Received: 4 April 2023 | Revised: 11 May 2023 | Accepted: 14 May 2023

DOI: 10.1111/dom.15150

ORIGINAL ARTICLE

WILEY

Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1b, multicentre, blinded, placebo-controlled, randomized, multiple-ascending-dose study in people with type 2 diabetes

Edward Pratt MD[1] | Xiaosu Ma PhD[2] | Rong Liu PhD[2] | Deborah Robins MS[2] | Tamer Coskun MD[2] | Kyle W. Sloop PhD[2] | Axel Haupt MD[2] | Charles Benson MD[2]

[1]Lilly Centre for Clinical Pharmacology Pte Ltd, Singapore

[2]Eli Lilly and Company, Indianapolis, Indiana, USA

Correspondence
Edward Pratt, MD, Exploratory Medicine & Pharmacology (EMP), Diabetes, Obesity & Complications, 3 Biopolis Drive, #02-11 Synapse, 138623, Singapore.
Email: pratt_edward_john@lilly.com

Funding information
Eli Lilly and Company

Abstract

Aim: To report the results of a Phase 1b trial evaluating the safety, pharmacokinetics and pharmacodynamics of orforglipron (LY3502970), an oral, non-peptide glucagon-like peptide-1 receptor agonist (GLP-1RA), in patients with type 2 diabetes (T2D).

Materials and Methods: This was a double-blind, placebo-controlled Phase 1 study evaluating five different dosing regimens. The first group established that weekly dose escalation of the daily doses of orforglipron was generally well tolerated. This enabled a parallel-arm design for the four groups following. Participants were randomized 3:1 to daily doses of orforglipron or placebo for 12 weeks. Eligible participants with T2D were aged 18 to 70 years and had glycated haemoglobin (HbA1c) levels ≥53.0 mmol/mol (7.0%) and ≤91.3 mmol/mol (10.5%).

Results: A total of 51 participants received orforglipron and 17 received placebo. In the placebo and orforglipron groups, respectively, baseline HbA1c was 8.1% and 8.0%, and baseline body weight was 90.3 and 88.4 kg. The most common adverse events were gastrointestinal-related, and occurred early in treatment, similar to findings with other GLP-1RAs. At Week 12, mean $t_{1/2}$ ranged from 29 to 49 hours. Mean HbA1c change ranged from −1.5% to −1.8% across orforglipron doses, versus −0.4% with placebo, and body weight change was −0.24 to −5.8 kg across orforglipron doses, versus 0.5 kg with placebo.

Conclusions: Orforglipron treatment resulted in meaningful reductions in HbA1c and body weight, with an adverse event profile consistent with that of other GLP-1RAs. Orforglipron may provide a safe and effective once-daily oral treatment alternative to injectable GLP-1RAs or peptide oral formulations without water and food restrictions.

KEYWORDS
GLP-1, glycaemic control, Phase I-II study, type 2 diabetes, weight control

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an established treatment option for type 2 diabetes (T2D) and chronic weight management.[1,2] GLP-1RAs have clinically significant effects on glycated haemoglobin (HbA1c) and body weight, a low risk of hypoglycaemia, and a well-established safety profile.[1] Cardiovascular (CV) outcomes trials have indicated GLP-1RAs have additional benefits in preventing events such as myocardial infarction, stroke, and/or CV-related mortality.[3] Other outcomes, including chronic kidney disease and non-alcoholic steatohepatitis, may also be attenuated by GLP-1RAs.[4,5]

Glucagon-like peptide-1 receptor agonist treatments were initially developed as peptide-based agents requiring daily (once- or twice-daily) subcutaneous injections, with the subsequent development of GLP-1RAs possessing prolonged pharmacokinetic (PK) characteristics that allow once-weekly injection, such as dulaglutide and semaglutide.[6] Currently, the only approved oral GLP-1RA is a specialized formulation of semaglutide that is only indicated for patients with T2D (sold as Rybelsus); however, this oral formulation of semaglutide (14 mg) does not match the greater efficacy of injectable semaglutide (1 mg).[7] As it is a peptide, the oral formulation of semaglutide requires an absorption enhancer for gastric delivery and needs to be taken at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 120 mL (4 oz) of plain water only.[8] An oral once-daily non-peptide GLP-1RA without such restrictions could improve the utilization and accessibility of incretin therapies to patients and remains an unmet need despite the increased number of agents under development.[9]

Orforglipron (LY3502970) belongs to a new class of chemically synthesized, oral non-peptide GLP-1RAs.[10,11] In preclinical models, orforglipron was highly potent, displaying pharmacological bias toward the cAMP second messenger signalling pathway, and it exhibited full efficacy at reducing hyperglycaemia in experimental animals.[10] Orforglipron is under development as a daily oral adjunct therapy to diet and exercise to improve glycaemic control in adults with T2D and chronic weight management in adults.[12,13] The aim of this Phase 1 proof-of-concept study was to evaluate the safety, tolerability, PK and pharmacodynamic (PD) profiles, and efficacy of orforglipron in patients with T2D with increasing oral daily doses.

2 | METHODS

2.1 | Clinical study design and randomization

This was a multicentre, randomized, double-blind, placebo-controlled, multiple-dose, Phase 1 study. The clinical trial (ClinicalTrials.gov NCT04426474) 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 Harmonization Good Clinical Practice guidelines. All participants provided written informed consent before participating in the study.

The trial evaluated five dosing regimens of orforglipron across five groups of participants with T2D, compared with a placebo control (Figures 1 and S1). Based on the safety, tolerability, and PD responses of participants after 4 weeks of dosing in the 21-mg group, the doses and dose-escalation steps were decided for the 9-, 15-, 27- and 45-mg groups. The intention was to evaluate a range of final doses (after 4 to 6 weeks of within-group dose escalation) that covers the potential estimated efficacious dose range.

2.2 | Participants

This study was conducted from October 8, 2020 to July 12, 2021 at study sites in the United States and Germany. Enrolled subjects were men and women aged between 18 and 70 years (18 and 64 years for investigational sites in Germany) with T2D for at least 6 months, who were treated with diet and exercise alone or a stable dose of metformin for at least 3 months prior to screening. Inclusion criteria included an HbA1c value of ≥7.0% to ≤10.5% (≥7.0% to ≤9% for investigational sites in Germany) at screening, a body mass index (BMI) of 18.5 to 45 kg/m^2 (18.5-35 kg/m^2 for investigational sites in Germany), and a stable body weight for the 3 months prior to screening (less than 5% body weight change). Subjects were excluded if they had an episode of ketoacidosis or hyperosmolar state requiring hospitalization in the 6 months prior to screening, severe or progressive diabetic retinopathy, specified CV events within the past 6 months prior to screening, or known allergies to the test compound.

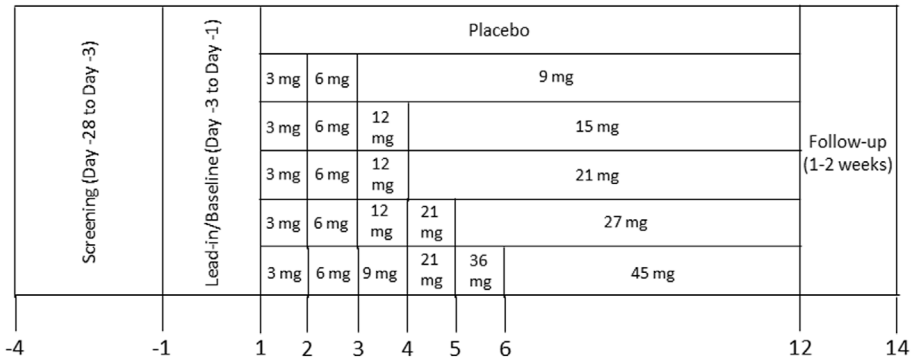
2.3 | Randomization and masking

Approximately 12 participants in each of the five orforglipron groups were randomly assigned in a 3:1 ratio to receive multiple daily doses of either orforglipron or placebo for 12 weeks. Participants, investigators, and all study site personnel except those who prepared, dispensed and administered study medication, were blinded to treatment allocation.

2.4 | Procedures

Capsules of different dose strengths were created by extemporaneous preparation and given orally once per day. In an initial cohort (Figures 1 and S1), participants were assigned to a treatment regimen starting with a low dose of 3 mg and escalating weekly to 6, 12 and then 21 mg over a 4-week period, and remained on this treatment dose for the remainder of the 12 weeks. Then, a review of available safety, tolerability, and PK and PD characteristics confirmed an adequate safety and tolerability profile for weekly escalation and determined the subsequent dose escalation schemes for the other dose cohorts. All participants started at 3 mg, escalated weekly, and the treatment dose levels achieved between 4 and 6 weeks were 9, 15, 27 and 45 mg, respectively (Figures 1 and S1).

FIGURE 1 Study design.



2.5 | Outcomes

The primary objective was to investigate the safety and tolerability of multiple oral doses of orforglipron in participants with T2D. Safety endpoints included treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) which were recorded by the investigator at each centre. The investigator determined if an adverse event (AE) had a reasonable possibility of being related to study treatment. Blood pressure and pulse rate were measured twice after the participant had been sitting for at least 5 minutes.

Secondary objectives were to characterize the PK characteristics of orforglipron after multiple oral doses and to investigate the effects of orforglipron on fasting plasma glucose and fasting insulin following multiple oral doses. Primary PK variables for analyses included maximum observed drug concentration (C_{max}) and area under the concentration curve (AUC). Change in fasting plasma glucose and fasting insulin were measured from baseline to Week 12.

Exploratory objectives were to investigate the PD effects of orforglipron following multiple oral doses. PD endpoints from baseline to Week 12 included absolute changes in HbA1c and body weight, change in C-peptide, glucose and insulin levels during a mixed-meal tolerance test (MMTT), change in visual analogue scale (VAS) score for appetite, and change in lipid profile.

2.6 | Statistics

We summarized TEAEs by treatment, severity, and relationship to the study drug. Estimates of PK variables for orforglipron were calculated using standard noncompartmental methods of analyses. All PK variables were listed and summarized using descriptive statistics. PK variables were evaluated to estimate dose proportionality. Log-transformed C_{max} and AUC values were evaluated using a power model to estimate ratios of dose-normalized geometric means and the corresponding 90% confidence interval. The t_{max} was analysed using a nonparametric method (Kruskal-Wallis test).

For changes from baseline values in vital signs and PD characteristics, a linear mixed-effect repeated-measures model was fitted. The model included treatment, time, and treatment-by-time interaction as fixed effects, baseline as a covariate, and participants as a random effect. The PD parameters were log-transformed, if deemed necessary. The data from placebo-treated participants within each part of the study were pooled for the final analysis. Overall appetite was quantified using the 0- to 100-mm validated VAS (higher scores indicating decreased appetite). Baseline (Day 1 pre-dose), post-dose values, and change from baseline were summarized by treatment and time point.

3 | RESULTS

Participants with T2D ($N = 69$) were enrolled (Figure S1). Of these, 68 participants received at least one dose of the study drug: 17 were assigned to the placebo group, nine were assigned to the orforglipron 9-mg group, 10 were assigned to the orforglipron 15-mg group, 14 were assigned to the orforglipron 21-mg group, nine were assigned to the orforglipron 27-mg group, and nine were assigned to the orforglipron 45-mg group. Eleven participants discontinued due to AEs. Fifty-three participants (75.4%) completed the study. The most common reason for study discontinuation (three participants) was COVID-19 infection.

Of the participants who received placebo ($N = 17$) or orforglipron ($N = 51$), 58.8% and 62.7% were male, mean age was 56.0 and 58.5 years, mean duration of diabetes was 8.6 and 11.1 years, mean HbA1c was 8.09% and 8.03%, mean body weight was 90.3 and 88.4 kg, and mean BMI was 31.3 and 30.9 kg/m^2, respectively (Table 1). There was variation between the groups for the majority of baseline characteristics, including age, weight, BMI, HbA1c level, and duration of diabetes. Variations were due to the small sample size. The majority of participants (~90%) used metformin during the study.

3.1 | Safety results

Of the 51 participants who received orforglipron, 44 (86.3%) reported TEAEs and of the 17 participants who received placebo, seven (41.2%) reported TEAEs (Table 2). Of the 51 participants who received orforglipron, 39 (76.5%) reported TEAEs considered related to study treatment, as determined by the investigator. The AE profile was consistent with GLP-1 receptor agonism, with common AEs related to

TABLE 1 Demographics and baseline characteristics

	Placebo once daily	Orforglipron once daily					
		OFG 9 mg	OFG 15 mg	OFG 21 mg	OFG 27 mg	OFG 45 mg	Overall OFG
Participants studied,[a] n	17	9	10	14	9	9	51
Age, years	56.0 ± 6.0	57.7 ± 6.4	59.6 ± 4.6	55.3 ± 8.0	58.8 ± 4.6	62.8 ± 4.4	58.5 ± 6.3
Sex: male, n (%)	10 (58.8)	4 (44.4)	7 (70.0)	10 (71.40)	7 (77.8)	4 (44.4)	32 (62.7)
Weight, kg, mean	90.29 ± 20.04	85.61 ± 12.76	88.02 ± 14.36	92.09 ± 18.78	92.80 ± 15.36	81.49 ± 10.24	88.40 ± 15.06
BMI, kg/m^2, mean	31.31 ± 4.86	30.14 ± 3.60	30.39 ± 3.61	32.60 ± 5.48	30.62 ± 3.55	29.82 ± 2.84	30.89 ± 4.09
HbA1c, mmol/mol, mean	64.9 ± 8.2	64.2 ± 6.8	62.2 ± 8.1	67.9 ± 14.3	62.0 ± 7.5	63.2 ± 8.6	64.3 ± 10.0
HbA1c, %, mean	8.09 ± 0.75	8.02 ± 0.62	7.84 ± 0.74	8.36 ± 1.31	7.82 ± 0.69	7.93 ± 0.79	8.03 ± 0.91
Metformin use, yes, n (%)	15 (88.2)	7 (77.8)	8 (80.0)	14 (100)	8 (88.9)	9 (100.0)	46 (90.2)
Duration of diabetes, years, mean	8.63 ± 4.89	13.48 ± 8.29	15.02 ± 11.97	9.48 ± 5.48	7.60 ± 4.39	10.38 ± 4.78	11.10 ± 7.64

Note: Data are mean ± SD unless otherwise indicated.
Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; OFG, orforglipron; SD, standard deviation.
[a]This indicates the safety population, who took at least one dose of study intervention.

TABLE 2 Summary of safety and treatment-emergent adverse events

	Placebo *N* = 17	OFG 9 mg *N* = 9	OFG 15 mg *N* = 10	OFG 21 mg *N* = 14	OFG 27 mg *N* = 9	OFG 45 mg *N* = 9
All TEAEs	7 (41.2)	8 (88.9)	9 (90.0)	10 (71.4)	8 (88.9)	9 (100)
Treatment-related TEAEs	4 (23.5)	8 (88.9)	8 (80.0)	7 (50.0)	7 (77.8)	9 (100)
SAEs	1 (5.88)	0	0	0	0	0
Deaths	0	0	0	0	0	0
TEAEs leading to study discontinuation	4 (23.5)	0	1 (10)	5 (35.7)	1 (11.1)	0
GI TEAEs[a]	3 (17.6)	8 (88.9)	7 (70.0)	6 (42.9)	7 (77.8)	9 (100)
Nausea	1 (5.9)	4 (44.4)	5 (50.0)	6 (42.9)	3 (33.3)	7 (77.8)
Decreased appetite	2 (11.8)	4 (44.4)	4 (40.0)	4 (28.6)	5 (55.6)	6 (66.7)
Vomiting	0	5 (55.6)	5 (50.0)	2 (14.3)	5 (55.6)	5 (55.6)
Dyspepsia	1 (5.9)	2 (22.2)	1 (10.0)	0	2 (22.2)	3 (33.3)
Eructation	0	1 (11.1)	3 (30.0)	0	2 (22.2)	2 (22.2)
Abdominal distension	0	0	1 (10.0)	1 (7.1)	2 (22.2)	2 (22.2)
Early satiety	0	1 (11.1)	2 (20.0)	0	1 (11.1)	2 (22.2)
Diarrhoea	3 (17.6)	0	1 (10.0)	1 (7.1)	2 (22.2)	1 (11.1)
AEs of special interest						
Cardiovascular events	0	0	0	0	0	0
Hypoglycaemic events	0	0	0	0	0	0
Hepatic events	0	0	0	0	0	0

Note: Data are number of participants with event (%). *n*, number of participants who were enrolled and received at least one dose of study drug (intention-to-treat population).
Abbreviations: AE, adverse event; GI, gastrointestinal; *N*, number of participants; OFG, orforglipron; SAE, serious adverse event; TEAE, treatment emergent adverse event.
[a]GI TEAEs include vomiting, nausea, dyspepsia, eructation, abdominal distension, diarrhoea, constipation, abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, breath odour, and flatulence.

gastrointestinal (GI) tolerability (nausea, vomiting, diarrhoea and constipation). GI TEAEs were reported in three participants (17.6%) who received placebo and 37 (72.5%) who received orforglipron (Table 2). Vomiting, nausea and decreased appetite were the most frequently reported GI TEAEs. Higher proportions of participants in the orforglipron 45-mg group reported GI-related TEAEs (including vomiting, nausea, dyspepsia, eructation, abdominal distension, diarrhoea, constipation, abdominal discomfort, abdominal pain, abdominal pain upper,

abdominal tenderness, breath odour, and flatulence) compared with the lower orforglipron dose groups (Table 2). Most TEAEs were of mild to moderate severity. GI tolerability events were commonly seen after the first dose of orforglipron, but also occurred following within-cohort dose escalation in some participants when they increased up to the next dose level. Four participants had their within-cohort dose escalation slowed or stopped by the investigator due to tolerability concerns, but these were the minority of participants, and doses for all the other participants were escalated within the first 6 weeks of the study as planned.

Eleven participants discontinued due to AEs, of whom seven were randomly assigned to orforglipron. The seven orforglipron-exposed participants were discontinued for AEs including nausea, intermittent diarrhoea, ventricular extrasystoles, COVID-19, and elevated lipase concentrations. One participant, in the placebo group had an SAE which was not related to study drug. No deaths or fatal SAEs were reported during the study. Regarding AEs of special interest for this compound, there were no reported TEAEs relating to CV events, hypoglycaemia, or hepatic events.

No significant changes were noted in either mean systolic (SBP) or diastolic blood pressure (DBP) across dose groups (Table S2). Pulse rate increased significantly compared with placebo in all dose groups (Table S2). Mean pulse rate at Week 12 changed from baseline by 4 to 10 beats/min, but not in a dose-dependent manner. The plasma orforglipron concentration-QTcF (QT interval corrected using Fridericia's formula) regression analysis demonstrated that the upper bound of the two-sided 90% confidence interval for the QTc effect of orforglipron, as estimated by exposure response analysis, was less than 10 ms at the highest exposure (geometric mean of C_{max} for the highest dose of 45 mg).

Two orforglipron-treated participants had elevated levels of amylase and lipase, which were considered clinically significant and related to study treatment by the investigator. These were listed as TEAEs. One of the participants was in the orforglipron 15-mg group and had elevated levels of amylase and lipase on Day 91 (7 days after the last dose of study drug), which were of mild and moderate severities, respectively. The other participant was in the orforglipron 27-mg group and had elevated levels of lipase on Day 15 (1 day after the 6-mg orforglipron dose), which was of mild severity. Apart from the two participants with the abnormalities in laboratory values described, no other clinically significant alterations were reported in pancreatic enzymes throughout the study (Table S2). No clinically significant trends or changes were noted in alanine aminotransferase or aspartate aminotransferase.

3.2 | Pharmacokinetics

The PK data are presented in Table S1. The pharmacokinetics of orforglipron increases for C_{max} and $AUC_{(0-24)}$ were approximately proportional to the dose increases ranging from 9 to 45 mg at Week 12. The median t_{max} was 4 to 8 hours across all orforglipron doses post-dose and the mean half-life ranged from 28.7 to 49.3 hours across all orforglipron doses.

3.3 | Pharmacodynamics

Pharmacodynamic characteristics at baseline and Week 12 are summarized in Table S3. Mean fasting plasma glucose levels at Week 12 were decreased significantly more in the 9- and 15-mg dose groups compared with placebo (Figure 2B). Mean fasting insulin levels at Week 12 were not significantly different from those observed with placebo, across all dose groups (Table S3).

Significant decreases in HbA1c were observed in all orforglipron groups from baseline to Week 12 (Figure 2A). At Week 12, the least squares mean (LSM) difference compared with placebo was −1.38% for the orforglipron 9-mg group, −1.34% for the orforglipron 15-mg group, −1.09% for the orforglipron 21-mg group, −1.34% for the orforglipron 27-mg group, and −1.02% for the orforglirpon 45-mg group.

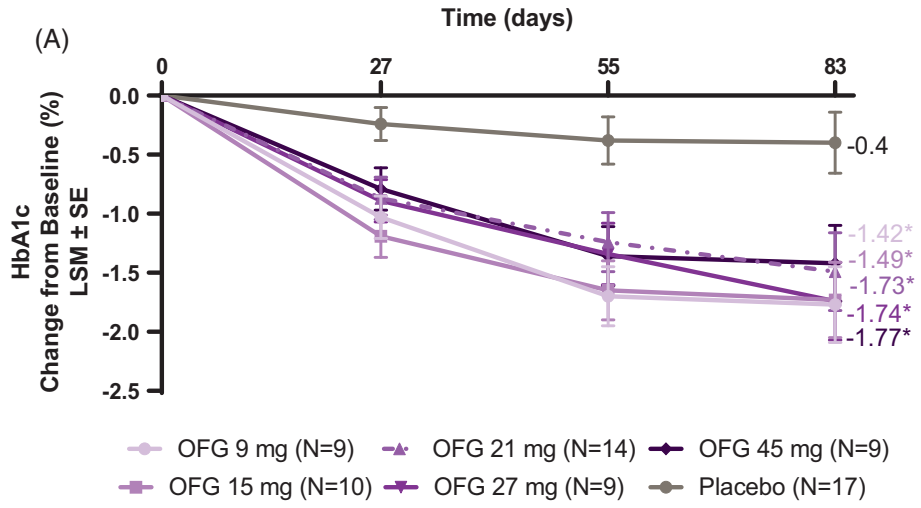
Following the MMTT, glucose concentrations were consistently lower in orforglipron-treated participants compared with placebo at Week 12. Across all orforglipron dose groups, a consistent decrease in $AUC_{(0-2h)}$ for glucose was observed for all orforglipron groups on Day 84. On Day 84 (Week 12), the mean glucose $AUC_{(0-2h)}$ was 14.4 to 16.9 mmol h/L across the orforglipron groups, compared with 21.9 mmol h/L for placebo.

At Week 12, a significant reduction in body weight from baseline was observed compared with placebo, across all orforglipron dose groups, except for the 21-mg dose group (Figure 3). Body weight reduced over time from Day 7 to Week 12. At Week 12, the LSM difference in change from baseline in body weight versus placebo was approximately −4 to −6 kg for all orforglipron-treated groups, except for the oforglipron 21-mg group, which was −0.75 kg, this was due to the small sample size and higher variability of response in that cohort.

Overall appetite VAS scores generally increased (indicating decreased appetite) in all treatment groups, but these increases were not statistically significant (Table S4). With respect to individual components of the overall score, prospective food consumption and hunger scores generally decreased from baseline in the orforglipron groups. Fullness and satiety scores generally increased from baseline with orforglipron treatment.

In general, orforglipron showed little effect on lipid variables (Table S2). At Week 12, a trend of decrease in triglyceride concentrations as compared with Day 1 pre-dose was noted for all orforglipron groups. However, the difference was not statistically significant or time-dependent. No noticeable time- or dose-associated trends were observed in either low-density lipoprotein or high-density lipoprotein cholesterol.

Following the administration of acetaminophen (approximately 5 to 10 minutes after meal completion for MMTT and 2 hours after orforglipron dose), a delay in gastric emptying was observed. The statistical analysis of t_{max} showed a delay of approximately 1 to 3.5 hours in acetaminophen t_{max} on Day 1, and a delay of 0 to 1.75 hours following multiple orforglipron dosing at Week 12 when participants were administered acetaminophen in combination with orforglipron compared with acetaminophen alone (Table S5). The gastric emptying delay reduced toward baseline following multiple orforglipron dosing at Week 12.



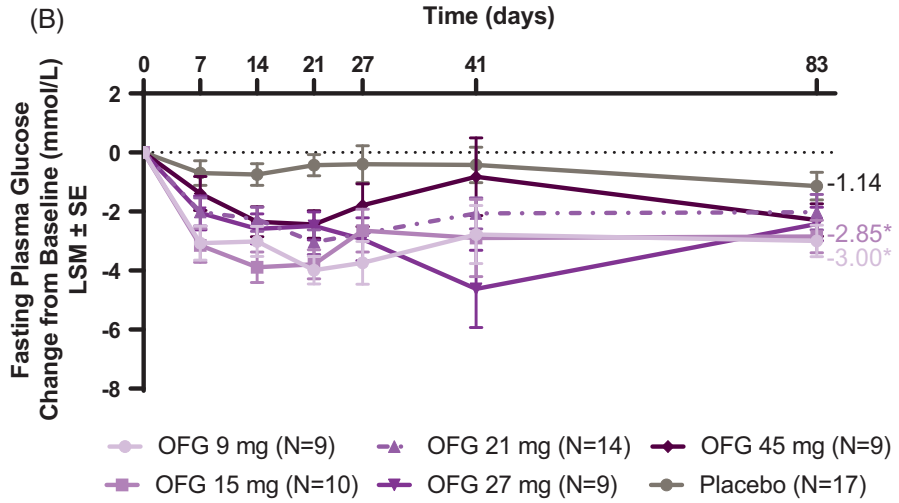


FIGURE 2 Glycated haemoglobin (HbA1c) and glucose levels at Week 12. Least squares mean (LSM) with standard error (SE) change from baseline in (A) HbA1c and (B) fasting plasma glucose over 12 weeks. *P < 0.10 versus placebo. The 21-mg dose group is represented as a dotted line. N, number of participants; OFG, orforglipron

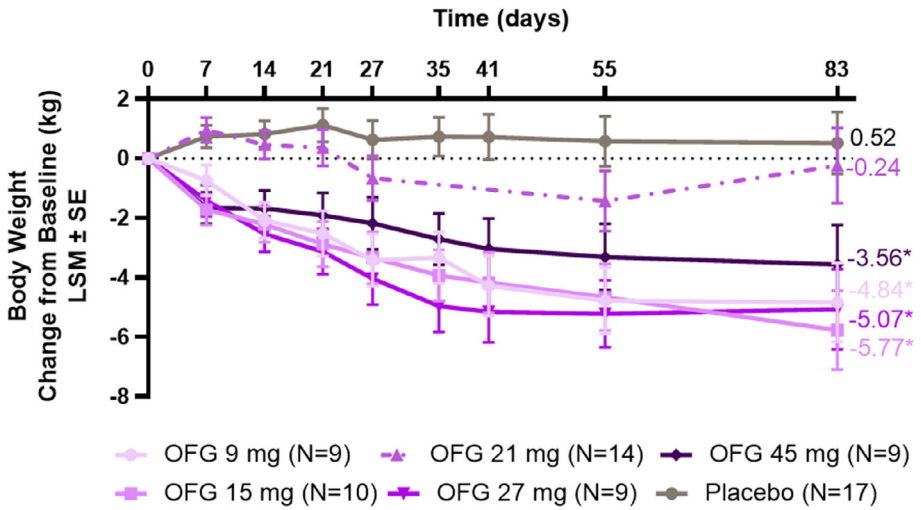


FIGURE 3 Body weight change from baseline at Week 12. Least squares mean (LSM) with standard error (SE) change from baseline in body weight (A) over 12 weeks and (B) at Week 12. *P < 0.10 versus placebo. The 21-mg dose group is represented as a dotted line. N, number of participants; OFG, orforglipron

4 | DISCUSSION

The results from this proof-of-concept, Phase 1b clinical trial provide initial evidence of the safety and efficacy of the oral GLP-1RA orforglipron in participants with T2D. Orforglipron showed a safety profile consistent with that reported for other GLP-1RA therapeutic agents in early phases of development.[11,14] The PK profile of orforglipron was dose-proportional, with a half-life that supports once-daily

dosing. PD results showed significant glycaemic improvements compared with placebo including reductions in HbA1c and fasting glucose levels. Body weight reductions were also significant in orforglipron-treated participants and overall appetite VAS scores generally increased (indicating decreased appetite) across all groups.

The oral bioavailability of peptide therapeutics, including incretin therapies, limits their oral application.[15] Currently available incretin therapies are restricted to injectable therapies or an oral formulation of semaglutide, which has a bioavailability of just 0.4% to 1.0%.[15] and requires a fasting state.[1,8] A non-peptide approach can improve the oral bioavailability of incretin therapies[11] and resulted in the bioavailability of oral orforglipron (~20%-40% determined from a reported preclinical model)[10] being greater than that of semaglutide. Orforglipron is a chemically synthesized, oral GLP-1RA that, when administered by once-daily dosing without regard to food and water, results in reductions in HbA1c and body weight that were similar to Phase 1 results comparing oral semaglutide with placebo in participants with T2D.[14]

To examine the safety and tolerability in short-duration Phase 1 GLP-1RA trials, the study drug is often escalated quickly and therefore frequent GI AEs are observed. In this regard, orforglipron behaved similarly to other GLP-1RAs. Interestingly, the majority of GI AEs for orforglipron-treated participants occurred in the first week after dosing (3 mg), indicating starting dose is as important as the frequency and magnitude of escalation steps.

Pulse rate increases were observed with orforlipron treatment. These were in line with Phase 1 studies of other GLP-1RAs, which showed increases of 4 to 10 beats/min.[14,16,17] We expect tachyphylaxis of the pulse rate with a longer duration of treatment. Small insignificant changes in SBP and DBP were seen with orforglipron treatment, and QTcF was not significantly impacted.

Safety laboratory values were in line with those for other selective GLP-1RAs. Although two orforglipron-treated participants experienced elevated levels of lipase and amylase, the severity was mild or moderate in both cases. Otherwise, no effects on pancreatic or hepatic enzymes were observed, indicating off-target effects of orforglipron treatment are unlikely. Larger Phase 2 studies will investigate this further.

Orforglipron treatment showed similar or enhanced HbA1c reductions and weight loss compared with other oral GLP-1RAs, with HbA1c reductions of up to 1.8% and body weight reductions of up to 5.8 kg. The PIONEER-1 Phase 3 study showed oral semaglutide 14 mg reduced HbA1c by 1.1% and body weight by 2.3 kg after 26 weeks of treatment.[18] Higher doses of oral semaglutide are under development. Danuglipron, another oral non-peptide GLP-1RA under development, when given twice daily, demonstrated HbA1c reductions of up to 1.2% and body weight reductions of up to 7.2 kg after 28 days of treatment in patients with T2D.[11]

Injectable GLP-1RA therapy can achieve HbA1c and body weight reductions of 1.6% and 4.5 kg, respectively, after 30 weeks.[19] The current data show this non-peptide agonist has the potential to achieve a similar efficacy to that of some injectable GLP-1RAs, while offering once-daily, oral dosing without fasting restrictions. Therefore, orforglipron could be an important treatment option for T2D and chronic weight management. To further explore the full potential of orforglipron, two Phase 2 trials are currently ongoing in patients with T2D (NCT05048719) and in patients with obesity (NCT05051579).[12,13]

Strengths of the current study were the comprehensive number of different treatment groups tested, the use of placebo as a comparator, and randomization and blinding of the study treatments. An inherent limitation of this study is its small sample size and short steady-state exposure. Differences in baseline characteristics were observed. No clear dose-dependent effects were noted. Larger trials with longer durations are needed to address these points, which is part of the aims on the ongoing Phase 2 studies.

In summary, after 12 weeks of treatment, orforglipron resulted in significant reductions in HbA1c, fasting blood glucose and body weight, with an AE profile consistent with that of other GLP-1RAs and a PK profile that allows once-daily oral dosing. Orforglipron does not have food or water administration restrictions[9] and may provide a safe and effective oral treatment option for patients with T2D and other indications.

ACKNOWLEDGMENTS

Orforglipron is also known as LY3502970 or OWL833 and was discovered by scientists at the Chugai Pharmaceutical Co., Ltd. The authors thank Ana Hickey PhD and Ciara O'Neill PhD, Eli Lilly and Company, for medical writing and editorial services.

FUNDING INFORMATION

This study was funded by Eli Lilly and Company.

CONFLICT OF INTEREST STATEMENT

Edward Pratt, Xiaosu Ma, Rong Liu, Tamer Coskun, Kyle Sloop, Axel Haupt and Charles Benson are employees and shareholders of Eli Lilly and Company. Deborah Robins is a former Eli Lilly and Company employee and current Eli Lilly and Company shareholder. The authors declare no conflict of interest.

ORCID

Edward Pratt https://orcid.org/0000-0003-4449-6231
Tamer Coskun https://orcid.org/0000-0002-2481-133X
Axel Haupt https://orcid.org/0000-0003-4502-0470

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15150.

DATA AVAILABILITY STATEMENT

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 US 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, 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.

REFERENCES

1. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes–state-of-the-art. *Mol Metab*. 2021;46:101102. doi:10.1016/j.molmet.2020.101102
2. Jepsen MM, Christensen MB. Emerging glucagon-like peptide 1 receptor agonists for the treatment of obesity. *Expert Opin Emerg Drugs*. 2021;26(3):231-243. doi:10.1080/14728214.2021.1947240
3. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.
4. Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G. Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. *Metabolites*. 2021;11(2):73. doi:10.3390/metabo11020073
5. von Scholten BJ, Kreiner FF, Rasmussen S, Rossing P, Idorn T. The potential of GLP-1 receptor agonists in type 2 diabetes and chronic kidney disease: from randomised trials to clinical practice. *Ther Adv Endocrinol Metab*. 2022;13:20420188221112490. doi:10.1177/20420188221112490
6. Gentilella R, Pechtner V, Corcos A, Consoli A. Glucagon-like peptide-1 receptor agonists in type 2 diabetes treatment: are they all the same? *Diabetes Metab Res Rev*. 2019;35(1):e3070. doi:10.1002/dmrr.3070
7. Hughes S, Neumiller JJ. Oral semaglutide. *Clin Diabetes*. 2020;38(1):109-111. doi:10.2337/cd19-0079
8. Hedrington MS, Davis SN. Oral semaglutide for the treatment of type 2 diabetes. *Expert Opin Pharmacother*. 2019;20(2):133-141. doi:10.1080/14656566.2018.1552258
9. Pratt E, Ma X, Liu R, et al. Results from a 12-week proof-of-concept study of a novel oral non-peptide GLP-1 receptor agonist in patients with type 2 diabetes. *Diabetologia*. Vol 65. Springer; 2022:S301.
10. Kawai T, Sun B, Yoshino H, et al. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. *Proc Natl Acad Sci*. 2020;117(47):29959-29967. doi:10.1073/pnas.2014879117
11. Saxena AR, Gorman DN, Esquejo RM, et al. Danuglipron (PF-06882961) in type 2 diabetes: a randomized, placebo-controlled, multiple ascending-dose phase 1 trial. *Nat Med*. 2021;27(6):1079-1087. doi:10.1038/s41591-021-01391-w
12. A Study of LY3502970 in Participants With Type 2 Diabetes Mellitus. ClinicalTrials.gov identifier: NCT05048719. Updated October 31, 2022. Accessed 2 December 2022 2022 https://clinicaltrials.gov/ct2/show/NCT05048719
13. A study of LY3502970 in participants with obesity or overweight with weight-related comorbidities. ClinicalTrials.gov identifier: NCT05051579. Updated October 12, 2022. Accessed 2 December 2022 https://clinicaltrials.gov/ct2/show/NCT05051579
14. Granhall C, Donsmark M, Blicher TM, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. *Clin Pharmacokinet*. 2019;58(6):781-791. doi:10.1007/s40262-018-0728-4
15. Brayden DJ, Hill TA, Fairlie DP, Maher S, Mrsny RJ. Systemic delivery of peptides by the oral route: formulation and medicinal chemistry approaches. *Adv Drug Deliv Rev*. 2020;157:2-36. doi:10.1016/j.addr.2020.05.007
16. Barrington P, Chien JY, Showalter HDH, et al. A 5-week study of the pharmacokinetics and pharmacodynamics of LY2189265, a novel, long-acting glucagon-like peptide-1 analogue, in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011;13(5):426-433. doi:10.1111/j.1463-1326.2011.01364.x
17. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care*. 2015;39(2):231-241. doi:10.2337/dc15-0165
18. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. *Diabetes Care*. 2019;42(9):1724-1732. doi:10.2337/dc19-0749
19. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(4):251-260. doi:10.1016/S2213-8587(17)30013-X

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pratt E, Ma X, Liu R, et al. Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1b, multicentre, blinded, placebo-controlled, randomized, multiple-ascending-dose study in people with type 2 diabetes. *Diabetes Obes Metab*. 2023;1-8. doi:10.1111/dom.15150