week 72 and ETD (95% CI) between orforglipron groups and placebo based on mixed model for repeated measures analysis (efficacy estimand). †N denotes number of participants with non-missing value at the specified timepoint; n denotes number of participants reaching threshold in observed data.

	Orforglipron 6 mg (n=329)	Orforglipron 12 mg (n=332)	Orforglipron 36 mg (n=322)	Placebo (n=630)
Primary endpoint*				
Percent change in weight, % (95% CI)	−5·1 (−6·0 to −4·2)	−7·0 (−7·8 to −6·2)	−9·6 (−10·5 to −8·7)	−2·5 (−3·0 to −1·9)
Treatment comparison (95% CI); p value	ETD −2·7 (−3·7 to −1·6); p<0·0001	ETD −4·5 (−5·5 to −3·6); p<0·0001	ETD −7·1 (−8·2 to −6·1); p<0·0001	..
Key secondary endpoints*				
Participants with weight reduction ≥5% at week 72, % (SE)†	47·7 (2·9)	54·6 (2·8)	67·2 (2·7)	26·6 (2·0)
Treatment comparison (95% CI); p value	RD 21·1 (14·1 to 28·0); p<0·0001	RD 28·0 (21·4 to 34·7); p<0·0001	RD 40·5 (34·2 to 46·9); p<0·0001	..
Participants with weight reduction ≥10% at week 72, % (SE)†	22·6 (2·5)	31·2 (2·6)	45·6 (2·7)	9·0 (1·4)
Treatment comparison (95% CI); p value	RD 13·6 (8·0 to 19·2); p<0·0001	RD 22·1 (16·5 to 27·7); p<0·0001	RD 36·6 (30·7 to 42·6); p<0·0001	..
Participants with weight reduction ≥15% at week 72, % (SE)†	NA	14·4 (1·9)	26·0 (2·4)	3·0 (0·7)
Treatment comparison (95% CI); p value	..	RD 11·4 (7·4 to 15·3); p<0·0001	RD 22·9 (18·0 to 27·9); p<0·0001	..
Change in waist circumference, cm (95% CI)	NA	NA	−8·3 (−9·2 to −7·5)	−2·8 (−3·4 to −2·3)
Treatment comparison (95% CI); p value	..	..	ETD −5·5 (−6·5 to −4·5); p<0·0001	..
Change in HbA_{1c}, % (95% CI)	−1·22 (−1·36 to −1·08)	−1·50 (−1·62 to −1·38)	−1·66 (−1·77 to −1·55)	−0·47 (−0·58 to −0·36)
Treatment comparison (95% CI); p value	ETD −0·76 (−0·93 to −0·58); p<0·0001	ETD −1·03 (−1·19 to −0·87); p<0·0001	ETD −1·20 (−1·35 to −1·04); p<0·0001	..
Change in HbA_{1c}, mmol/mol (95% CI)	−13·4 (−14·9 to −11·8)	−16·4 (−17·7 to −15·0)	−18·2 (−19·4 to −16·9)	−5·1 (−6·3 to −3·9)
Treatment comparison (95% CI); p value	ETD −8·3 (−10·1 to −6·4); p<0·0001	ETD −11·3 (−13·1 to −9·5); p<0·0001	ETD −13·1 (−14·8 to −11·4); p<0·0001	..
Participants with HbA_{1c} <7%, % (SE)†	64·6 (2·8)	75·9 (2·5)	75·5 (2·5)	30·5 (2·0)
Treatment comparison (95% CI); p value	RD 34·2 (27·4 to 41·0); p<0·0001	RD 45·4 (38·9 to 51·9); p<0·0001	RD 45·1 (38·8 to 51·4); p<0·0001	..
Participants with HbA_{1c} ≤6·5%, % (SE)†	52·5 (3·0)	57·6 (2·8)	66·6 (2·7)	15·4 (1·7)
Treatment comparison (95% CI); p value	RD 37·1 (30·5 to 43·8); p<0·0001	RD 42·2 (35·9 to 48·5); p<0·0001	RD 51·2 (45·0 to 57·5); p<0·0001	..
Change in fasting serum glucose, mg/dL (95% CI)	−30·5 (−35·1 to −26·0)	−38·6 (−42·2 to −35·0)	−42·4 (−46·4 to −38·4)	−9·3 (−13·2 to −5·4)
Treatment comparison (95% CI); p value	ETD −21·2 (−26·8 to −15·6); p<0·0001	ETD −29·2 (−34·2 to −24·3); p<0·0001	ETD −33·1 (−38·3 to −27·8); p<0·0001	..
Change in fasting serum glucose, mmol/L (95% CI)	−1·7 (−1·9 to −1·4)	−2·1 (−2·3 to −1·9)	−2·4 (−2·6 to −2·1)	−0·5 (−0·7 to −0·3)
Treatment comparison (95% CI); p value	ETD −1·2 (−1·5 to −0·9); p<0·0001	ETD −1·6 (−1·9 to −1·4); p<0·0001	ETD −1·8 (−2·1 to −1·5); p<0·0001	..
Additional secondary endpoints (at week 72)				
Change in absolute bodyweight, kg (95% CI)	−5·3 (−6·3 to −4·4)	−7·2 (−8·0 to −6·3)	−9·6 (−10·6 to −8·7)	−2·7 (−3·3 to −2·1)
Treatment comparison (95% CI)	ETD −2·6 (−3·7 to −1·6)	ETD −4·5 (−5·5 to −3·5)	ETD −7·0 (−8·0 to −5·9)	..
Participants with weight reduction ≥15% at week 72, % (SE)†	6·8 (1·5)	NA	NA	3·0 (0·7)
Treatment comparison (95% CI)	RD 3·8 (0·4 to 7·1)	..	..	..
Change in waist circumference, cm (95% CI)	−5·4 (−6·3 to −4·5)	−6·3 (−7·1 to −5·5)	NA	−2·8 (−3·4 to −2·3)
Treatment comparison (95% CI)	ETD −2·6 (−3·6 to −1·5)	ETD −3·5 (−4·5 to −2·5)	..	..
Change in BMI, kg/m² (95% CI)	−1·9 (−2·2 to −1·6)	−2·6 (−2·8 to −2·3)	−3·4 (−3·8 to −3·1)	−1·0 (−1·2 to −0·8)
Treatment comparison (95% CI)	ETD −0·9 (−1·2 to −0·5)	ETD −1·6 (−1·9 to −1·2)	ETD −2·5 (−2·8 to −2·1)	..
Participants with HbA_{1c} <5·7%, % (SE)†	6·6 (1·4)	15·7 (2·0)	23·7 (2·4)	1·6 (0·6)
Treatment comparison (95% CI)	RD 5·0 (2·1 to 7·9)	RD 14·1 (10·0 to 18·2)	RD 22·0 (17·3 to 26·8)	..
Percent change in fasting insulin, % (95% CI)	−5·1 (−10·4 to 0·5)	−11·9 (−17·4 to −6·0)	−19·8 (−24·7 to −14·7)	−4·2 (−8·8 to 0·7)
Treatment comparison (95% CI)	ETD −1·0 (−8·1 to 6·6)	ETD −8·0 (−15·2 to −0·3)	ETD −16·4 (−22·5 to −9·7)	..
Exploratory objective (at week 72)				
Percent change in hsCRP, % (95% CI)	−32·4 (−39·8 to −24·2)	−41·8 (−47·0 to −36·1)	−47·5 (−52·7 to −41·7)	−10·0 (−16·4 to −3·1)
Treatment comparison (95% CI)	ETD −24·9 (−34·4 to −14·1)	ETD −35·3 (−42·3 to −27·5)	ETD −41·6 (−48·6 to −33·7)	..

Data are model-based estimate and 95% CI assessed with the use of ANCOVA according to the treatment regimen estimand. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. All changes are at week 72 from baseline. Lipid parameters, fasting insulin, and hsCRP were analysed using log-transformation. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin. hsCRP=high-sensitivity C-reactive protein. NA=not applicable (the corresponding endpoint does not belong to the category of endpoints [primary, key secondary, or additional secondary] presented in that section of the table). RD=risk difference. *The primary and key secondary endpoints were tested under type I error control procedure using a two-sided nominal significance level of 0·05. †Data presented as model-based estimate (SE) from logistic regression according to the treatment regimen estimand. The percentage was calculated by combining the percentages of participants who met the target in imputed datasets with the use of Rubin's rules.

Table 2: **Primary and secondary endpoints by treatment group—treatment regimen datapoint set**

For the efficacy estimand, the mean percent change from baseline in bodyweight 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 2B, appendix p 28). Estimated treatment differences were –3·3% (95% CI –4·1 to –2·5) for the 6 mg dose, –5·6% (–6·5 to –4·7) for the 12 mg dose, and –8·3% (–9·3 to –7·3) for the 36 mg dose versus placebo (p<0·0001 for all comparisons; appendix pp 48–52).



(Figure 3 continues on next page)

For both estimands, more participants in the orforglipron groups reached weight reduction thresholds of 5% or greater, 10% or greater, and 15% or greater from baseline than participants in the placebo group. At week 72, bodyweight reduction of 10% or greater for the treatment regimen estimand was reached 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<0·0001 for comparisons with placebo; figure 2C; table 2). 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

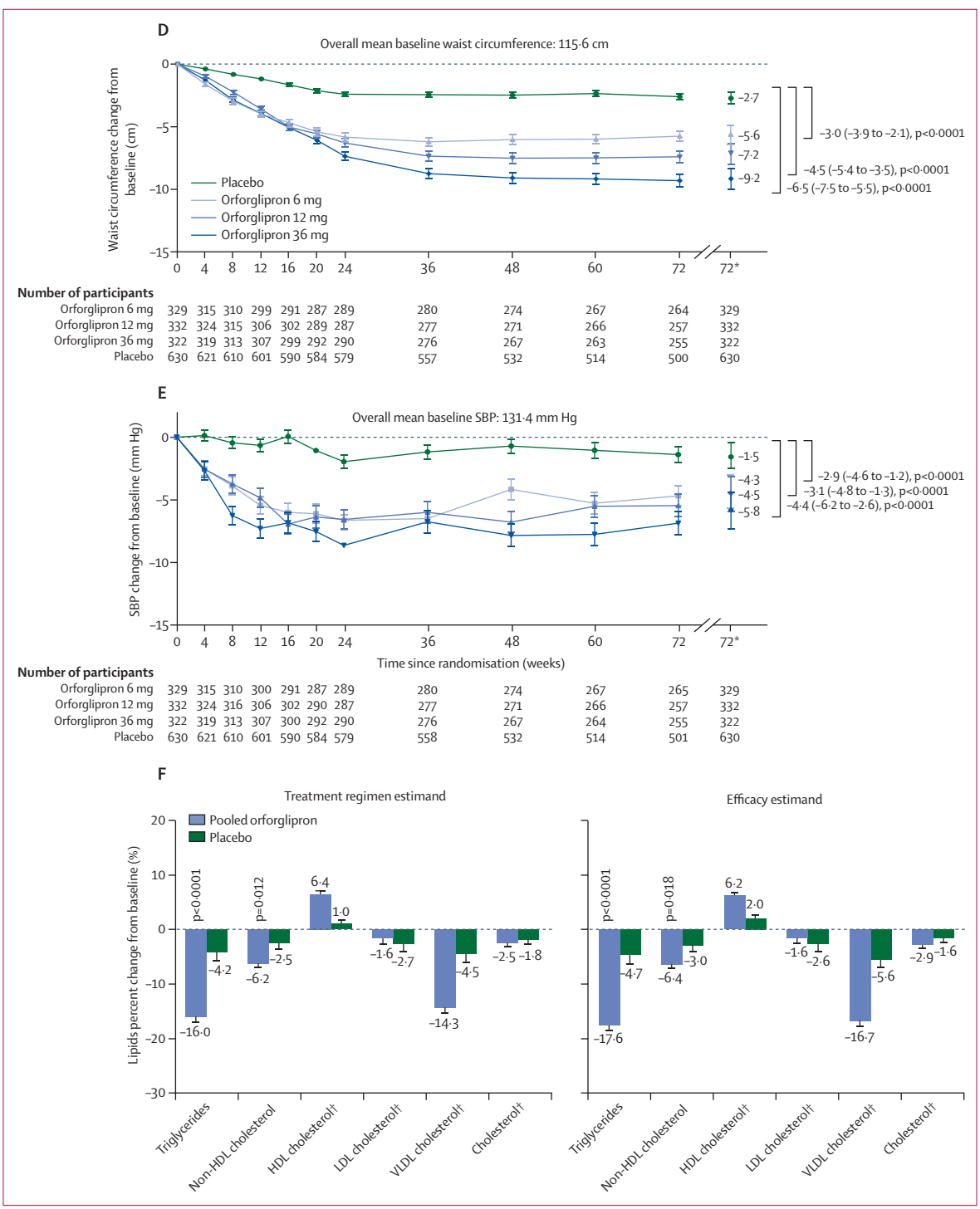


Figure 3: **Effects of orforglipron on HbA_{1c}, FSG, waist circumference, SBP, and lipid levels**

Data are model-based estimate (MBE) unless otherwise stated. Error bars indicate 95% CI. (A, C–E) The curves shown from week 0 to week 72 are based on observed mean with standard errors using the efficacy estimand datapoints set, including all datapoints obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments (or glycaemic rescue therapy or prohibited glycaemic therapy for glycaemic endpoints only) for change in HbA_{1c} (A), FSG (C), waist circumference (D), and SBP (E). (B) Proportion of participants reaching HbA_{1c} targets (<7·0%, ≤6·5%, and <5·7%) from logistic regression with multiple imputation analysis for the treatment regimen estimand (left) and the efficacy estimand (right). (F) Percent change in fasting lipid levels for pooled orforglipron doses (contains all orforglipron groups: 6 mg, 12 mg, and 36 mg) and placebo from baseline to week 72 from ANCOVA for the treatment regimen estimand and mixed model for repeated measures (MMRM) for the efficacy estimand; results for the orforglipron by-dose analysis are available in the appendix (pp 48–52). FSG=fasting serum glucose. HbA_{1c}=glycated haemoglobin. SBP=systolic blood pressure. *MBE (95% CI) for change in HbA_{1c} (A), FSG (C), waist circumference (D), and SBP (E) from baseline to week 72 and estimated treatment difference (95% CI) between orforglipron groups and placebo based on MMRM analysis (efficacy estimand). †Not controlled for multiplicity.

placebo group (figure 2D; appendix pp 48–52). Figures 2E and F show the cumulative distribution of percent change in bodyweight. The appendix (pp 29–31) shows waterfall plots depicting each participant's percentage weight reduction from baseline for all treatment groups for the treatment regimen estimand.

At week 72, HbA_{1c} decreased statistically 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<0·0001 for all comparisons *vs* placebo; table 2). For the efficacy estimand, HbA_{1c} decreased by 1·29% with 6 mg, 1·60% with 12 mg, 1·79% with 36 mg, and 0·14% with placebo (figure 3A; appendix pp 48–52). The proportion of participants reaching HbA_{1c} concentrations of less than 7% and less than or equal to 6·5% at week 72 was statistically significantly higher in all orforglipron groups compared with placebo (with orforglipron 36 mg: 75·5% *vs* 30·5%, and 66·6% *vs* 15·4%, respectively; figure 3B). Decrease in fasting serum glucose was also statistically significantly greater among participants in all orforglipron groups compared with placebo participants (ranging from –30·5 to –42·4 mg/dL *vs* –9·3 mg/dL; table 2, figure 3C). In addition, the seven-point SMBG profiles demonstrated greater reductions in the mean daily, pre-meal, and 2-h post-meal glucose values with orforglipron than with placebo at week 72 (appendix p 32).

Mean reduction in waist circumference was statistically significantly greater with orforglipron 36 mg compared with placebo (–8·3 cm *vs* –2·8 cm; table 2; figure 3D). Improvements with pooled orforglipron treatment (6 mg, 12 mg, and 36 mg) were statistically significantly greater versus placebo for key secondary endpoints: systolic blood pressure (–4·2 mm Hg *vs* –1·6 mm Hg; 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, table 3). There was a decrease from baseline in hsCRP with all orforglipron doses (ranging from –32·4% to –47·5%) versus –10·0% with placebo (table 2; appendix pp 33, 48–52). Results were consistent for the efficacy estimand, showing greater improvements with orforglipron treatment compared with placebo for all secondary endpoints (appendix pp 48–52).

Orforglipron pooled doses achieved statistically significant improvements in SF-36v2 role-physical and general health domains, and in all IWQOL-Lite-CT scores, indicating better levels of functioning, better health, or both, when compared with placebo from baseline to week 72 (appendix pp 34–35).

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 4; appendix pp 36–40). Serious adverse events were reported by 148 (9·2%) participants overall, with no significant differences in reporting across groups (table 4). 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 p 53). One death in the 36 mg group was due to cardiopulmonary arrest. For the other five deaths in the orforglipron groups (four in the 12 mg group and one in the 36 mg group), the cause was undetermined. In all these cases, either no autopsy was conducted or autopsy data were not available, and no further information regarding the cause of death was available. In the placebo group, one death was due to myocardial infarction, and three others had non-cardiovascular causes. Of the six deaths in the orforglipron groups, the investigators considered all but one (in the 12 mg group) to be unrelated to study drug. No relationship was reported for this case, and the patient had not received study drug treatment in the year prior to death. Of the four deaths in the placebo group, all but one (advanced pancreatic cancer) were considered unrelated to study treatment.

There were three reported cases of adjudication-confirmed pancreatitis, one in the 12 mg orforglipron group and two in the placebo group (table 4). Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations decreased in the

	Pooled orforglipron (n=983)	Placebo (n=630)
Key secondary endpoints*		
Change in SBP, mm Hg (95% CI)	–4·2 (–5·1 to –3·3)	–1·6 (–2·7 to –0·4)
Treatment comparison (95% CI); p value	ETD –2·6 (–4·0 to –1·3); p=0·0002	..
Percent change in non-HDL cholesterol, % (95% CI)	–6·2 (–8·0 to –4·4)	–2·5 (–4·9 to –0·2)
Treatment comparison (95% CI); p value	ETD –3·8 (–6·6 to –0·8); p=0·0124	..
Percent change in triglycerides, % (95% CI)	–16·0 (–18·2 to –13·7)	–4·2 (–7·6 to –0·8)
Treatment comparison (95% CI); p value	ETD –12·2 (–15·9 to –8·4); p<0·0001	..
Additional secondary endpoints (at week 72)		
Change in DBP, mm Hg (95% CI)	–1·5 (–2·1 to –1·0)	–1·3 (–2·0 to –0·5)
Treatment comparison (95% CI)	ETD –0·3 (–1·2 to 0·6)	..
Percent change in total cholesterol, % (95% CI)	–2·5 (–3·9 to –1·2)	–1·8 (–3·7 to 0·1)
Treatment comparison (95% CI)	ETD –0·7 (–3·0 to 1·6)	..
Percent change in LDL cholesterol, % (95% CI)	–1·6 (–3·8 to 0·6)	–2·7 (–5·6 to 0·4)
Treatment comparison (95% CI)	ETD 1·1 (–2·6 to 4·8)	..
Percent change in HDL cholesterol, % (95% CI)	6·4 (5·2 to 7·7)	1·0 (–0·6 to 2·5)
Treatment comparison (95% CI)	ETD 5·4 (3·4 to 7·4)	..

Pooled refers to pooled orforglipron 6 mg, 12 mg, and 36 mg groups. Model estimates for pooled orforglipron are estimated via a linear contrast that averages estimates from individual treatment groups. All changes are at week 72 from baseline. DBP=diastolic blood pressure. ETD=estimated treatment difference. SBP=systolic blood pressure.
*The primary and key secondary endpoints were tested under type I error control procedure using a two-sided nominal significance level of 0·05.

Table 3: **Secondary endpoints by pooled treatment group—treatment regimen datapoint set**

	Orforglipron 6 mg (n=328)	Orforglipron 12 mg (n=331)	Orforglipron 36 mg (n=321)	Placebo (n=628)	Overall (n=1608)	Risk difference (95% CI)		
						Orforglipron 6 mg *vs* placebo	Orforglipron 12 mg *vs* placebo	Orforglipron 36 mg *vs* placebo
Participants with ≥1 TEAE	270 (82·3%)	290 (87·6%)	284 (88·5%)	545 (86·8%)	1389 (86·4%)	−4·5 (−9·4 to 0·4)	0·8 (−3·6 to 5·3)	1·7 (−2·7 to 6·1)
Serious adverse events	24 (7·3%)	34 (10·3%)	35 (10·9%)	55 (8·8%)	148 (9·2%)	−1·4 (−5·0 to 2·1)	1·5 (−2·4 to 5·5)	2·2 (−1·9 to 6·2)
Deaths*	0	4 (1·2%)	2 (0·6%)	4 (0·6%)	10 (0·6%)	−0·6 (−1·3 to −0·01)	0·6 (−0·8 to 1·9)	−0·01 (−1·1 to 1·1)
Adverse events leading to discontinuation of study drug	20 (6·1%)	35 (10·6%)	34 (10·6%)	29 (4·6%)	118 (7·3%)	1·5 (−1·6 to 4·6)	6·0 (2·3 to 9·7)	6·0 (2·2 to 9·7)
Nausea	2 (0·6%)	8 (2·4%)	6 (1·9%)	0	16 (1·0%)	0·6 (−0·2 to 1·5)	2·4 (0·8 to 4·1)	1·9 (0·4 to 3·4)
Vomiting	5 (1·5%)	5 (1·5%)	4 (1·2%)	0	14 (0·9%)	1·5 (0·2 to 2·9)	1·5 (0·2 to 2·8)	1·3 (0·0 to 2·5)
Diarrhoea	2 (0·6%)	5 (1·5%)	3 (0·9%)	1 (0·2%)	11 (0·7%)	0·5 (−0·5 to 1·4)	1·4 (0·0 to 2·7)	0·8 (−0·3 to 1·9)
Abdominal pain	0	1 (0·3%)	1 (0·3%)	1 (0·2%)	3 (0·2%)	−0·2 (−0·5 to 0·2)	0·1 (−0·5 to 0·8)	0·2 (−0·5 to 0·8)
TEAEs occurring in ≥5% of participants in any treatment group (preferred term)								
Nausea	66 (20·1%)	103 (31·1%)	117 (36·4%)	53 (8·4%)	339 (21·1%)	11·7 (6·8 to 16·5)	22·7 (17·2 to 28·1)	28·0 (22·3 to 33·7)
Diarrhoea	70 (21·3%)	82 (24·8%)	88 (27·4%)	94 (15·0%)	334 (20·8%)	6·4 (1·1 to 11·6)	9·8 (4·4 to 15·2)	12·5 (6·8 to 18·1)
Constipation	58 (17·7%)	70 (21·1%)	72 (22·4%)	49 (7·8%)	249 (15·5%)	9·9 (5·3 to 14·5)	13·4 (8·5 to 18·2)	14·6 (9·6 to 19·7)
Vomiting	42 (12·8%)	67 (20·2%)	74 (23·1%)	24 (3·8%)	207 (12·9%)	9·0 (5·1 to 12·9)	16·4 (11·8 to 21·0)	19·2 (14·4 to 24·1)
Dyspepsia	30 (9·1%)	51 (15·4%)	35 (10·9%)	22 (3·5%)	138 (8·6%)	5·6 (2·2 to 9·1)	11·9 (7·8 to 16·1)	7·4 (3·7 to 11·1)
Decreased appetite	27 (8·2%)	30 (9·1%)	49 (15·3%)	18 (2·9%)	124 (7·7%)	5·4 (2·1 to 8·6)	6·2 (2·8 to 9·6)	12·4 (8·3 to 16·5)
Eructation	21 (6·4%)	38 (11·5%)	28 (8·7%)	4 (0·6%)	91 (5·7%)	5·8 (3·0 to 8·5)	10·8 (7·4 to 14·3)	8·1 (4·9 to 11·2)
Headache	17 (5·2%)	19 (5·7%)	22 (6·9%)	33 (5·3%)	91 (5·7%)	−0·1 (−3·0 to 2·9)	0·5 (−2·6 to 3·5)	1·6 (−1·7 to 4·9)
Abdominal pain	19 (5·8%)	20 (6·0%)	18 (5·6%)	17 (2·7%)	74 (4·6%)	3·1 (0·3 to 5·9)	3·3 (0·5 to 6·2)	2·9 (0·1 to 5·7)
Dizziness	19 (5·8%)	11 (3·3%)	22 (6·9%)	18 (2·9%)	70 (4·4%)	2·9 (0·1 to 5·8%)	0·5 (−1·9 to 2·8)	4·0 (0·9 to 7·0)
Adverse events of special interest								
Treatment-emergent hepatic events†	0	5 (1·5%)	2 (0·6%)	2 (0·3%)	9 (0·6%)	..	..	..
Malignancies	4 (1·2%)	3 (0·9%)	8 (2·5%)	11 (1·8%)	26 (1·6%)	−0·5 (−2·1 to 1·0)	−0·9 (−2·3 to 0·6)	0·7 (−1·3 to 2·7)
Diabetic retinopathy	23 (7·0%)	23 (6·9%)	22 (6·9%)	43 (6·8%)	111 (6·9%)	0·2 (−3·2 to 3·6)	0·1 (−3·3 to 3·5)	0·01 (−3·4 to 3·4)
Pancreatitis (adjudication-confirmed)	0	1 (0·3%)	0	2 (0·3%)	3 (0·2%)	..	..	..
MACE (adjudication-confirmed)	1 (0·3%)	8 (2·4%)	7 (2·2%)	9 (1·4%)	25 (1·6%)	..	..	..
Treatment-emergent cardiac events‡	4 (1·2%)	3 (0·9%)	5 (1·6%)	6 (1·0%)	18 (1·1%)	..	..	..
Gastrointestinal events†	12 (3·7%)	15 (4·5%)	14 (4·4%)	8 (1·3%)	49 (3·0%)	2·4 (0·2 to 4·6)	3·3 (0·9 to 5·7)	3·1 (0·7 to 5·5)
Gallbladder disease†	1 (0·3%)	3 (0·9%)	3 (0·9%)	4 (0·6%)	11 (0·7%)	..	..	..
Renal events†	0	4 (1·2%)	0	1 (0·2%)	5 (0·3%)	..	..	..
MDD or suicidal ideation†	1 (0·3%)	1 (0·3%)	0	2 (0·3%)	4 (0·2%)	..	..	..
Hypersensitivity†	1 (0·3%)	0	0	0	1 (0·1%)	..	..	..
Dysaesthesia§	5 (1·5%)	3 (0·9%)	8 (2·5%)	8 (1·3%)	24 (1·5%)	0·3 (−1·3 to 1·8);	−0·4 (−1·7 to 1·0);	1·2 (−0·7 to 3·1);
Other TEAEs of interest								
Hypoglycaemia¶	5 (1·5%)	7 (2·1%)	8 (2·5%)	2 (0·3%)	22 (1·4%)	0·9 (0·1 to 9·9)	1·2 (0·1 to 12·5)	1·2 (0·1 to 12·1)
Severe hypoglycaemia‖	1 (0·3%)	0	0	0	1 (<0·1%)	..	..	..
Initiation of rescue therapy for severe persistent hyperglycaemia	34 (10·4%)	23 (6·9%)	15 (4·7%)	239 (38·1%)	311 (19·3%)	..	..	..
Cholelithiasis	4 (1·2%)	7 (2·1%)	2 (0·6%)	2 (0·3%)	15 (0·9%)	0·9 (−0·4 to 2·2)	1·8 (0·2 to 3·4)	0·3 (−0·7 to 1·3)
Acute cholecystitis	1 (0·3%)	1 (0·3%)	2 (0·6%)	2 (0·3%)	6 (0·4%)	−0·01 (−0·8 to 0·7)	−0·02 (−0·8 to 0·7)	0·3 (−0·7 to 1·3)
Chronic cholecystitis	0	0	1 (0·3%)	0	1 (0·1%)	0	0	0·3 (−0·3 to 0·9)

Data are shown as number of participants (%) unless otherwise stated. For the blank cells, data were unavailable. MACE=major adverse cardiovascular event. MDD=major depressive disorder. TEAE=treatment-emergent adverse event. *Deaths are also included as serious adverse events and discontinuations due to adverse events. †Events were classified as severe or serious adverse events. ‡Events that were classified as severe or serious arrhythmias and cardiac conduction disorders. §Includes MedDRA search terms of burning sensation, hyperaesthesia, dysaesthesia, sensitive skin, pain of skin, and paraesthesia. ¶Hypoglycaemia was defined as a blood glucose of <54 mg/dL (3·0 mmol/L). Events occurring within a 1-h period were considered as one event. The event with the highest severity was selected for analysis. ‖Severe hypoglycaemia was defined as a hypoglycaemic event characterised by altered mental status and/or altered physical status that the participant was unable to resolve without assistance. Events occurring within a 1-h period were considered as one event. The event with the highest severity was selected for analysis.

Table 4: **Adverse events in the safety population**

orforglipron groups over 72 weeks (appendix pp 54–55). The rates of post-baseline ALT or AST concentrations that were at least three times the upper limit of normal (ULN), or at least five times the ULN, were similar across all treatment groups. Three orforglipron-treated participants and one in the placebo group had ALT or

AST concentrations at least ten times the ULN (appendix pp 56–57), one of whom on orforglipron also showed total bilirubin more than two times the 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 and one case of pancreatic neoplasm (in the 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 pp 58–59). There was a mean increase in pulse rate up to 4·4 beats per minute in the orforglipron groups compared with 0 beats per minute in the placebo group at week 72 from baseline. Additional safety data are available in the appendix (pp 54–55).

Discussion

In the ATTAIN-2 study, in adults with obesity and co-existing type 2 diabetes, once-daily orforglipron at doses of 6 mg, 12 mg, and 36 mg given as an adjunct to lifestyle modification demonstrated mean bodyweight reductions of 5·1%, 7·0%, and 9·6% respectively, compared with 2·5% with placebo, after 72 weeks of treatment. Among participants assigned to the 36 mg orforglipron dose, 67·2%, 45·6%, and 26·0% reached bodyweight reductions of 5% or greater, 10% or greater, and 15% or greater, 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-1 receptor monoagonists, daily liraglutide and weekly semaglutide, and a weekly dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, tirzepatide. These therapies have been evaluated in phase 3 clinical trials in people with obesity and co-existing type 2 diabetes. In the SCALE Diabetes study, treatment with once-daily 3 mg of liraglutide for 56 weeks was associated with a 6·0% reduction in bodyweight, compared with 2·0% in the placebo group.[7] 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.[6] Subsequently, once-weekly tirzepatide at a dose of 15 mg led to a 14·7% reduction in bodyweight versus 3·2% with placebo in the 72-week SURMOUNT-2 trial; the even larger weight reduction was potentially due to the addition of GIP receptor agonism.[8] Although differences in trial design and population limit cross-trial comparisons, patients treated with orforglipron, an oral GLP-1 receptor monoagonist, in the current trial experienced weight reduction similar to injectable semaglutide in people with obesity and type 2 diabetes. As such, orforglipron might have the potential to offer the clinical benefits of the well established GLP-1 receptor agonist class without the known limitations of injectable therapies.

In terms of oral GLP-1 receptor agonist therapies, oral semaglutide is approved at low doses (7 mg and 14 mg) for the treatment of type 2 diabetes and has been investigated at higher doses (25 mg and 50 mg) for both type 2 diabetes and obesity.[22–24] In PIONEER PLUS, a type 2 diabetes trial, in patients with uncontrolled glycaemia and BMI above 25 kg/m², 7·3% and 8·5% reductions in bodyweight were observed after 52 weeks of treatment with once-daily, oral semaglutide 25 mg and 50 mg, respectively, compared with 4·7% weight decrease with the 14 mg dose.[25] The potential of oral medicines to reduce bodyweight should be interpreted in the context of their use in clinical practice. Oral semaglutide as a peptide has low bioavailability of less than 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.[23] As a small molecule, orforglipron has an improved bioavailability of 79·1%, which enables it to be taken without food and water restrictions.[26] This next advance in incretin therapies has the potential to simplify use in clinical practice and improve adherence, all of which could reduce barriers for patients.

American Diabetes Association Standards of Care in Diabetes recommend weight management in patients with type 2 diabetes, indicating that weight reduction of 3–7% improves glycaemia and other cardiovascular risk factors, and that sustained weight loss of more than 10% usually confers greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and can improve long-term cardiovascular outcomes and mortality.[5] In the ATTAIN-2 trial, among participants assigned to the 36 mg orforglipron dose, 67·2%, 45·6%, and 26·0% had bodyweight reductions of 5% or greater, 10% or greater, and 15% or greater, 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 bodyweight 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 could enable health-care providers to individualise treatment plans to optimise efficacy and minimise side-effects based on patient feedback and shared decision making, resulting in improvements in health-care providers' prescribing behaviour and patient time on treatment, the ultimate goal.

As previously observed in studies investigating lifestyle modifications and obesity management medications, bodyweight reduction is more difficult to achieve for

people with obesity and co-existing type 2 diabetes compared with those without type 2 diabetes.[5,8] Results of the ATTAIN-2 trial are consistent with this observation, showing less weight reduction than in the ATTAIN-1 trial, in participants with obesity without diabetes.[18] The mechanisms responsible for less effective weight reduction with interventions for weight management in people with type 2 diabetes are not fully understood. Contributing factors might include energy conservation due to reduced glucosuria on treatment, hyperinsulinaemia, and the use of weight-promoting antidiabetic medications.[27] For the efficacy estimand, the placebo-adjusted bodyweight 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 and ATTAIN-2, respectively. These results can help healthcare providers and patients understand the average expected response in different populations (ie, with or without type 2 diabetes) when the patient tolerates and stays on medication. In managing a diverse population, dosing flexibility allows treatment tailoring such that patients with a high response 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 the ATTAIN-2 and ATTAIN-1 trials included an individualised approach to lifestyle modification. Participants followed a healthy balanced diet with a goal of weight reduction achieved through mindfulness and healthy choices, rather than prescribed calorie restriction. This is novel compared with most previous obesity clinical trials, which typically recommended a 500-kcal-deficit diet.[6,7,22]

In this trial, in addition to weight reduction, dose-dependent clinically meaningful improvements in HbA_{1c} were observed with all investigated orforglipron doses. Among participants assigned to the 36 mg dose, 75·5%, 66·6%, and 23·7% reached an HbA_{1c} target of less than 7%, less than or equal to 6·5%, and less than 5·7% (normoglycaemia), 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 type 2 diabetes and BMI of 23 kg/m² or higher.[13]

The greater HbA_{1c} reduction observed with orforglipron in this trial, compared with peptide-based GLP-1 receptor agonists such as oral semaglutide in PIONEER 1,[28] subcutaneous semaglutide in SUSTAIN 1,[29] and liraglutide in SCALE Diabetes,[30] might be related to the fact that orforglipron, unlike semaglutide and liraglutide, is a biased GLP-1 receptor agonist.[31] In preclinical settings, GLP-1 receptor biased agonism—ie, preferential activation of the cAMP pathway over β-arrestin recruitment after binding with the GLP-1 receptor—has been shown to augment GLP-1 receptor agonist effects, such as insulin secretion and weight reduction.[32]

Additional findings in this trial included significant improvements in important cardiorenal-metabolic 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.[33] These improvements in cardiorenal-metabolic 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 type 2 diabetes with and without established cardiovascular disease have shown that GLP-1 receptor agonists reduce the risk of MACE; however, it is unknown for orforglipron without confirmatory cardiovascular outcomes trials.[10] While there are other non-incretin oral obesity management medications (phentermine–topiramate, buproprion–naltrexone, phentermine), they have generally shown less mean weight reduction and have not demonstrated the reduction in MACE seen with the GLP-1 receptor agonist 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.[34,35]

The safety profile of orforglipron in the present trial was consistent with the GLP-1 receptor agonist class and with previous findings from ATTAIN-1 in people with obesity, and ACHIEVE-1 in those with type 2 diabetes.[13,18] 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 medullary thyroid cancer were reported. No liver safety signal was detected. There were no imbalances in adjudication-confirmed pancreatitis between the treatment groups. Despite substantial reductions in HbA_{1c}, the incidence of level 2 hypoglycaemia was low. 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.[6,8,25]

The discontinuation of clinical development of other small-molecule GLP-1 receptor agonists, danuglipron and lotiglipron, due to liver enzyme elevations, has raised concern about whether this reflects compound-specific liabilities, such as off-target effects or metabolic byproducts, or a class effect.[36,37] Small-molecule GLP-1 receptor agonists engage the GLP-1 receptor via G protein-biased or allosteric mechanisms. Structural differences between molecules may result in differences in receptor

binding, signalling bias, and pharmacokinetics, which underscore the relevance of scaffold design for receptor engagement and pharmacokinetics. However, the underlying mechanism for observed hepatotoxicity of danuglipron and lotiglipron remains unclear, and these events could represent coincidental outcomes related to early candidate selection.[38] In the current trial, liver safety was thoroughly evaluated and no signal was detected.

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 antihyperglycaemic medications based on their potential effect on bodyweight.

Limitations for this study include the lack of direct comparison with other approved pharmacological treatments for weight management. Body composition was not assessed, precluding evaluation of changes in fat and lean mass. Information on how recommended lifestyle modifications were implemented was not recorded; thus, treatment groups might have differed in diet and exercise habits, potentially confounding outcomes. Finally, in this study, weight changes with orforglipron were assessed for up to 72 weeks, and the effects on long-term weight maintenance remain unknown. The ongoing 3-year ATTAIN-1 trial (NCT05869903) will provide information on the longer-term effects of orforglipron treatment, while ATTAIN-MAINTAIN (NCT06584916) is investigating maintenance with orforglipron following successful injectable GLP-1-based therapy.

In conclusion, in patients with type 2 diabetes and obesity (BMI of 27 kg/m² or higher), statistically significantly greater reductions in bodyweight compared with placebo were demonstrated with all three investigated doses of orforglipron, with a safety profile similar to other GLP-1 receptor agonists.

Contributors

The sponsor (Eli Lilly) conceived, designed, and supervised the trial which included site monitoring, data collation, and analysis. DBH, SGKis, SA, ES, QW, AS, and IJ accessed and verified the data. DBH, DHR, SGKis, BA, YM, SGKim, 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 SGKim were investigators in the study. ES and QW conducted the statistical analysis. All authors contributed to the data interpretation and manuscript writing assisted by medical writers. All authors approved the final version as well as previous versions of the manuscript, and vouch for data accuracy and the fidelity of the trial to the protocol. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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 USA and EU 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, and 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.

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