Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study

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Summary

Background Orforglipron, an oral, non-peptide glucagon-like peptide-1 (GLP-1) receptor agonist, is in development for type 2 diabetes and obesity. We assessed the efficacy and safety of orforglipron versus placebo or dulaglutide in participants with type 2 diabetes.

Methods In this 26-week, phase 2, double-blind, randomised, multicentre study, participants were recruited from 45 centres (private clinics, hospitals, and research centers) in the USA, Hungary, Poland, and Slovakia. Adult participants aged 18 years or older with type 2 diabetes treated with diet and exercise, with or without metformin, and with a glycated haemoglobin (HbA_{1c}) of 7·0–10·5%, and stable BMI of 23 kg/m² or more, were randomly assigned (5:5:5:5:5:3:3:3:3) via an interactive web-response system to placebo, dulaglutide 1·5 mg once per week, or orforglipron 3 mg, 12 mg, 24 mg, 36 mg (group 1), 36 mg (group 2), 45 mg (group 1), or 45 mg (group 2) once per day with no food or water restrictions. Two different dose escalation regimens were evaluated for each of the 36 mg and 45 mg cohorts. Participants were masked to the study drug, dulaglutide, and placebo. The primary efficacy outcome The primary efficacy outcome was mean change in HbA_{1c} from baseline with orforglipron versus placebo at week 26. Efficacy was analysed in all randomly assigned participants who received at least one dose of study drug and excluded data after the permanent discontinuation of study drug or initiation of rescue medication. Safety was analysed in all participants who received at least one dose of study treatment. This trial is registered at ClinicalTrials.gov (NCT05048719) and is completed.

Findings Between Sept 15, 2021, and Sept 30, 2022, 569 participants were screened and 383 were enrolled and randomly assigned to a group. 352 (92%) completed the study and 303 (79%) completed 26 weeks of treatment. At baseline, the mean age was 58·9 years, HbA_{1c} was 8·1%, BMI was 35·2 kg/m², 226 (59%) were men, and 157 (41%) were women. At week 26, mean change in HbA_{1c} with orforglipron was up to –2·10% (–1·67% placebo adjusted), versus –0·43% with placebo and –1·10% with dulaglutide. HbA_{1c} reduction was statistically superior with orforglipron versus placebo (estimated treatment difference –0·8% to –1·7%). Change in mean bodyweight at week 26 was up to –10·1 kg (95% CI –11·5 to –8·7; –7·9 kg placebo adjusted [–9·9 to –5·9]) with orforglipron versus –2·2 kg (–3·6 to –0·7) for placebo and –3·9 kg (–5·3 to –2·4) for dulaglutide. The incidence of treatment-emergent adverse events ranged from 61·8% to 88·9% in orforglipron-treated participants, compared with 61·8% with placebo and 56·0% with dulaglutide. The majority were gastrointestinal events (44·1% to 70·4% with orforglipron, 18·2% with placebo, and 34·0% with dulaglutide) of mild to moderate severity. Three participants receiving orforglipron and one participant receiving dulaglutide had clinically significant (<54 mg/dL [<3 mmol/L]) hypoglycaemia and no participants had severe hypoglycaemia. One death occurred in the placebo group and was not related to study treatment.

Interpretation In this phase 2 trial the novel, oral, non-peptide GLP-1 receptor agonist orforglipron at doses of 12 mg or greater showed significant reductions in HbA_{1c} and bodyweight compared with placebo or dulaglutide. The adverse event profile was similar to other GLP-1 receptor agonists in similar stage of development. Orforglipron might provide an alternative to injectable GLP-1 receptor agonists and oral semaglutide, with the prospect of less burdensome administration to achieve treatment goals in people with type 2 diabetes.

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Introduction

Glucagon-like peptide 1 (GLP-1) receptor agonists have become an increasingly important class of therapeutics for the management of type 2 diabetes with many important effects beyond glucose lowering, including bodyweight reduction and cardiovascular benefits.[1–5] Agents that are approved are peptide based and administered by subcutaneous injection or orally.[6] The only approved orally administered GLP-1 receptor agonist for the management of type 2 diabetes is oral semaglutide (Novo Nordisk,

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Research in context

Evidence before this study

We searched PubMed on Jan 9, 2023, using the terms "glucagon-like peptide-1 receptor agonist", "semaglutide", "type 2 diabetes", "dulaglutide", "medication adherence", and "oral semaglutide" with no date or study duration restrictions. Non-English references were excluded. Reports in the literature describe glycated haemoglobin (HbA_{1c}) reductions of up to –1·7% and bodyweight reduction up to –4·8 kg with semaglutide, an injected GLP-1 receptor agonist, at 12 weeks in participants with type 2 diabetes. Oral semaglutide resulted in a HbA_{1c} reduction of 1·6% and bodyweight reduction of 6·9 kg in phase 2. A small molecule glucagon-like peptide-1 (GLP-1) receptor agonist, danuglipron (PF-06882961), was investigated in a phase 1 study of 98 participants with twice per day dosing. In that study, danuglipron had a safety profile consistent with other GLP-1 receptor agonists and HbA_{1c} reductions up to 1·2%.

Added value of this study

In this phase 2 study, we compared oral orforglipron with dulaglutide, an injected peptide based GLP-1 receptor agonist, and placebo. We showed that this novel, non-peptide receptor agonist resulted in statistically significant and clinically meaningful improvements in glucose lowering and bodyweight reductions compared with injectable dulaglutide. Safety was similar to other GLP-1 receptor agonists when studied in phase 2, although reflecting a need for dose regimen optimisation. These observations support the further development of orforglipron.

Implications of all the available evidence

Orforglipron does not have food or water administration restrictions and might provide a safe, effective, and convenient oral treatment option for people with type 2 diabetes. Large confirmatory studies are needed to assess whether orforglipron has an advantageous efficacy and safety profile for glycaemic control and bodyweight reduction.

Bagsvaerd, Denmark), a peptide that is co-formulated with a gastric mucosal permeation enhancer, salcaproate sodium, that helps protect semaglutide from proteolytic degradation and enhances its absorption across the gastric epithelium.[6,7] To maximise its absorption and efficacy, it should be taken in a fasting state and no food, liquid, or other medication should be ingested for at least 30 min after its intake. An oral non-peptide, GLP-1 receptor agonist taken with or without food, with comparable efficacy and tolerability to injectable agents could enhance medication uptake in this important therapeutic class.

Orforglipron, danuglipron (PF-06882961, ClinicalTrials.gov NCT03985293), and PF-07081532 (ClinicalTrials.gov number NCT04305587) are the first small molecules developed in the non-peptide GLP1-receptor agonist class for the management of type 2 diabetes.[8] In preclinical and early clinical evaluations, orforglipron displayed an oral bioavailability of 20–40%.[6] The pharmacokinetic profile of orforglipron is dose dependent, with a half-life of 29–49 h, supporting once-per-day dosing.[6,9]

Orforglipron is under development for the treatment of type 2 diabetes and obesity. This phase 2 study aimed to show that orforglipron is superior in terms of the change in HbA_{1c} from baseline compared with placebo by evaluating the efficacy, safety, and tolerability of orforglipron in participants with type 2 diabetes compared with placebo and 1·5 mg dulaglutide.

Methods

Study design and participants

This 26-week, phase 2, multicentre, randomised, double-blind, parallel-group, placebo-controlled dose response study used dulaglutide (1·5 mg, once per week) as an active comparator. This study was conducted in four countries (the USA, Hungary, Poland, and Slovakia) at 45 study sites (private clinics, hospitals, or research centres). Participants aged 18 years or older with type 2 diabetes and a glycated haemoglobin (HbA_{1c}) of 7·0–10·5%, treated with diet and exercise, with or without a stable dose of metformin for at least 3 months, a BMI of 23 kg/m² or more, and a stable bodyweight (≤5% bodyweight gain or loss) for 3 months before random assignment were included. Key exclusion criteria included proliferative diabetic retinopathy, diabetic maculopathy, or severe non-proliferative diabetic retinopathy; an estimated glomerular filtration rate of less than 30 mL per min per 1·73 m²; poorly controlled hypertension; and New York Health Association Class 3 or 4 heart failure. A complete list of inclusion and exclusion criteria is available in the appendix (p 3). The trial was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, and the International Conference on Harmonisation Good Clinical Practice Guideline. Local institutional review boards approved the protocol. All participants provided written informed consent before participating in the study. The study protocol is included in the appendix (p 27).

See Online for appendix

Randomisation and masking

Participants meeting the eligibility criteria after screening were randomly assigned (5:5:5:5:5:3:3:3:3) to placebo, once per week subcutaneous dulaglutide (1·5 mg), or orforglipron based on once per day maintenance doses of 3 mg, 12 mg, 24 mg, 36 mg (two subgroups), or 45 mg

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(two subgroups; appendix p 24) using an interactive web-response computer-based system, with block randomisation and stratified by country and HbA_{1c} stratum (≤8·0% or >8·0%) at their screening (visit 1). The 36 mg and 45 mg cohorts were each divided in two subgroups to assess different dosing schemes and dose escalation strategies: 36 mg group 1 had rapid dose escalation and a 2 mg initial dose, and 36 mg group 2 had slow dose escalation and a 3 mg initial dose. The 45 mg subgroups were titrated up every 2 weeks until the maintenance dose was reached, however the escalation doses in the first 6 weeks and initial dose were different: 45 mg group 1 had a 3 mg initial dose, and 45 mg group 2 had a 2 mg initial dose. A double-blind, double-dummy design was used in which participants received both a daily capsule (active orforglipron or placebo) and a once per week injection (active dulaglutide or placebo).

Procedures

The study period included a screening and study lead-in period of approximately 2 weeks, study treatment period of 26 weeks, and a 2-week safety follow-up (appendix p 24). Participants taking metformin at baseline continued its use during the study. All participants were provided healthy eating and physical activity education periodically by study personnel, along with education regarding the signs, symptoms, and management of hypoglycaemia. Participants were instructed on self-monitoring blood glucose and the administration of study treatment. A complete list of study measurements is available in the appendix (p 27).

Outcomes

The study was designed to test the hypothesis that at least one dose of daily orforglipron is superior in terms of the change in HbA_{1c} from baseline relative to placebo at week 26, in participants with type 2 diabetes inadequately controlled with diet and exercise alone or with or without a stable dose of metformin. The primary endpoint was the effect of orforglipron versus placebo on the change in HbA_{1c} from baseline to week 26. A secondary endpoint was the effect of orforglipron versus dulaglutide on the change in HbA_{1c} from baseline to week 26. The other secondary endpoints evaluated were the percentage of participants who had an HbA_{1c} of less than 7% and less than or equal to 6·5%, change from baseline in fasting serum glucose, change from baseline in bodyweight (kg), bodyweight percentage change from baseline, and percentage of participants who had a 5% or more and 10% or more bodyweight reduction. Safety and tolerability endpoints included the frequency of participant-reported and investigator-reported adverse events, rate and incidence of hypoglycaemia events (glucose <70 mg/dL [3·9 mmol/L] and ≥54 mg/dL [3·0 mmol/L], or glucose <54 mg/dL [3·0 mmol/L]), change in safety laboratory variables, change in electrocardiogram, and change in vital signs. Adverse events and vital signs were assessed at each participant visit. Adverse events of special interest adjudicated by an external adjudication committee included pancreatitis, major cardiovascular events, supraventricular arrhythmias and cardiac conduction disorders, drug-induced liver injury, and death.

Statistical analysis

The sample size was calculated to ensure a power of at least 90% for testing the superiority of orforglipron versus placebo in change in HbA_{1c} from baseline to week 26. Assuming a treatment effect of –0·9%, an SD of 1·1%, an effect size of 0·8%, a two-sided α level of 0·05, and a 20% dropout rate for dulaglutide and orforglipron, it was estimated that a total sample size of 370 randomly assigned participants were needed (ie, 50 participants per group for placebo, dulaglutide, and orforglipron 3 mg, 12 mg, and 24 mg; and 60 participants per treatment group for orforglipron 36 mg and 45 mg [30 participants per subgroup]), considering a potentially higher dropout rate from gastrointestinal events for higher dose treatment groups (36 mg and 45 mg).

Treatment comparisons were performed for the primary objective at the full significance level of $p<0·05$. No multiplicity adjustments were made for type 1 error control for the analyses of secondary and exploratory objectives. All tests of treatment effects were conducted with a two-sided significance level of $p<0·05$, and two-sided 95% CIs were calculated.

An efficacy estimand, using the hypothetical strategy to handle intercurrent events, was used to compare the efficacy of orforglipron doses with placebo and represents the average treatment effect of orforglipron for all randomly assigned participants, if the treatment was administered as intended (according to the hypothetical strategy in the International Conference on Harmonisation E9[R1] addendum).[10] From our own experience, phase 2 estimates for the efficacy estimand can predict the phase 3 efficacy estimand well. Therefore, the efficacy estimand included data from all randomly assigned participants who were exposed to at least one dose of the study drug (orforglipron), excluding data after the permanent discontinuation of the study drug or initiation of rescue medication (efficacy analysis set). A restricted maximum likelihood-based, mixed-effect model for repeated measures analysis was used to analyse the primary efficacy endpoint of change in HbA_{1c} from baseline. The mixed-effect model for repeated measures included the fixed class effects of treatment group, strata (country, baseline HbA_{1c} stratum [≤8% or >8%]), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline HbA_{1c} value. To identify the efficacy of orforglipron with adequate statistical power, efficacy endpoints were also evaluated after pooling the groups given 36 mg or 45 mg orforglipron through alternate dose escalation approaches. For other continuous variables, including fasting glucose and bodyweight, a mixed-effect

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model for repeated measures was used to evaluate the treatment effect. For binary efficacy variables (ie, HbA_{1c} <7%, percentage of participants reaching an HbA1c of ≤6·5% and <5·7%, and weight reduction targets of ≥5%, ≥10%, and ≥15%), a logistic regression model was used for treatment comparisons.

Safety assessments were guided by an estimand comparing the safety of orforglipron with placebo and dulaglutide, irrespective of adherence to study drug. Thus, safety analyses were conducted on the safety population using data obtained during the treatment period plus safety follow-up from all randomly assigned participants exposed to at least one dose of the study drug, regardless of adherence. SAS version 8.2 was used for statistical calculations. A data monitoring committee was not used.

This trial is registered at ClinicalTrials.gov (NCT05048719 and EudraCT 2021–002806–29) and is completed.

Role of the funding source

The funder of the study provided study drugs and was involved in study design, data collection, data analyses, data interpretation, and writing of the report.

Results

Between Sept 15, 2021, and Sept 30, 2022, 569 participants were screened and 383 were enrolled and randomly assigned to a treatment group. In total, 303 participants (79%) completed 26 weeks of treatment, and 352 participants (92%) completed the study (figure 1). The efficacy and safety population included 383 participants. Treatment discontinuation ranged from 19% (six of 31 people) to 24% (eight of 34 people) in most treatment groups, with the exception of orforglipron 24 mg (16 [34%] of 47 discontinued) and dulaglutide (five [10%] of 50 discontinued). At baseline, study participants had a mean age of 58·9 years, HbA_{1c} of 8·1% (64·8 mmol/mol), BMI of 35·2 kg/m², type 2 diabetes duration of 8 years, 226 (59%) were men, and 157 (41·%) were women. Baseline demographics and clinical variables were generally similar between the nine study groups (table 1). Rescue therapy for hyperglycaemia was required by two participants in the orforglipron 3 mg group, three participants in the 24 mg group, three participants in 36 mg groups 1 and 2, one participant in 45 mg groups 1 and 2, and seven participants in the placebo group. None of the participants in the dulaglutide group required rescue therapy.

At week 26, mean changes in HbA_{1c} from baseline to week 26 for orforglipron were –1·2% (95% CI –1·5 to –0·9) for 3 mg, –1·9% (–2·2 to –1·7) for 12 mg, –1·8% (–2·1 to –1·5) for 24 mg, –2·0% (–2·3 to –1·8) for 36 mg, –2·1% (–2·3 to –1·9) for 45 mg, –1·1% (–1·4 to –0·8) for dulaglutide, and –0·4% (–0·7 to –0·2) for placebo (figure 2A). All doses of orforglipron were superior to

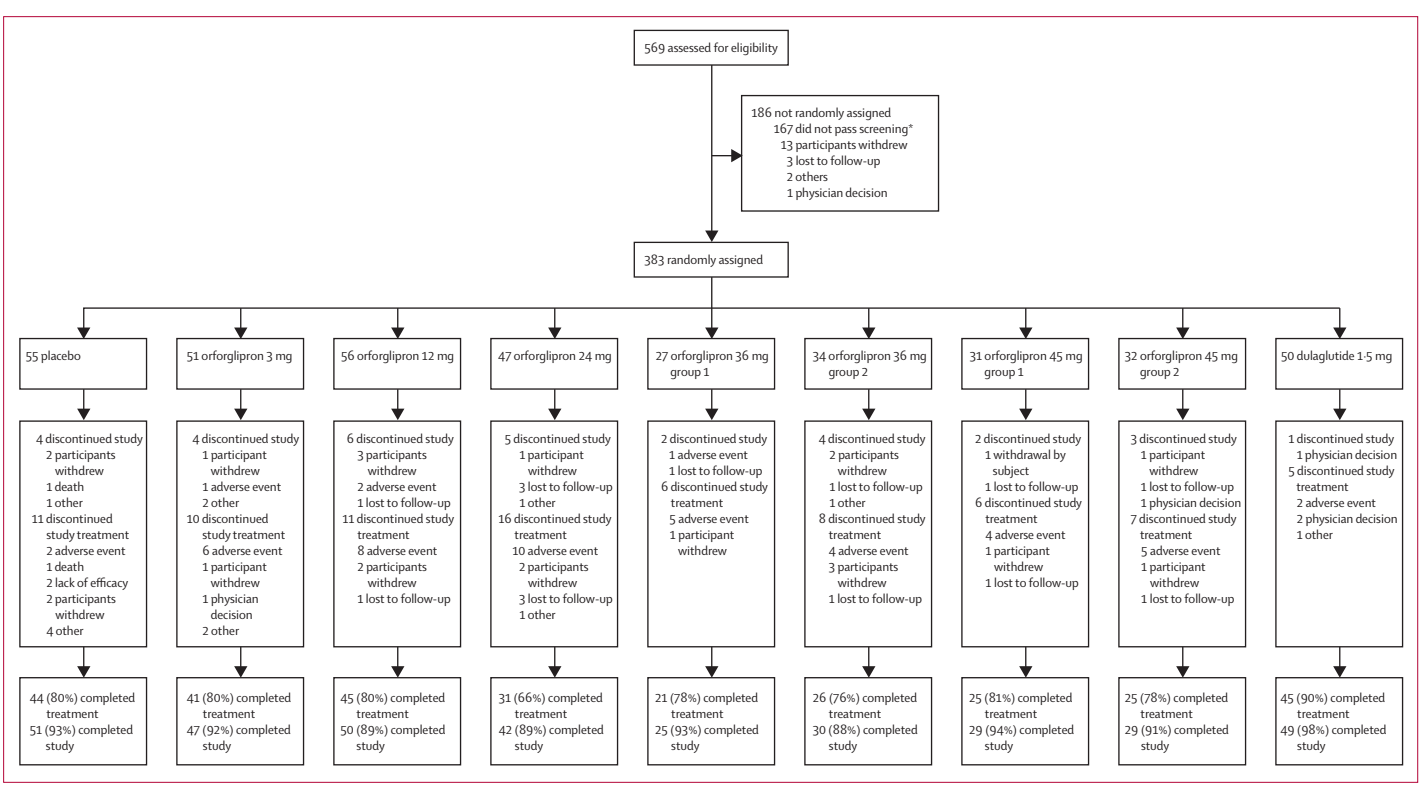

Figure 1: **Trial profile**

*Participants who did not pass screening are listed in the appendix (p 22).

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placebo (estimated treatment difference –0·8% [95% CI –1·13 to –0·40] with 3 mg, –1·5% [–1·85 to –1·12] with 12 mg, –1·4% [–1·75 to –0·98] with 24 mg, –1·6% [–1·96 to –1·25] with 36 mg, –1·7% [–2·02 to –1·32] with 45 mg; p<0·0001 for all doses) and superior to dulaglutide (estimated treatment difference –0·8% [–1·18 to –0·44; p<0·0001] with 12 mg, –0·7% [–1·08 to –0·30; p=0·0006] with 24 mg, –0·9% [–1·29, –0·57; p<0·0001] with 36 mg, –1·0% [–1·36 to –0·64] with 45 mg; p<0·0001) in decreasing HbA_{1c}. 12 mg or greater of orforglipron was superior to dulaglutide and provided lowering in HbA_{1c} in all treatment groups compared with placebo.

With orforglipron, 65–96% of participants had an HbA_{1c} of less than 7·0% at 26 weeks versus 64% in the dulaglutide group and 24% in the placebo group. An HbA_{1c} of less than or equal to 6·5% was present in 45–84% of participants in the orforglipron groups, and an HbA_{1c} of less than 5·7% was present with orforglipron doses greater than or equal to 12 mg in 18–34% of participants. More study participants who received orforglipron reached an HbA_{1c} target of less than 7·0% and 6·5% or less compared with placebo and dulaglutide (figure 2C; appendix pp 10–11). Mean changes from baseline in fasting serum glucose for all doses of orforglipron were superior to placebo with up to –2·48 mmol/L (95% CI –3·07 to –1·90) with 45 mg, and doses 12 mg and more were superior to dulaglutide 1·5 mg with up to –1·26 mmol/L (–1·85 to –0·67) with 45 mg in decreasing fasting glucose (figure 2B; table 2), which was evident as early as at 4 weeks of treatment.

At week 26, mean changes from baseline in bodyweight for participants who received orforglipron were up to –10·1 kg (–11·5 to –8·7) for 45 mg versus –3·9 kg (–5·3 to –2·4) for dulaglutide and –2·2 kg (–3·6 to –0·7) for placebo (figure 2D). Orforglipron doses of 12 mg and more were superior to placebo with up to –7·9 kg (95% CI –9·9 to –5·9) with

	Placebo (n=55)	Orforglipron					Dulaglutide (n=50)
		3 mg (n=51)	12 mg (n=56)	24 mg (n=47)	36 mg (n=61)	45 mg (n=63)	
Demographic variables							
Sex							
Women	27 (49%)	25 (49%)	20 (36%)	17 (36%)	25 (41%)	23 (37%)	20 (40%)
Men	28 (51%)	26 (51%)	36 (64%)	30 (64%)	36 (59%)	40 (63%)	30 (60%)
Age, years	58·3 (9·5)	59·0 (9·4)	57·4 (9·2)	60·5 (9·1)	59·7 (9·2)	58·5 (9·4)	58·8 (10·2)
Race							
White	50 (91%)	47 (92%)	49 (88%)	43 (91%)	58 (95%)	57 (90%)	44 (88%)
Black or African American	4 (7%)	2 (4%)	5 (9%)	2 (4%)	0	5 (8%)	4 (8%)
Asian	0	1 (2%)	1 (2%)	1 (2%)	1 (2%)	0	1 (2%)
American Indian or Alaska Native	1 (2%)	0	1 (2%)	1 (2%)	0	1 (2%)	0
Other	0	1 (2%)	0	0	2 (3%)	0	1 (2%)
Ethnicity							
Hispanic or Latino	14 (25%)	7 (14%)	15 (27%)	5 (11%)	13 (21%)	13 (21%)	7 (14%)
Not Hispanic or Latino	41 (75%)	44 (86%)	41 (73%)	42 (89%)	48 (79%)	50 (79%)	43 (86%)
Clinical variables							
HbA_{1c}, %	8·1 (0·9)	8·0 (0·8)	8·2 (0·9)	8·2 (0·9)	8·0 (0·7)	8·1 (0·9)	8·0 (0·7)
HbA_{1c}, mmol/mol	64·5 (9·5)	64·0 (9·2)	66·2 (10·1)	65·6 (9·7)	64·3 (8·0)	65·1 (9·6)	63·8 (7·4)
Fasting serum glucose, mg/dL	172·0 (42·9)	164·0 (40·9)	172·1 (42·8)	171·7 (44·4)	157·9 (28·7)	166·4 (35·0)	167·6 (38·0)
Fasting serum glucose, mmol/L	9·6 (2·4)	9·1 (2·3)	9·6 (2·4)	9·5(2·5)	8·8 (1·6)	9·2 (2·0)	9·3(2·1)
Diabetes duration, years	7·8 (4·0–12·5)	5·0 (2·9–11·9)	7·1 (3·7–12·6)	5·9 (3·3–9·9)	5·9 (3·1–9·3)	6·8 (2·9–10·6)	7·9 (4·1–12·5)
Metformin use	51 (93%)	44 (86%)	52 (93%)	46 (98%)	54 (89%)	56 (89%)	47 (94%)
Bodyweight, kg	102·0 (18·8)	99·3 (25·4)	99·3 (18·1)	98·5 (22·9)	98·9 (17·5)	104·6 (25·1)	98·8 (22·1)
BMI, kg/m^2	35·8 (6·2)	35·3 (8·2)	34·8 (6·3)	34·1 (7·7)	34·4 (5·4)	36·4 (6·9)	35·4 (8·0)
Waist circumference, cm	115·0 (12·4)	112·9 (18·4)	113·7 (11·8)	113·2 (15·3)	112·1 (12·7)	116·0 (16·6)	114·0 (16·4)
Estimated glomerular filtration rate*, mL per min per 1·73 m^2	90·2 (17·7)	88·9 (17·4)	91·3 (17·0)	87·5 (19·3)	90·2 (16·7)	87·2 (17·1)	87·8 (18·4)
Systolic blood pressure, mm Hg	135·2 (14·6)	132·5 (11·9)	134·9 (12·6)	129·7 (11·9)	132·9 (12·7)	136·7 (14·0)	135·7 (12·7)
Diastolic blood pressure, mm Hg	81·5 (7·1)	78·3 (7·7)	80·2 (8·5)	78·4 (8·8)	80·5 (7·3)	81·2 (8·9)	81·2 (8·9)

Data are mean (SD), n (%), or median (IQR). Sex is self-reported. HbA_{1c}=glycated haemoglobin. *Chronic Kidney Disease Epidemiology Collaboration formula used to estimate glomular filtration rate.

Table 1: **Baseline demographics and clinical variables of all randomly assigned population**

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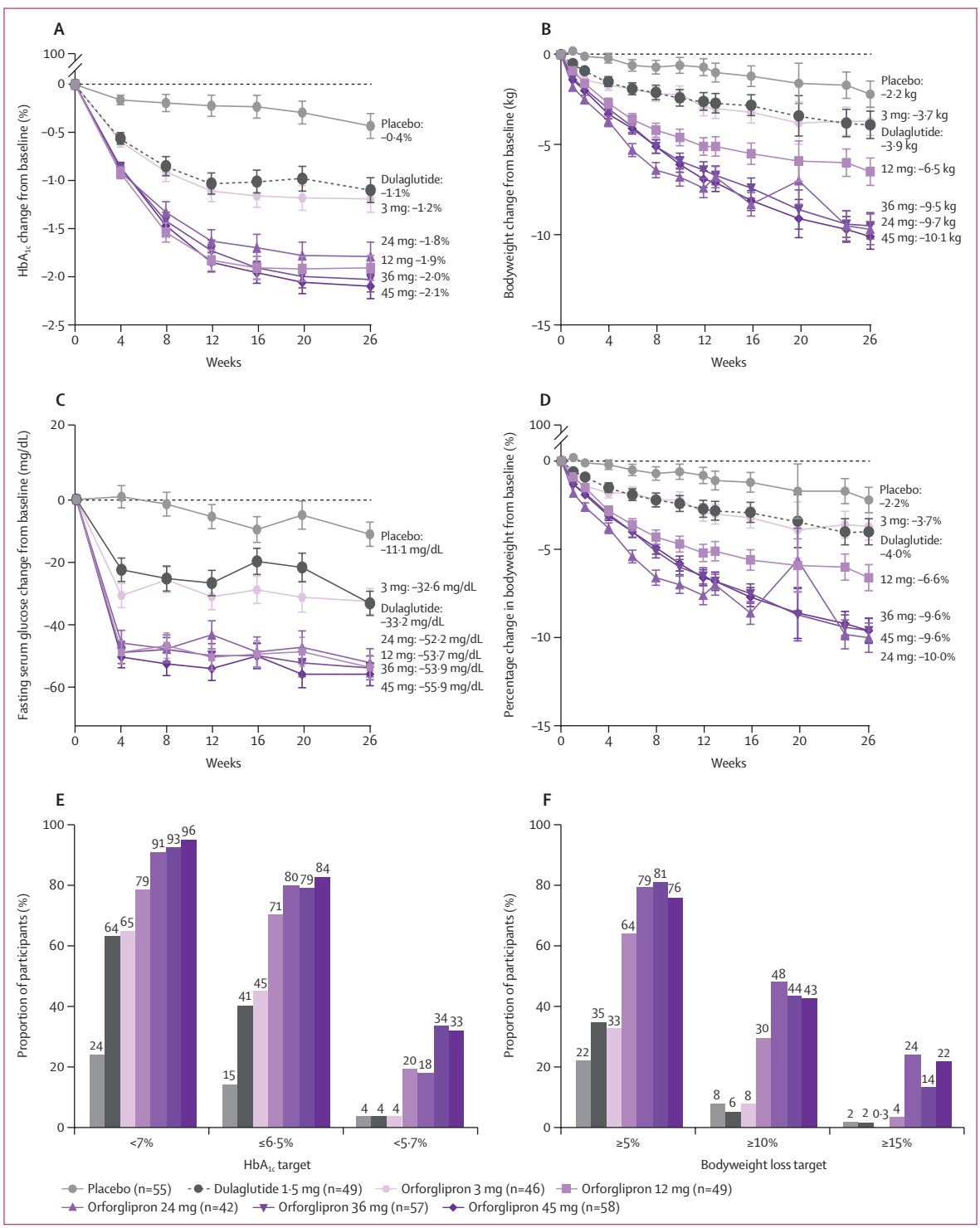

Figure 2: **Efficacy outcomes at week 26 in efficacy analysis set**
(A) Mean change in HbA_{1c} from baseline to week 26. (B) Mean change in bodyweight. (C) Mean change in fasting serum glucose. (D) Percentage change in bodyweight. (E) Proportion that reached HbA_{1c} targets at week 26. (F) Proportion that reached weight loss targets at week 26. Data are shown as least squares mean (SE). Analyses included participants with non-missing baseline values and at least one non-missing post-baseline measurement. HbA_{1c}=glycated haemoglobin.

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	Placebo (n=55)	Orforglipron 3 mg (n=51)	Orforglipron 12 mg (n=56)	Orforglipron 24 mg (n=47)	Orforglipron 36 mg (n=61)	Orforglipron 45 mg (n=63)	Dulaglutide 1·5 mg (n=50)
HbA_{1c}, %							
Baseline	8·06 (7·84 to 8·28)	8·03 (7·79 to 8·28)	8·23 (8·00 to 8·46)	8·07 (7·82 to 8·32)	8·03 (7·82 to 8·25)	8·11 (7·90 to 8·32)	8·00 (7·76 to 8·23)
Change from baseline at 26 weeks	−0·43 (−0·68 to −0·18)	−1·19 (−1·46 to −0·92)	−1·91 (−2·17 to −1·65)	−1·79 (−2·08 to −1·50)	−2·03 (−2·28 to −1·78)	−2·10 (−2·34 to −1·86)	−1·10 (−1·36 to −0·84)
Compared with placebo	··	−0·77 (−1·13 to −0·40); p<0·0001	−1·49 (−1·85 to −1·12); p<0·0001	−1·36 (−1·75 to −0·98); p<0·0001	−1·60 (−1·96 to −1·25); p<0·0001	−1·67 (−2·02 to −1·32); p<0·0001	−0·67 (−1·03 to −0·31); p=0·0003
Compared with dulaglutide 1·5 mg	··	−0·09 (−0·47 to 0·28)	−0·81 (−1·18 to −0·44)	−0·69 (−1·08 to −0·30)	−0·93 (−1·29 to −0·57)	−1·00 (−1·36 to −0·64)	··
HbA_{1c}, mmol/mol							
Baseline	64·6 (62·2 to 67·0)	64·3 (61·7 to 66·9)	66·5 (63·9 to 69·0)	64·7 (62·0 to 67·5)	64·3 (61·9 to 66·7)	65·1 (62·8 to 67·5)	63·9 (61·3 to 66·4)
Change from baseline at 26 weeks	−4·7 (−7·4 to −1·9)	−13·0 (−15·9 to −10·1)	−20·9 (−23·7 to −18·0)	−19·5 (−22·7 to −16·3)	−22·1 (−24·9 to −19·4)	−22·9 (−25·6 to −20·3)	−12·0 (−14·8 to −9·2)
Compared with placebo	··	−8·4 (−12·4 to −4·3)	−16·2 (−20·2 to −12·3)	−14·9 (−19·1 to −10·7)	−17·5 (−21·4 to −13·6)	−18·3 (−22·1 to −14·5)	−7·4 (−11·3 to −3·4)
Compared with dulaglutide 1·5 mg	··	−1·0 (−5·1 to 3·1)	−8·9 (−12·9 to −4·9)	−7·5 (−11·8 to −3·3)	−10·1 (−14·1 to −6·2)	−10·9 (−14·8 to −7·0)	··
Fasting serum glucose, mmol/L							
Baseline	9·55 (8·97 to 10·12)	9·13 (8·50 to 9·76)	9·58 (8·97 to 10·19)	9·42 (8·76 to 10·08)	8·79 (8·22 to 9·36)	9·24 (8·68 to 9·80)	9·28 (8·67 to 9·89)
Change from baseline at 26 weeks	−0·62 (−1·04 to −0·19)	−1·81 (−2·26 to −1·36)	−2·98 (−3·41 to −2·55)	−2·90 (−3·39 to −2·41)	−2·99 (−3·40 to −2·58)	−3·10 (−3·50 to −2·70)	−1·85 (−2·27 to −1·42)
Compared with placebo	··	−1·19 (−1·81 to −0·57)	−2·36 (−2·97 to −1·76)	−2·28 (−2·93 to −1·63)	−2·37 (−2·97 to −1·78)	−2·48 (−3·07 to −1·90)	−1·23 (−1·83 to −0·62)
Compared with dulaglutide 1·5 mg	··	0·03 (−0·59 to 0·66)	−1·14 (−1·74 to −0·53)	−1·05 (−1·70 to −0·40)	−1·15 (−1·74 to −0·55)	−1·26 (−1·85 to −0·67)	··
Fasting serum glucose, mg/dL							
Baseline	172·0 (161·7 to 182·3)	164·4 (153·2 to 175·7)	172·6 (161·6 to 183·5)	169·7 (157·9 to 181·5)	158·4 (148·1 to 168·6)	166·4 (156·4 to 176·5)	167·2 (156·2 to 178·1)
Change from baseline at 26 weeks	−11·1 (18·8 to −3·5)	−32·6 (−40·7 to −24·5)	−53·7 (−61·4 to −46·0)	−52·2 (−61·0 to −43·4)	−53·9 (−61·3 to −46·5)	−55·9 (−63·1 to −48·7)	−33·2 (−40·9 to −25·6)
Compared with placebo	··	−21·5 (−32·7 to −10·3)	−42·5 (−53·4 to −31·7)	−41·0 (−52·7 to −29·3)	−42·7 (−53·5 to −32·0)	−44·7 (−55·3 to −34·2)	−22·1 (−33·0 to −11·2)
Compared with dulaglutide 1·5 mg	··	0·6 (−10·6 to 11·8)	−20·5 (−31·4 to −9·5)	−19·0 (−30·7 to −7·2)	−20·7 (−31·4 to −9·9)	−22·7 (−33·2 to −12·1)	··
Bodyweight, kg							
Baseline	101·9 (96·2 to 107·7)	98·6 (92·6 to 104·6)	99·9 (94·1 to 105·7)	98·4 (92·1 to 104·61	99·0 (93·3 to 104·6)	104·8 (99·4 to 110·1)	98·8 (92·8 to 104·8)
Change from baseline at 26 weeks	−2·2 (−3·6 to −0·7)	−3·7 (−5·3 to −2·2)	−6·5 (−8·0 to −5·0)	−9·7 (−11·4 to −8·1)	−9·5 (−11·0 to −8·1)	−10·1 (−11·5 to −8·7)	−3·9 (−5·3 to −2·4)
Compared with placebo	··	−1·6 (−3·7 to 0·6)	−4·3 (−6·4 to −2·2)	−7·6 (−9·8 to −5·3)	−7·4 (−9·4 to −5·3)	−7·9 (−9·9 to −5·9)	−1·7 (−3·8 to 0·4)
Compared with dulaglutide 1·5 mg	··	0·1 (−2·0 to 2·3)	−2·6 (−4·7 to −0·5)	−5·9 (−8·1 to −3·6)	−5·7 (−7·8 to −3·6)	−6·2 (−8·3 to −4·2)	··
Percentage bodyweight change, kg							
Baseline	101·9 (96·2 to 107·7)	98·6 (92·6 to 104·6)	99·9 (94·1 to 105·7)	98·4 (92·1 to 104·6)	99·0 (93·3 to 104·6)	104·8 (99·4 to 110·1)	98·8 (92·8 to 104·8)
Change from baseline at 26 weeks	−2·2 (−3·6 to −0·7)	−3·7 (−5·2 to −2·2)	−6·6 (−8·0 to −5·1)	−10·0 (−11·6 to −8·4)	−9·6 (−11·0 to −8·2)	−9·6 (−10·9 to −8·2)	−4·0 (−5·5 to −2·6)
Compared with placebo	··	−1·5 (−3·6 to 0·6)	−4·4 (−6·5 to −2·4)	−7·8 (−10·0 to −5·6)	−7·4 (−9·4 to −5·4)	−7·4 (−9·4 to −5·4)	−1·9 (−3·9 to 0·2)
Compared with dulaglutide 1·5 mg	··	0·4 (−1·7 to 2·5)	−2·5 (−4·6 to −0·5)	−6·0 (−8·2 to −3·8)	−5·6 (−7·6 to −3·5)	−5·5 (−7·5 to −3·5)	··

(Table 2 continues on next page)

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	Placebo (n=55)	Orforglipron 3 mg (n=51)	Orforglipron 12 mg (n=56)	Orforglipron 24 mg (n=47)	Orforglipron 36 mg (n=61)	Orforglipron 45 mg (n=63)	Dulaglutide 1·5 mg (n=50)
(Continued from previous page)							
BMI, (kg/m²)							
Baseline	35·8 (34·0 to 37·6)	34·9 (33·0 to 36·8)	35·1 (33·2 to 36·9)	34·0 (32·0 to 36·0)	34·6 (32·8 to 36·4)	36·4 (34·7 to 38·1)	35·4 (33·5 to 37·3)
Change from baseline at 26 weeks	−0·8 (−1·3 to −0·3)	−1·3 (−1·8 to −0·7)	−2·3 (−2·8 to −1·8)	−3·4 (−4·0 to −2·8)	−3·3 (−3·8 to −2·8)	−3·5 (−4·0 to −3·0)	−1·4 (−2·0 to −0·9)
Compared with placebo	··	−0·5 (−1·2 to 0·3)	−1·5 (−2·2 to −0·8)	−2·6 (−3·4 to −1·8)	−2·5 (−3·2 to −1·8);	−2·7 (−3·4 to −2·0)	−0·6 (−1·4 to 0·1)
Compared with dulaglutide 1·5 mg	··	0·1 (−0·6 to 0·9)	−0·9 (−1·6 to −0·1)	−1·9 (−2·7 to −1·2)	−1·9 (−2·6 to −1·2)	−2·1 (−2·8 to −1·4)	··
Waist circumference, cm							
Baseline	115·0 (111·0 to 118·9)	112·5 (108·2 to 116·9)	114·4 (110·2 to 118·6)	114·2 (109·7 to 118·8)	112·0 (108·1 to 115·9)	116·5 (112·7 to 120·4)	113·9 (109·7 to 118·1)
Change from baseline at 26 weeks	−2·8 (−4·5 to −1·0)	−2·6 (−4·4 to −0·8)	−5·3 (−7·0 to −3·5)	−8·7 (−10·7 to −6·7)	−7·3 (−9·0 to −5·6)	−7·2 (−8·8 to −5·5)	−4·2 (−5·9 to −2·5)
Compared with placebo	··	0·1 (−2·4 to 2·6)	−2·5 (−5·0 to −0·1)	−5·9 (−8·6 to −3·3)	−4·5 (−6·9 to −2·1)	−4·4 (−6·8 to −2·0)	−1·4 (−3·9 to 1·0)
Compared with dulaglutide 1·5 mg	··	1·6 (−0·9 to 4·1)	−1·1 (−3·5 to 1·4)	−4·5 (−7·2 to −1·8)	−3·1 (−5·5 to −0·6)	−3·0 (−5·3 to −0·6)	··

Baseline and change from baseline values are least squares mean (95% CI); the other values are least squares mean difference (95% CI) from mixed model for repeated measures in the efficacy analysis set. HbA_{1c}=glycated haemoglobin.

Table 2: **Efficacy outcomes at week 26 in the efficacy analysis set**

45 mg, and superior to dulaglutide with up to –6·2 kg (–8·3 to –4·2) with 45 mg in terms of mean change from baseline in bodyweight (table 2).

With orforglipron treatment, 33–81% of participants had a weight loss of 5% or more of their bodyweight versus 36% in the dulaglutide group and 22% in the placebo group at week 26. More participants who received orforglipron (8–48%) had a weight loss of 10% or more compared with dulaglutide (6%) or placebo (8%); more participants who received orforglipron doses of more than 12 mg (4–24%) had a weight loss of 15% or more, compared with 2% of participants who received dulaglutide and 2% of participants who received placebo (figure 2F; appendix pp 10–11). More study participants who received doses of greater than or equal to 12 mg of orforglipron had a weight loss of 5% or 10% or more compared with placebo and dulaglutide (figure 2F; appendix pp 10–11). The change from baseline in mean waist circumference at week 26 ranged from –2·6 cm to –8·7 cm for participants who received any dose of orforglipron, compared with –4·2 cm in those who received dulaglutide and –2·8 cm in those who received placebo (table 2); and doses of 24 mg or greater were superior to dulaglutide 1·5 mg at week 26.

At week 26, the daily mean values of self-monitored blood glucose concentrations, including pre-meal and 2-hour post-prandial concentrations, were reduced from baseline for all doses of orforglipron compared with placebo (appendix p 14). Compared with dulaglutide, orforglipron doses of 12 mg or more resulted in greater reductions in self-monitored plasma glucose variables (appendix p 14). At week 26, fasting plasma glucagon concentrations were decreased with orforglipron doses 24 mg and 45 mg compared with placebo (appendix p 14). Compared with participants treated with dulaglutide, similar decreases in plasma glucagon concentrations were noted in participants who received any dose of orforglipron.

One or more treatment-emergent adverse events were reported by 61·8–88·9% (21/34 to 24/27) of orforglipron treated participants, and 61·8% (34/55) treated with placebo and 56·0% (28/50) treated with dulaglutide. The majority of treatment-emergent adverse events were gastrointestinal, reported by 44·1–70·4% (15/34 to 19/27) of participants who received orforglipron, compared with 18·2% (10/55) of those who received placebo and 34·0% (17/50) of those who received dulaglutide (table 3). Of the 152 gastrointestinal adverse events that occurred after the first dose, 146 (96·1%) were mild to moderate in severity; two participants reported severe nausea and four participants reported severe vomiting while receiving orforglipron (appendix p 18). Nausea occurred in up to 37·5% (21/56) of orforglipron participants, 5·5% (3/55) of placebo participants, and 18·0% (9/50) of dulaglutide participants, whereas vomiting occurred in up to 35·5% (11/31) of orforglipron participants, 1·8% (1/55) of placebo participants, and 8·0% (4/50) of dulaglutide participants. Most gastrointestinal events occurred early during therapy and were associated with dose escalations. Gastrointestinal adverse events occurred more frequently with participants receiving rapid dose escalation (once per week, every 2 weeks, or every 3 weeks). For example, 70·4% (19/27) of participants in the orforglipron 36 mg group 1 had a

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	Placebo (n=55)	Orforglipron 3 mg (n=51)	Orforglipron 12 mg (n=56)	Orforglipron 24 mg (n=47)	Orforglipron 36 mg group 1 (n=27)	Orforglipron 36 mg group 2 (n=34)	Orforglipron 45 mg group 1 (n=31)	Orforglipron 45 mg group 2 (n=32)	Dulaglutide 1·5 mg (n=50)
Any TEAE	34 (61·8% [49·0 to 74·7])	36 (70·6% [58·1 to 83·1])	44 (78·6% [67·8 to 89·3])	35 (74·5% [62·0 to 86·9])	24 (88·9% [77·0 to 100])	21 (61·8% [45·4 to 78·1])	24 (77·4% [62·7 to 92·1])	26 (81·3% [67·7 to 94·8])	28 (56·0% [42·2 to 69·8])
Risk difference compared with placebo, %	..	8·8 (–9·2 to 26·7)	16·8 (0·0 to 33·5)	12·7 (–5·2 to 30·5)	27·1 (9·6 to 44·5)	0 (–20·8 to 20·7)	15·6 (–3·9 to 35·1)	19·4 (0·8 to 38·1)	–5·8 (–24·6 to 13·0)
Serious adverse events	3 (5·5% [0·0 to 11·5])	3 (5·9% [0·0 to 12·3])	1 (1·8% [0·0 to 5·3])	5 (10·6% [1·8 to 19·5])	1 (3·7% [0 to 10·8])	1 (2·9% [0 to 8·6])	0	1 (3·1% [0 to 9·2])	1 (2·0% [0 to 5·9])
Risk difference compared with placebo, %	..	0·4 (–8·4 to 9·2)	–3·7 (–10·6 to 3·3)	5·1 (–5·5 to 15·8)	–1·8 (–11·1 to 7·6)	–2·6 (–10·8 to 5·7)	–5·5 (–11·5 to 0·5)	–2·4 (–10·8 to 6·2)	–3·5 (–10·6 to 3·7)
Deaths	1 (1·8% [0 to 5·3])	0	0	0	0	0	0	0	0
Study discontinuation because of an adverse event	1 (1·8% [0 to 5·3])	1 (2·0% [0 to 5·8])	2 (3·6% [0·0 to 8·4])	0	1 (3·7% [0·0 to 10·8])	0	0	0	0
Risk difference compared with placebo, %	..	0·1 (–5·0 to 5·3)	1·8 (–4·3 to 7·8)	–1·8 (–5·3 to 1·7)	1·9 (–6·1 to 9·8)	–1·8 (–5·3 to 1·7)	–1·8 (–5·3 to 1·7)	–1·8 (–5·3 to 1·7)	–1·8 (–5·3 to 1·7)
Study treatment discontinuation because of an adverse event	3 (5·5% [0·0 to 11·5])	6 (11·8% [2·9 to 20·6])	8 (14·3% [5·1 to 23·5])	9 (19·1% [7·9 to 30·4])	5 (18·5% [3·9 to 33·2])	4 (11·8% [0·9 to 22·6])	4 (12·9% [1·1 to 24·7])	4 (12·5% [1 to 24])	2 (4·0% [0·0 to 9·4])
Risk difference compared with placebo, %	..	6·3 (–4·4 to 17·0)	8·8 (–2·1 to 19·8)	13·7 (0·9 to 26·4)	13·1 (–2·8 to 28·9)	6·3 (–6·1 to 18·7)	7·4 (–5·8 to 20·7)	7·0 (–5·9 to 20·0)	–1·5 (–9·5 to 6·6)
Adverse events of special interest									
Acute pancreatitis*	0	0	0	1 (2·1% [0·0 to 6·3])	0	0	0	0	0
Total hypoglycaemia with plasma glucose <70 mg/dL	2 (3·6% [0·0 to 8·6])	4 (7·8% [0·5 to 15·2])	3 (5·4% [0·0 to 11·3]	1 (2·1% [0·0 to 6·3])	4 (6·6% [0·3 to 12·8])†	..	4 (6·4% [0·3 to 12·4])†	..	2 (4·0% [0·0 to 9·4])
Hypoglycaemia with plasma glucose <54 mg/dL	0	0	0	1 (2·1% [0·0 to 6·3])	1 (1·6% [0·0 to 4·8])†	..	1 (1·6% [0·0 to 4·7])†	..	1 (2·0% [0·0 to 5·9])
Rescue therapy for severe persistent hyperglycaemia	7 (12·7% [3·9 to 21·5])	2 (3·9% [0 to 9·2])	0	3 (6·4% [0·0 to 13·4]	3 (4·9% [0·0 to 10·3])†	..	1 (1·6% [0·0 to 4·7])†	..	0
TEAE gastrointestinal adverse events	10 (18·2% [8·0 to 28·4])	27 (52·9% [39·2 to 66·6])	33 (58·9% [46·0 to 71·8])	27 (57·4% [43·3 to 71·6])	19 (70·4% [53·1 to 87·6])	15 (44·1% [27·4 to 60·8])	19 (61·3% [44·1 to 78·4])	19 (59·4% [42·4 to 76·4])	17 (34·0% [20·9 to 47·1])
TEAE thyroid malignancies and c-cell hyperplasia	0	0	0	0	0	0	0	0	0
TEAE renal disorders	1 (1·8% [0 to 5·3])	0	0	1 (2·1% [0·0 to 6·3])	1 (1·6% [0·0 to 4·8])†	..	2 (3·2% [0·0 to 7·5])†	..	0
TEAE cardiac events	3 (5·5% [0·0 to 11·5])	4 (7·8% [0·5 to 15·2])	6 (10·7% [2·6 to 18·8])	5 (10·6% [1·8 to 19·5])	5 (8·2% [1·3 to 15·1])†	..	3 (4·8% [0·0 to 10·0])†	..	1 (2·0% [0·0 to 5·9])
Treatment–emergent hepatobiliary disorders	0	2 (3·9% [0 to 9·2])	1 (1·8% [0·0 to 5·3])	2 (4·3% [0·0 to 10·1])	0	0	0	0	0
TEAE severe hypersensitivity reactions	0	0	0	0	0	0	0	0	0
TEAEs occurring in 5% or more of participants									
Nausea	3 (5·5% [0·0 to 11·5])	12 (23·5% [11·9 to 35·2])	21 (37·5% [24·8 to 50·2])	16 (34·0% [20·5 to 47·6])	10 (37·0% [18·8 to 55·3])	9 (26·5% [11·6 to 41·3])	9 (29·0% [13·1 to 45·0])	8 (25·0% [10·0 to 40·0])	9 (18·0% [7·4 to 28·6]
Diarrhoea	4 (7·3% [0·4 to 14·1])	11 (21·6% [10·3 to 32·9])	9 (16·1% [6·5 to 25·7])	7 (14·9% [4·7 to 25·1])	7 (25·9% [9·4 to 42·5])	2 (5·9% [0 to 13·8])	9 (29·0% [13·1 to 45·0]	9 (28·1% [12·5 to 43·7])	6 (12·0% [3·0 to 21·0])
Vomiting	1 (1·8% [0 to 5·3])	3 (5·9% [0·0 to 12·3])	12 (21·4% [10·7 to 32·2])	13 (27·7% [14·9 to 40·4])	9 (33·3% [15·6 to 51·1])	7 (20·6% [7·0 to 34·2])	11 (35·5% [18·6 to 52·3])	7 (21·9% [7·6 to 36·2])	4 (8·0% [0·5 to 15·5])
Constipation	1 (1·8% [0 to 5·3])	7 (13·7% [4·3 to 23·2])	7 (12·5% [3·8 to 21·2])	6 (12·8% [3·2 to 22·3])	6 (22·2% [6·5 to 37·9])	1 (2·9% [0 to 8·6]	1 (3·2% [0·0 to 9·4])	4 (12·5% [1·0 to 24·0])	0
Dyspepsia	2 (3·6% [0·0 to 8·6])	6 (11·8% [2·9 to 20·6]	4 (7·1% [0·4 to 13·9])	3 (6·4% [0·0 to 13·4]	3 (11·1% [0·0 to 23·0])	2 (5·9% [0 to 13·8])	2 (6·5% [0·0 to 15·1]	2 (6·3% [0·0 to 14·6])	1 (2·0% [0·0 to 5·9])
Eructation	0	4 (7·8% [0·5 to 15·2])	2 (3·6% [0·0 to 8·4])	3 (6·4% [0·0 to 13·4]	5 (18·5% [3·9 to 33·2])	3 (8·8% [0 to 18·4]	2 (6·5% [0·0 to 15·1]	1 (3·1% [0·0 to 9·2])	1 (2·0% [0·0 to 5·9])
COVID–19	3 (5·5% [0·0 to 11·5])	2 (3·9% [0 to 9·2])	6 (10·7% [2·6 to 18·8])	2 (4·3% [0·0 to 10·0])	0	2 (5·9% [0 to 13·8])	1 (3·2% [0·0 to 9·4])	2 (6·3% [0·0 to 14·6])	2 (4·0% [0·0 to 9·4])

Data are n (% [95% CI]) and risk difference (95% CI). TEAE=treatment–emergent adverse event. *Confirmed by adjudication as acute pancreatitis (mild). †Combined adverse events for 36 mg and 45 mg treatment group; TEAE severity and hypoglycaemia incidence is combined for 36 mg and 45 mg cohorts.

Table 3: **Adverse events in safety population**

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gastrointestinal adverse event compared with 44·1% (15/34) in the 36 mg group 2 because of rapid titration. Serious adverse events ranged from 1·8% to 10·6% in orforglipron-treated participants, 5·5% with placebo treatment, and 2·0% with dulaglutide treatment (table 3; appendix p 19).

Discontinuation of study treatment related to an adverse event occurred most often with orforglipron 24 mg (21%) and orforglipron 36 mg (19%; figure 1). Based on the study dosing schemes, these two study groups included higher initial doses of orforglipron or rapid dose escalation, or both. The orforglipron 24 mg treatment group began with 3 mg for 2 weeks, then increased the dose once per week to 6 mg, 8 mg, 12 mg, and finally 24 mg. Orforglipron 36 mg group 1 began with 2 mg, and increased the dose once per week until the maintenance dose was reached (appendix p 24). Three participants receiving orforglipron and one participant receiving dulaglutide had clinically significant hypoglycaemia (<54 mg/dL [<3 mmol/L]) and no participants had severe hypoglycaemia. One participant in the placebo group died because of cardiac failure from ischaemic stroke and heart failure during the study, which was deemed by the investigator to be unrelated to study treatment.

Changes in calcitonin concentrations were observed with orforglipron at doses of 3, 24, 36, and 45 mg ranging from 3·2 to 11·4%, and –9·5% with dulaglutide, compared with –2·4% with placebo (appendix p 15). Increased calcitonin concentration was noted with orforglipron 12 mg compared with placebo (20·0%; estimated treatment difference 95% CI 4·7–41·3). No statistical differences were noted with other orforglipron doses or dulaglutide to placebo (appendix pp 15–16). Liver function tests were not different in participants receiving orforglipron compared with dulaglutide and placebo (appendix pp 15–16). An elevated alanine aminotransferase of three or more times the upper limit of normal occurred in one participant receiving orforglipron 36 mg, two participants receiving placebo, and one participant receiving dulaglutide; and an elevation of five or more times the upper limit of normal occurred in one participant treated with orforglipron 3 mg. An elevated alanine aminotransferase and aspartate aminotransferase of ten or more times the upper limit of normal occurred in one participant receiving orforglipron 45 mg. Study treatment was not discontinued, and hepatic enzymes improved without the need for intervention. Changes from baseline in serum amylase and lipase in participants receiving orforglipron were not significantly different compared with dulaglutide (appendix pp 15–16). One participant in the orforglipron 24 mg treatment group was reported to have acute pancreatitis 9 days after the completion of the treatment period; the study adjudication committee confirmed the event as pancreatitis (mild). No other clinically relevant changes in laboratory results were noted across treatment groups.

A decrease in systolic blood pressure was reported in all orforglipron treatment groups. At week 26, orforglipron treatment groups had mean changes from baseline from –8·7 mm Hg to –6·7 mm Hg compared with –7·9 mm Hg with dulaglutide and –5·5 mm Hg with placebo. Only the orforglipron 24 mg treatment group had a significant change in diastolic blood pressure from baseline, of –2·3 mm Hg (appendix p 17). An increase in mean pulse rate was reported in all orforglipron treatment groups, with the maximum change occurring around week 12. At week 26, orforglipron treatment groups had mean changes in beats per minute (bpm) from baseline of 3·0 to 6·1 compared with 2·3 bpm in dulaglutide and –1·6 bpm with placebo. Two participants receiving orforglipron 3 mg developed atrial fibrillation during the study period; both episodes were resolved, and the investigator concluded that they were not related to study treatment.

Discussion

In this randomised, double-blind, phase 2 study, treatment with orforglipron, a novel non-peptide, small molecule GLP-1 receptor agonist, led to clinically meaningful reductions in HbA_{1c}, fasting glucose concentration, and bodyweight from baseline to week 26, with a significant reduction compared with placebo. All orforglipron doses of 12 mg or more had significant reduction in HbA_{1c}, fasting serum glucose, and bodyweight compared with dulaglutide. An HbA_{1c} of less than 7·0% was reached in a greater proportion of participants taking orforglipron (up to 96%) compared with dulaglutide (64%), and approximately 30% of participants receiving the higher doses of orforglipron achieved normoglycaemia as indicated by an HbA_{1c} of less than 5·7%. Additionally, orforglipron-treated participants had significant reductions in bodyweight from baseline, with up to 81% with a weight loss of 5% or more of their bodyweight, 48% with a weight loss of 10% or more, and 24% with a weight loss of 15% or more. Health benefits for patients, such as improvements in cardiovascular risk factors (ie, hypertension and dyslipidaemia), have been reported with a weight loss of 5–10% of bodyweight.[11] Weight loss of more than 15% is associated with more pronounced health benefits, including reduced cardiovascular mortality.[11] In the context of the American Diabetes Association and European Association for the Study of Diabetes guidelines for the management of hyperglycaemia in type 2 diabetes, which stress the importance of antihyperglycaemic agents with weight-lowering effects and highlights the value of reducing the complexity of treatment regimens to help improve adherence and persistence, these early efficacy results with the orforglipron are potentially clinically meaningful.[5]

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In this phase 2 study, treatment with orforglipron resulted in a mean change in HbA_{1c} from baseline of up to –2·1% (placebo corrected 1·67%) and weight loss of up to 10·1 kg (placebo corrected 7·9 kg) at week 26. At similar stages of development, injected GLP-1 receptor agonists have shown HbA_{1c} reductions of –1·7% with 12 weeks of semaglutide 1·6 mg and –1·4% with 18 weeks of dulaglutide 4·5 mg.[12,13] These trials also observed bodyweight reductions of –4·8 kg with semaglutide and –4·1 kg with dulaglutide in participants with type 2 diabetes.[12,13] When these medications progressed to phase 3, injectable GLP-1 receptor agonists lowered HbA_{1c} in the range of 1·8–2·2% and bodyweight reductions in the range of 5·0–6·9 kg.[14,15] Orforglipron has therefore shown, in phase 2, a promising efficacy profile and has moved into phase 3 trials. The ACHIEVE phase 3 programme, with its first study (NCT05803421), will further characterise the therapeutic potential of this agent.

Orforglipron is a biased agonist at the GLP-1 receptor that induces cyclic adenosine monophosphate accumulation through activating the GLP-1 receptor with minimal observed recruitment of the GLP-1 receptor-mediated β-arrestin, which might affect the timing of receptor internalisation after binding and activation.[6] This mechanism is shared with tirzepatide, a dual GLP-1-receptor and GIP-receptor agonist at the GLP-1 receptor that has demonstrated clinically superior efficacy compared with selective GLP-1 receptor agonists.[16–20] The clinical significance of biased agonism on the GLP-1 receptor by orforglipron will require further investigation.

We observed high rates of treatment discontinuation and frequent gastrointestinal adverse events with orforglipron. Most of the gastrointestinal events were reported to be mild to moderate in severity and were associated with dose escalation and were more present in the rapid dose escalation groups, as well as different starting doses (2 mg verses 3 mg). Such effects are commonly observed in phase 2 trials of incretins, where the best starting dose, optimal titration approach, and dose for efficacy are unknown.[8,12,13] The short duration of phase 2 trials also limits the time available for dose escalation. This study demonstrated that 3 mg starting doses and a once-per-week dose escalation produced increased rates of nausea, vomiting, and diarrhoea. The phase 3 studies will evaluate the dosing approaches intended for broad clinical use optimised for tolerability, using low starting doses and slower dose escalation informed by this phase 2 trial. With these modifications we anticipate the gastrointestinal tolerability of orforglipron to be similar to other agents in GLP-1 receptor agonists class.

The safety profile of orforglipron was consistent with that of other GLP-1 receptor agonists.[21,22] The incidence of hypoglycaemic events with orforglipron was low and similar to other GLP-1 receptor agonists.[22,23] The observed modest increase in pulse rate is consistent with the known effects of the GLP-1 receptor agonists class, including when delivered orally.[7,23] The effect of orforglipron on monitored safety laboratory results, including pancreatic enzymes and calcitonin, was consistent with the observed effects of other GLP-1 receptor agonists, including semaglutide and dulaglutide.[7,22,24,25]

The limitations of this study include the small treatment group sample sizes compared with a phase 3 study, the homogenous study population with a short duration of type 2 diabetes, and the high visit frequency, which is common in this early investigational setting; thus, the results might not be generalisable to a broader population or to people with more advanced type 2 diabetes. As is commonly done in phase 2 studies, people with notable comorbidities such as New York Heart Association class 3 and 4 and renal dysfunction (an estimated glomerular filtration rate of <30 mL per min per 1·73 m^2) were not included. The study duration was only 26 weeks, therefore we are unable to know the complete bodyweight loss potential of orforglipron, or the long-term safety profile in this patient population.

In summary, in this phase 2 study, orforglipron demonstrated superior glycaemic and bodyweight loss compared with placebo and dulaglutide and a safety and tolerability profile similar to GLP-1 receptor agonists at this stage of development. The ACHIEVE phase 3 programme will further characterise the therapeutic potential of this oral GLP-1 receptor agonist.

Contributors

DR, AH, EP, RL, and XM contributed to the study design. DR and MK provided medical oversight during the trial. DR was the clinical research scientist. JPF and SH were study investigators. RL and SE were responsible for the statistical analyses. MK and DR wrote the first draft with medical writing support. All authors are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in interpretation of the data and critical review of the manuscript, had full access to the data, and approved this manuscript to be submitted for publication.

Declaration of interests

JPF reports research funding from Akero, AstraZeneca, Boehringer Ingelheim, 89bio, Eli Lilly, Intercept, Ionis, Janssen, Madrigal, Metacrine, Merck, NorthSea Therapeutics, Novartis, Novo Nordisk, Oramed, Pfizer, Poxel, and Sanofi; consulting fees from Akero, Altimmune, Boehringer Ingelheim, Carmot Therapeutics, Echosens, 89bio, Eli Lilly, Merck, Novo Nordisk, Pfizer, and Sanofi; speaker bureau from Eli Lilly; support for attending meetings or travel from Eli Lilly, Novo Nordisk, Pfizer, and Sanofi; participant advisory boards and consulting for Altimmune, Becton Dickinson, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gilead, Intercept, Merck, Novo Nordisk, Pfizer, and Sanofi; and is on the board of directors for T1D Exchange. SH reports research funding from Eli Lilly. SE reports funding from Eli Lilly for statistical services provided by employer Tigermed and travel support from Eli Lilly. RL, XM, MK, CK, KJM, AH, and EP are employees and shareholders of Eli Lilly. DR is a shareholder and retired employee of Eli Lilly.

Data sharing

Eli Lilly provides access to all individual participant data collected during the trial, after anonymisation, except for pharmacokinetic or genetic data. Data are available upon request 6 months after the study has been approved in both the USA and EU and after primary publication acceptance, whichever is later. There is no expiration date for data requests once data are made available. Access will be provided after a

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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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