Check for updates

Received: 4 April 2023 | Revised: 2 June 2023 | Accepted: 5 June 2023

DOI: 10.1111/dom.15184

ORIGINAL ARTICLE

WILEY

Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study in healthy participants

Edward Pratt MD[1] | Xiaosu Ma PhD[2] | Rong Liu PhD[2] | Deborah Robins MS[2] | Axel Haupt MD[2] | Tamer Coskun MD[2] | Kyle W. Sloop PhD[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 evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of orforglipron (LY3502970), an oral, non-peptide glucagon-like peptide-1 receptor agonist (GLP-1RA) in healthy participants.

Materials and Methods: This was a double-blind, placebo-controlled, Phase 1 study. Overtly healthy adults aged 18 to 65 years with body mass index of 20 to 40 kg/m^2 and glycated haemoglobin concentration of 47.5 mmol/mol (<6.5%) were eligible. In Part A, participants received single-dose orforglipron, with four cohorts receiving escalating doses (0.3-6 mg). In Part B, participants received 4 weeks of daily repeated oral orforglipron with doses escalating weekly to four different final target doses (2-24 mg).

Results: Ninety-two participants enrolled and received at least one study drug dose (32 in Part A [mean age 43.4 years] and 60 in Part B [mean age 42.5 years]). The most common adverse events were gastrointestinal tract-related. Pharmacokinetics were approximately dose proportional, and the mean $t_{1/2}$ was 24.6 to 35.3 hours after a single dose (0.3-6 mg). On Day 28, the mean $t_{1/2}$ was 48.1 to 67.5 hours across the dose range (2-24 mg). Substantial reductions in body weight of up to 5.4 kg were observed after 4 weeks in orforglipron-treated participants, compared to a reduction of 2.4 kg with placebo ($P < 0.05$). Orforglipron decreased fasting glucose levels across Days 1 to 28, and gastric emptying was delayed on Day 28.

Conclusions: Orforglipron's long half-life (25-68 hours) allows once-daily oral dosing, without water and food restrictions. Orforglipron had a pharmacodynamic and safety profile similar to that of injectable GLP-1RAs, which supports continued clinical development.

KEYWORDS
antidiabetic drug, GLP-1, pharmacodynamics, pharmacokinetics, phase I-II study, weight control

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2023 Eli Lilly and Company. *Diabetes, Obesity and Metabolism* published by Diabetes, Obesity and Metabolism.

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become established as a leading class of type 2 diabetes (T2D) and chronic weight management medications.[1,2] Currently available GLP-1RAs improve glycaemic control, reduce body weight, and have cardiovascular (CV) benefits in people with T2D.[3] However, these drugs are peptide-based and are administered by subcutaneous injection or by a complex oral dosing regimen involving significant food and water restrictions. To simplify oral delivery of GLP-1RAs, efforts are underway to develop non-peptide agonists of the glucagon-like peptide-1 receptor (GLP-1R).

Orforglipron is among the first of a new generation of chemically synthesized, non-peptide GLP-1RAs that feature oral bioavailability without the need of co-formulations containing complex absorption enhancing agents.[4,5] In preclinical studies, cryogenic electron microscopy has shown that orforglipron binds within the upper helical bundle of the GLP-1R.[5] Pharmacologically, it is a highly potent partial agonist that stimulates GLP-1R-induced cAMP accumulation with little effect on GLP-1R-mediated β-arrestin recruitment.[5] This design feature may be therapeutically beneficial for orforglipron, since β-arrestin proteins are associated with receptor internalization, intracellular trafficking, and desensitization.[6] Indeed, such a profile is reported to enhance the efficacy of GLP-1R agonism.[7] In animal studies, orforglipron has been shown to stimulate insulin secretion and reduce food consumption in non-human primates, and it is fully efficacious at lowering hyperglycaemia in mice expressing the human GLP-1R but inactive in GLP-1R knockout animals.[5] These results, in part, supported the development of orforglipron as an orally delivered GLP-1RA in clinical testing.

The current study evaluated the safety, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of single and multiple doses of orforglipron in healthy participants.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a Phase 1a, double-blind, placebo-controlled, randomized, multipart study (study registered at ClinicalTrials.gov as NCT03929744). Part A assessed single ascending doses (SADs) of orforglipron while Part B assessed multiple ascending doses (MADs) of orforglipron (Figure 1). The study was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines. All participants provided written informed consent before study entry.

2.2 | Participants

This study was carried out from June 12, 2019 until November 2, 2020 at one study centre in the United States. Overtly healthy adults aged 18 to 65 years with glycated haemoglobin (HbA1c) concentration lower than 6.5% at screening and body mass index (BMI) of 20 to 40 kg/m^2 were eligible. Participants could not have a significant history of or current CV, respiratory, hepatic, renal, gastrointestinal (GI) tract, endocrine, haematological or neurological disorders, pancreatitis, medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

2.3 | Randomization and masking

Participants were randomly assigned to receive orforglipron or placebo via a computer-generated random sequence using an interactive web-response system. For Part A, participants were randomly assigned to receive an oral SAD of either orforglipron (0.3-6 mg) or placebo (orforglipron to placebo ratio 6:2 per cohort; Figure S1). In Part B, randomization

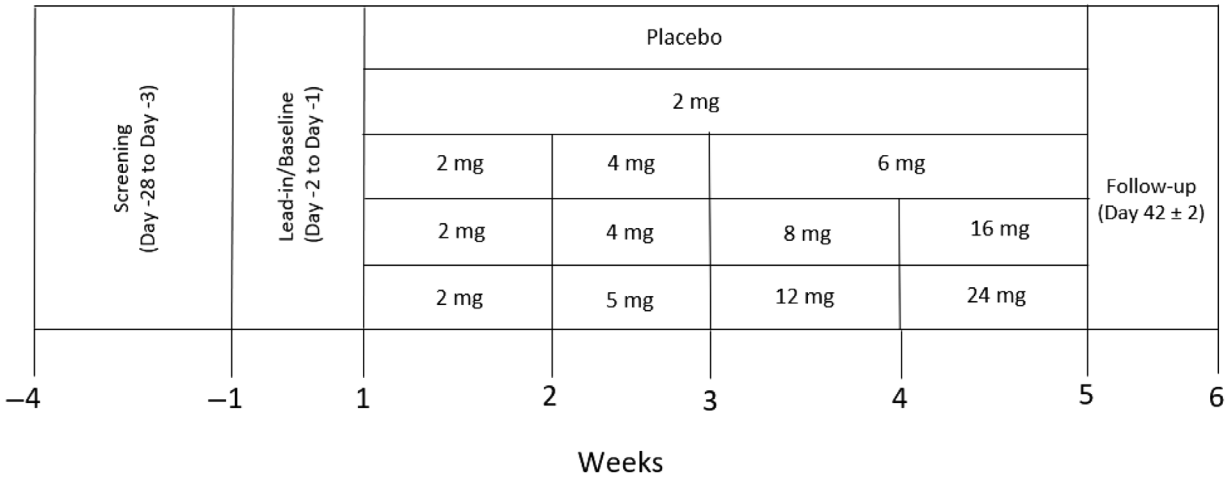

FIGURE 1 Part B study design for multiple ascending doses of orforglipron

was across four cohorts; in each cohort, nine participants received orforglipron (2-16 mg) and three received placebo, except for the highest dose (24 mg) where 18 participants were randomized to orforglipron (Figure S1). Participants, investigators and all study-site personnel, except those who prepared, dispensed and administered the study medication, were blinded to treatment allocation.

2.4 | Procedures

Capsules of different dose strengths were made by extemporaneous preparation and given orally once per day. In Part A, participants were assigned to four cohorts, which consisted of four SAD levels of orforglipron (0.3, 1, 3 and 6 mg). In Part B, participants were assigned to four cohorts, which consisted of four MADs of orforglipron with or without within-group dose escalation for 4 weeks. Dose levels given were 2 mg, 6 mg (escalated weekly from 2/4 mg), 16 mg (escalated weekly from 2/4/8 mg) and 24 mg (escalated weekly from 2/5/12 mg) (Figures 1, S1). Part B was initiated after review of the safety, tolerability and available PK and PD data collected up to Day 5 of the third SAD level. Dose escalations were based on the evaluation of safety, tolerability and available PK and PD data from at least five participants who received orforglipron through to Day 15 of the previous MAD level.

After screening, participants were admitted for baseline safety and PD procedures and then received treatment. In Part A, participants had an outpatient visit on Day 5 and were discharged on Day 15. Participants in Part B had weekly outpatient visits to complete safety, PK and PD procedures and an inpatient visit to collect safety, PK and PD data at the end of treatment before discharge on Day 42 (±2 days). All participants' data with measurable PK concentrations were included in the PK analysis. Participants who discontinued early were encouraged to return for a follow-up visit at least 14 days after study drug administration. None of the participants in Part A or B who discontinued were replaced.

For the oral glucose tolerance test (OGTT), participants maintained their regular carbohydrate intake 3 days before and fasted for approximately 8 hours overnight before administration of the OGTT. A 75-g glucose dose was given orally 2 hours after orforglipron administration and the OGTT was sampled at 0, 0.5, 1, 1.5 and 2 hours post-test glucose. Food was not allowed for at least 4 hours after the orforglipron morning dose on days of OGTT administration or when dosing was followed by PK and PD sample collections. Otherwise, the study drug was administered without regard to food and water at approximately the same time in the morning on each day.

An acetaminophen dose to assess gastric emptying was administered approximately 2 hours post-orforglipron dose, so that the t_{max} of acetaminophen was approximately at the same time as the orforglipron t_{max}.

2.5 | Outcomes

The primary objective was to investigate the safety and tolerability of SADs and MADs of orforglipron in healthy participants. Safety endpoints included treatment-emergent adverse events (TEAEs) and serious adverse events (AEs), 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 after the participant was sitting for at least 5 minutes. Laboratory data were also monitored to assess safety.

The PK variables measured included plasma concentration profiles, area under the concentration-time curve (AUC) during one dosing interval ($AUC_{0\text{-}\tau}$), maximum observed drug concentration (C_{max}), time of C_{max} (t_{max}), half-life associated with the terminal rate constant in noncompartmental analyses ($t_{1/2}$), apparent total body clearance calculated after extravascular administration, apparent volume of distribution during the terminal phase after extravascular administration, accumulation ratio based on $AUC_{0\text{-}\tau}$, and peak-to-trough ratio. PD objectives were to describe change from baseline during an OGTT for glucose and insulin and change from baseline in body weight. Gastric emptying was measured using the acetaminophen method, where a 1-g dose of acetaminophen was administered soon after a 75-g glucose dose for the OGTT.

2.6 | Statistical analysis

Safety was evaluated in the safety population, which consisted of all participants who received at least one dose of the study drug whether or not they completed all protocol requirements. PK and PD characteristics were assessed in all patients who received at least one dose of the study drug and had evaluable data (PK and PD population). Safety data were summarized using descriptive methodology, and least squares regression analyses were used for statistical evaluation. For the single- and multiple-dose parts of the study, PK dose proportionality of orforglipron was assessed separately. PK parameter estimates for orforglipron were calculated using standard noncompartmental methods of analysis and summarized using descriptive statistics. Log-transformed C_{max} and AUC estimates were evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals. The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses was used to assess dose proportionality. The variable t_{max} was analysed using a nonparametric method. Descriptive statistics were used to summarize PD variables with regard to absolute values and change from baseline in each variable. Least squares regression analyses were used for the statistical evaluation of PD variables. The AUC for glucose and insulin during an OGTT was calculated using the trapezoidal rule.

3 | RESULTS

Of the 92 participants enrolled and who received at least one study drug dose, 32 participated in Part A (mean age 43.4 years; 59% males; mean weight 84 kg; mean BMI 28.8 kg/m^2) and 60 participated in

Part B (mean age 42.5 years; 73% males; mean weight 84 kg; mean BMI 28.5 kg/m^2). Most participants completed the study; two participants were lost to follow-up in Part A, two participants withdrew from the study in Part B, three were lost to follow-up, and two discontinued due to AEs (Figure S1).

3.1 | Safety results

The majority of TEAEs were GI tract-related and mild in severity; the most common TEAEs were vomiting, nausea and headache in Part A and nausea, headache and constipation in Part B (Table 1). Nausea and constipation were most commonly observed with the first dose and with the dose escalations across the 4 weeks of treatment. Abdominal pain was reported more commonly in the first week and vomiting more commonly in the first week and in the last week of the 24-mg-treated participants.

In Part B, two participants discontinued due to AEs—one in the placebo group due to arthralgia and one in the 2-mg orforglipron group due to nausea (Figure S1). Weekly dose escalations in Part B were well tolerated, allowing doses of up to 24 mg to be administered in all participants in the highest dose cohort. Regarding AEs of special interest, there were no reported TEAEs related to hypoglycaemia, CV events, or hepatic events. There were no deaths or serious AEs.

Vital signs and clinical and safety laboratory parameters are shown in Table S1. In general, no substantial changes were noted in mean systolic (SBP) or diastolic blood pressure (DBP) across dose groups on Day 28 (Table S1); however, pulse rate significantly increased on Day 28 in all orforglipron dose groups by 5 to 13 beats/min, but not in a dose-dependent manner, compared to that with placebo (Table S1). No AEs of tachycardia or increased heart rate were reported in this study.

In Part B, one orforglipron-treated participant received a single dose of 2 mg and had elevated amylase levels on Day 1, which normalized by Day 7. The participant did not experience any AEs. No other clinically significant alterations were reported in pancreatic enzymes throughout the study. No clinically significant trends or changes were noted in alanine or aspartate aminotransferase levels (Table S1).

3.2 | Pharmacokinetics

Geometric mean PK parameters across doses are shown in Table 2. Following single oral dosing of orforglipron in healthy participants, the plasma concentration profile for orforglipron was characterized by a steady absorption phase, with a mean C_{max} of 1.5 to 14.9 ng/mL and median t_{max} of 4.1 to 12.0 hours across the 0.3- to 6-mg dose range. The geometric mean $t_{1/2}$ was 24.6 to 35.3 hours across the 0.3- to 6-mg dose range, supporting a once-daily dosing regimen. The PK profile of the orforglipron increase was approximately proportional for AUC from time 0 extrapolated to infinity and C_{max} with dose increase.

Following 28 days of once-daily orally administered orforglipron, mean C_{max} increased in a dose-dependent manner (11.1–99.6 ng/mL; Table 2), and t_{max} occurred approximately 4.1 to 8.1 hours after dosing. The geometric mean $t_{1/2}$ for orforglipron was approximately 48 to

TABLE 1 Summary of treatment-emergent adverse events

	Part A[a]			
	OFG 0.3 mg (N = 6)	OFG 1 mg (N = 6)	OFG 3 mg (N = 6)	OFG 6 mg (N = 6)
Nausea	0	0	3 (50)	3 (50)
Vomiting	0	0	3 (50)	4 (67)
Headache	0	1 (17)	0	2 (33)
	Part B[b]			
	OFG 2 mg (N = 45)	OFG 2/4/6 mg (N = 18)	OFG 2/4/8/16 mg (N = 8)	OFG 2/5/12/24 mg (N = 17)
Nausea	5 (11)	4 (22)	1 (13)	2 (12)
Headache	3 (7)	4 (22)	0	5 (29)
Constipation	5 (11)	6 (33)	0	2 (12)
Abdominal pain	6 (13)	1 (6)	0	1 (6)
Vomiting	2 (4)	0	0	3 (18)
Decreased appetite	4 (9)	1 (6)	0	0
Dizziness	3 (7)	2 (11)	0	0
Cough	2 (4)	0	0	1 (6)

Note: Data are n (%). No deaths or serious adverse events were reported.
Abbreviation: OFG, orforglipron.
[a]After a single dose.
[b]Over 28 days.

TABLE 2 Geometric mean (geometric coefficient of variation, %) pharmacokinetic parameters across orforglipron doses

	Part A[a]			
	OFG 0.3 mg (N = 6)	**OFG 1 mg (N = 6)**	**OFG 3 mg (N = 6)**	**OFG 6 mg (N = 6)**
$AUC_{0-\infty}$, ng × h/mL	39.2 (45)	104.0 (59)	387.0 (28)	496.0 (4)
C_{max}, ng/mL	1.5 (48)	4.0 (36)	14.9 (20)	12.9 (43)
t_{max}, h[b]	8.0 (4–16)	4.1 (4–8)	6.0 (4–8)	12.0 (8–16)
$t_{1/2}$, h[c]	29.4 (21–49)	35.3 (18–53)	24.6 (21–30)	27.9 (26–31)
CL/F, L/h	7.7 (45)	9.6 (59)	7.8 (28)	12.1 (4)
Vz/F, L	325 (18)	489 (48)	275 (34)	488 (17)
	Part B[d]			
	OFG 2 mg (N = 9)	**OFG 2/4/6 mg (N = 8)**	**OFG 2/4/8/16 mg (N = 8)**	**OFG 2/5/12/24 mg (N = 17)**
AUC_{0-24}, ng × h/mL	175 (34)	550 (27)	1110 (40)	1520 (89)
C_{max}, ng/mL	11.1 (36)	34.4 (23)	68.2 (51)	99.6 (92)
t_{max}, h[b]	4.1 (2–8)	8.0 (4–12)	6.1 (2–12)	8.1 (0–24)
$t_{1/2}$, h[c]	67.5 (34–297)	55.1 (23–105)	58.3 (19–87)	48.1 (25–95)
CL/F, L/h	11.4 (34)	10.9 (27)	14.4 (40)	15.8 (89)
Vz/F, L	1110 (102)	866 (48)	1210 (50)	1100 (95)
RA (AUC)	1.6 (13)	–	–	–
RA (C_{max})	1.5 (21)	–	–	–

Note: Data are *n* (%), unless otherwise indicated.
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from 0 to 24 h postdose; AUC0-∞, area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum observed concentration; CL/F, total body clearance; OFG, orforglipron; $t_{1/2}$, half-life; t_{max}, time of maximum observed concentration; RA, accumulation ratio; Vz/F, volume of distribution during elimination.
[a]After a single dose.
[b]Median (range).
[c]Geometric mean (range).
[d]On Day 28.

68 hours across the 2- to 24-mg dose range. The geometric mean accumulation ratios based on AUC from 0 to 24 hours post dose (AUC_{0-24}) and C_{max} ranged from 1.5 to 1.6 following once-daily oral dosing of 2 mg orforglipron. The C_{max} of orforglipron increased approximately proportionally and the AUC_{0-24} slightly less than proportionally to dose increase across the 2- to 24-mg dose range.

3.3 | Pharmacodynamics

The PD parameters are presented in Figures 2 and 3, and Table S2. After 28 days, fasting glucose was significantly lower with orforglipron doses than with placebo (2 and 6 mg), while fasting insulin was not significantly different between orforglipron and placebo, except in the 24-mg dose group ($P < 0.10$; Table S2). Dose-dependent reductions in OGTT glucose values were observed after 2 hours on Day 1, ranging from −27.0 to −79.3 mg/dL and reaching statistical significance for all doses (Figure 2A). These significant OGTT glucose value reductions were maintained on Day 28 in the higher dose groups, ranging from −51.0 to −63.6 mg/dL, but not in a dose-dependent manner (Figure 2B). Reductions in OGTT insulin values were also observed after 2 hours on Day 1, with the 3-mg dose showing a significantly greater reduction than placebo (Figure 2C); however, these significant reductions were not maintained on Day 28, as no significant differences were observed compared with placebo (Figure 2D). A summary of OGTT data at baseline and Day 28 is also shown in Table S2.

Significant reductions in mean body weight (kg) from baseline were observed on Day 28, ranging from −4.8 to −5.4 kg for doses ≥6 mg (Figure 3). These reductions were observed to be time-dependent and dose-dependent in that increasing weight loss was noted with increasing orforglipron dose levels. All orforglipron-treated participants who completed 28 days dosing lost weight (ranging from −1.1 to −9.2 kg), while placebo-treated participant weight change over 28 days ranged from +0.4 kg to −5.2 kg. On Day 28, the least squares mean difference from placebo was approximately −2.4 to −3.0 kg for all doses, except for the lowest dose (2 mg) at −0.9 kg.

Acetaminophen concentration-time profiles suggested that gastric emptying was delayed following multiple-dose administration of orforglipron on Day 28 (Figure S2). At the 3- and 6-mg dose levels, some participants vomited soon after ingestion, which may have impacted the acetaminophen concentration profiles.

4 | DISCUSSION

This SAD and MAD Phase 1a clinical trial provides initial evidence of the safety and pharmacology of the oral GLP-1RA orforglipron over

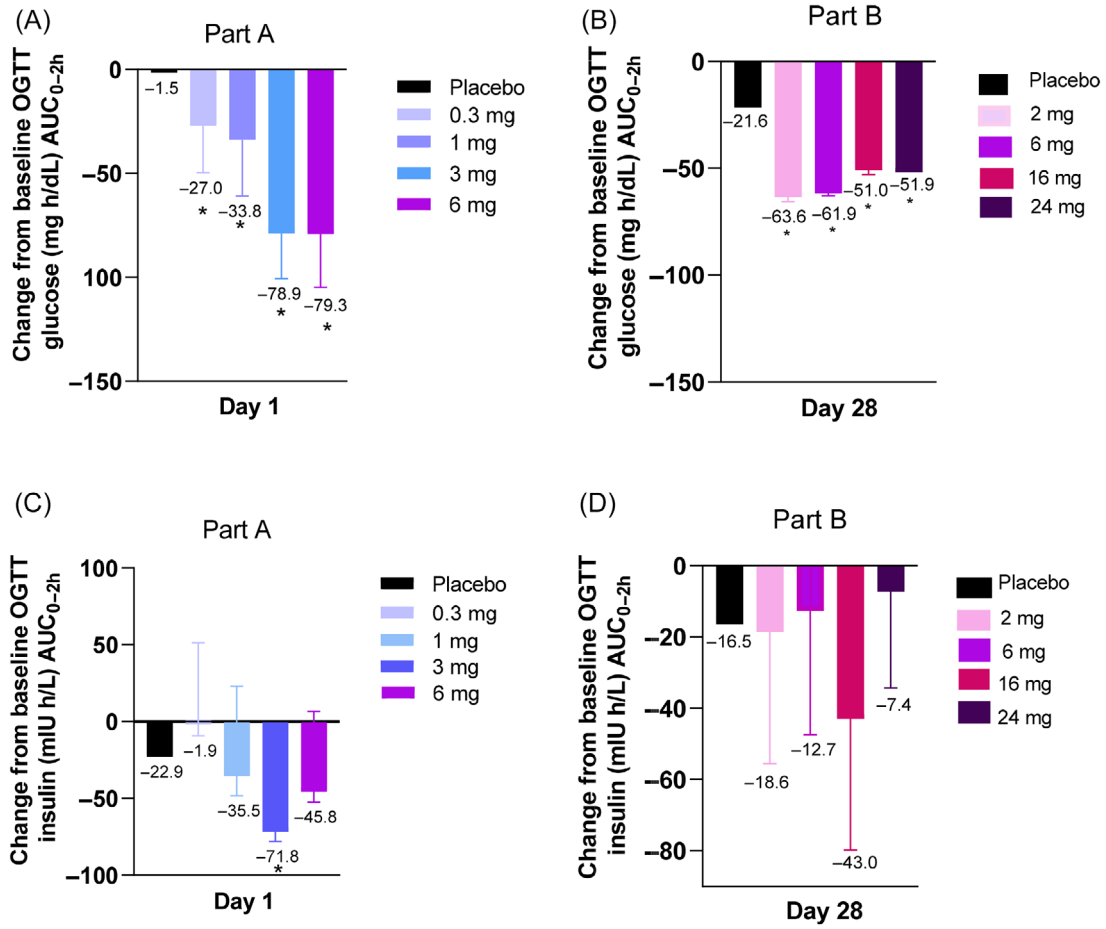

FIGURE 2 Change from baseline in oral glucose tolerance test (OGTT) glucose and insulin. (A) Part A – change from baseline in OGTT glucose; (B) Part A – change from baseline in OGTT insulin; (C) Part B – change from baseline in OGTT glucose; (D) Part B – change from baseline in OGTT insulin. Fasting values are pre-orforglipron dose. Data are least squares mean (90% confidence interval). AUC_{0-2h}, area under the concentration-time curve from 0 to 2 h post-dose; *P < 0.10 versus placebo

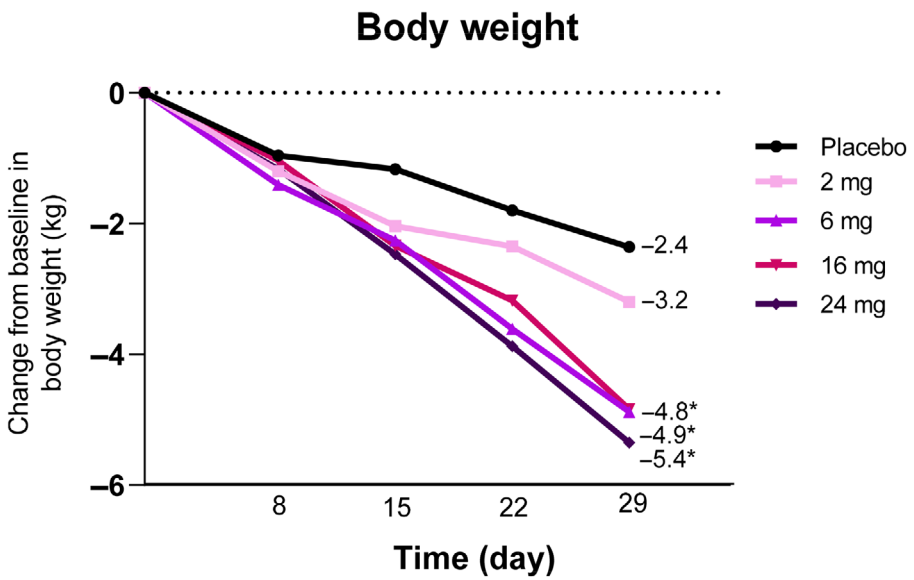

FIGURE 3 Change from baseline in body weight. Data are least squares mean (90% confidence interval) for body weight. *P < 0.10 for the difference versus placebo

28 days in healthy participants. Orforglipron had a safety profile comparable to that reported for other early-phase oral and injectable compounds in the GLP-1RA pharmaceutical class.[4,8] The PK profile of orforglipron was dose proportional, with a half-life that supports once-daily dosing. PD results showed significant improvements in plasma glucose during fasting and following an OGTT for some orforglipron doses compared with placebo. Significant body weight reductions were also observed, and gastric emptying was delayed. These observations suggest that orforglipron is a safe and effective GLP-1RA, suitable for once-daily oral delivery.

The poor bioavailability of oral peptide incretins is a major limitation in their application. This is due to hydrolysis by digestive enzymes in the GI tract and the low permeability of intestinal epithelial cells, significant obstacles that limit the oral absorption of peptide drugs.[9] Current incretin therapies are restricted to injectable therapies or an oral peptide formulation containing an absorption enhancer and requiring fasting before administration.[10] Orforglipron is a chemically synthesized oral GLP-1RA that, when administered once daily in both the fed and fasted states (fasted when PK or PD sampling was required) during the 28-day multiple-dose study, resulted in significant improvements in body weight, as seen in Phase 1 research comparing oral semaglutide to placebo in healthy participants.[8] The non-peptide agonist approach resulted in greater bioavailability of oral orforglipron (approximately 20%-40% determined from a reported preclinical model)[5] than semaglutide, which has significantly lower bioavailability of just 0.4% to 1%[11] and requires a fasting state for sufficient systemic exposure.[12] This greater bioavailability aligns with initial findings on danuglipron, another non-peptide GLP-1RA under development.[13]

With regard to safety and tolerability, GLP-1RAs have been associated with GI tract-related AEs that are more frequent during dose escalation.[14] Similarly, in this study, orforglipron-treated participants reported more GI tract-related TEAEs than those who received placebo; however, these were not serious. Most of the GI tract-related AEs in orforglipron-treated participants occurred in the first week after initial dosing, indicating that the starting dose is as important as the frequency and magnitude of escalation. The incidence of hypoglycaemia was not significant in this trial, which included healthy participants (baseline HbA1c <6.5%). This may be expected for GLP-1RAs that improve glucose via glucose-dependent insulin secretion.

The GLP-1RAs are known to increase heart rate[15]; however, a systematic review and meta-analysis of CV outcome studies has shown that, despite this increase, GLP-1RAs reduce major adverse CV events and all-cause mortality.[16] Effects of orforglipron on CV variables (SBP, DBP and pulse rate) are consistent with those observed for other GLP-1RAs at this stage of development.[8,17] While increases in pulse rate were observed with orforglipron, other vital signs (SBP and DBP) and safety laboratory results were generally no different from those with placebo. The significant pulse rate increases observed are commonly observed in Phase 1 studies because of the aggressive dose-escalation regimen and are in line with those (increases of up to 10 beats/min) seen in Phase 1 studies of other GLP-1RAs.[8,18] We expect reduced pulse rate increases via tachyphylaxis of the pulse rate with longer treatment duration.

One orforglipron-treated participant experienced elevated amylase levels that normalized by Day 7, and the participant did not experience any AEs. Otherwise, no effects on pancreatic or hepatic enzymes were observed, indicating that off-target effects of orforglipron treatment are unlikely. This will be investigated further in Phase 2.

Orforglipron has the potential to become a valuable GLP-1RA therapy, as it demonstrated significant glycaemic reductions in OGTT glucose and, if repeated in patients with T2D, could represent clinically meaningful changes. Mean body weight decreases (up to 5.4 kg) in orforglipron-treated participants were generally dose-dependent and were of a similar or greater magnitude relative to those with another GLP-1RA within the short 4-week duration of this study.[18] Danuglipron, another oral non-peptide GLP-1RA under development, demonstrated body weight reductions of up to 7.2 kg after 4 weeks of treatment in patients with T2D, although this required twice-daily dosing.[4] Decreases in appetite and delayed gastric emptying likely contributed to the significant weight reductions observed with orforglipron treatment.

Current data show that this non-peptide agonist has efficacy potential similar to that of injectable GLP-1RAs while offering patient-friendly, once-daily oral dosing without food and water restrictions. Therefore, orforglipron could be an important treatment option for T2D and chronic weight management. To further explore the full potential of orforglipron, a Phase 1b proof-of-concept trial was conducted and two Phase 2 trials are currently ongoing in patients with T2D (NCT05048719) and in patients with obesity (NCT05051579).

The strengths of our study include the large number of different dose groups tested, the use of placebo as a comparator, and randomization and blinding of the study treatments. Limitations of this study are its inclusion of healthy people and the fact that it was not targeted to those with T2D or obesity, the small sample sizes, the short-term exposure, and the aggressive dose escalation, which resulted in pulse rate increases and GI tract-related AEs.

In summary, treatment with orforglipron resulted in significant glycaemic and body weight reductions, with an AE profile similar to that of other GLP-1RAs and a PK profile that allowed once-daily oral dosing without water and food restrictions. The data support the continued development of orforglipron as a once-daily, oral GLP-1RA, matching the pharmacology of some injectable GLP-1RA therapies, which could therefore be an attractive treatment option that may broaden the utilization of this important mechanism for T2D and obesity GLP–1 receptor agonism.

ACKNOWLEDGMENTS

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report through the assistance of a medical writer employed by Eli Lilly and Company. The authors thank Ciara O′ Neill, PhD (Eli Lilly and Company) for medical writing and editorial assistance.

CONFLICT OF INTEREST STATEMENT

Edward Pratt, Xiaosu Ma, Rong Liu, Deborah Robins, Tamer Coskun, Axel Haupt, Kyle Sloop and Charles Benson are employees and shareholders of Eli Lilly and Company.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15184.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, 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.

ORCID

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

REFERENCES

1. Romera I, Cebrián-Cuenca A, Álvarez-Guisasola F, Gomez-Peralta F, Reviriego J. A review of practical issues on the use of glucagon-like peptide-1 receptor agonists for the management of type 2 diabetes. *Diabetes Ther*. 2019;10(1):5-19.
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.
3. American Diabetes Association. Standards of medical care in diabetes-2022 abridged for primary care providers. *Clin Diabetes*. 2022;40(1):10-38.
4. 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.
5. 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 U S A*. 2020;117(47):29959-29967.
6. Marchese A, Paing MM, Temple BRS, Trejo J. G protein-coupled receptor sorting to endosomes and lysosomes. *Annu Rev Pharmacol Toxicol*. 2008;48:601-629.
7. Jones B, Buenaventura T, Kanda N, et al. Targeting GLP-1 receptor trafficking to improve agonist efficacy. *Nat Commun*. 2018;9(1):1602.
8. 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.
9. Cao SJ, Xu S, Wang HM, et al. Nanoparticles: oral delivery for protein and peptide drugs. *AAPS PharmSciTech*. 2019;20(5):190.
10. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: a pathophysiological update. *Diabetes Obes Metab*. 2021;23(Suppl 3):5-29.
11. 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.
12. RYBELSUS® (semaglutide) package insert. 2023.
13. Griffith DA, Edmonds DJ, Fortin JP, et al. A small-molecule oral agonist of the human glucagon-like peptide-1 receptor. *J Med Chem*. 2022;65(12):8208-8226.
14. Patel D, Smith A. Patient initiation and maintenance of GLP-1 RAs for treatment of obesity. *Expert Rev Clin Pharmacol*. 2021;14(10):1193-1204.
15. Sun F, Wu S, Guo S, et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Res Clin Pract*. 2015;110(1):26-37.
16. Kristensen SL, Rørth R, Jhund PS, 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 cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7(10):776-785.
17. Inagaki N, Takeuchi M, Oura T, Imaoka T, Seino Y. Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 trial. *Lancet Diabetes Endocrinol*. 2022;10(9):623-633.
18. 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.

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 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study in healthy participants. *Diabetes Obes Metab*. 2023;1-8. doi:10.1111/dom.15184