Diabetes Ther (2024) 15:819–832
https://doi.org/10.1007/s13300-024-01554-1

ORIGINAL RESEARCH

Effect of Food Consumption on the Pharmacokinetics, Safety, and Tolerability of Once-Daily Orally Administered Orforglipron (LY3502970), a Non-peptide GLP-1 Receptor Agonist

Xiaosu Ma · Rong Liu · Edward J. Pratt · Charles T. Benson · Shobha N. Bhattachar · Kyle W. Sloop

Received: December 20, 2023 / Accepted: February 9, 2024 / Published online: February 24, 2024

ABSTRACT

Introduction: We assessed the effect of the prandial state on the pharmacokinetics, safety, and tolerability of single and multiple doses of orforglipron (LY3502970), an oral, non-peptide glucagon-like peptide 1 receptor agonist (GLP-1 RA), in two studies (A and B).

Methods: Study A and study B were phase 1, randomized, crossover studies in healthy adults aged 18–65 years and 21–70 years, respectively. Participants received single (3 mg, study A) or multiple (16 mg, study B) oral doses of orforglipron under fasted and fed conditions. Blood samples were collected pre- and postdose to assess area under the concentration–time curve (AUC), maximum observed drug concentration (C_{max}), time of C_{max} (t_{max}), and half-life ($t_{1/2}$) associated with terminal rate constant. AUC and C_{max} were analyzed using a linear mixed-effects model. Treatment differences were presented as ratios of geometric least squares means (GLSM). Treatment-emergent adverse events (TEAEs), adverse events of special interest, and serious adverse events were assessed.

Results: Study A included 12 participants (mean age 45.0 years; male 66.7%); study B included 34 participants (mean age 42.8 years; male 88.2%). GLSM AUC and C_{max} were lower by 23.7% and 23.2% in study A, and 17.6% and 20.9% in study B, in the fed versus fasted states, respectively. In both studies, $t_{1/2}$ and median t_{max} were comparable between fed and fasted states. The majority of TEAEs in both studies were gastrointestinal tract-related conditions. No serious adverse events or deaths were reported in either study.

Conclusion: The observed pharmacokinetic differences due to the prandial state are unlikely to contribute to clinically meaningful differences in the efficacy of orforglipron. The safety profile was consistent with the known profiles of other GLP-1 RAs. Given the absence of prandial restrictions, orforglipron may emerge as a convenient oral treatment option for patients with type 2 diabetes or obesity.

Prior Presentation: This manuscript is based on work that was presented at the American Diabetes Association—83rd Annual Scientific Sessions, San Diego, CA, USA, 23–26 June 2023: 769-P: Effect of food on the pharmacokinetics, safety and tolerability of orforglipron (LY3502970) an oral, non-peptide GLP-1 receptor agonist. Xiaosu Ma, Rong Liu, Edward Pratt, Charles T. Benson, Shobha N. Bhattachar.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-024-01554-1.

X. Ma (✉) · R. Liu · E. J. Pratt · C. T. Benson · S. N. Bhattachar · K. W. Sloop
Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46240, USA
e-mail: ma_xiaosu@lilly.com

Trial Registration: ClinicalTrials.gov identifiers, NCT03929744 and NCT05110794.

Keywords: Food-effect; GLP-1; Glycemic control; Obesity; Orforglipron; Prandial state; T2D

Key Summary Points
Why carry out this study?
Restrictions on food, water, and other medications for oral medication intake may impact type 2 diabetes and obesity treatment adherence and compliance.
This study investigated the effect of food on the pharmacokinetics, safety, and tolerability of single and multiple oral doses of orforglipron in healthy adults.
What was learned from the study?
AUC and C_{max} were approximately 18–24% lower when orforglipron was administered with food, while t_{max} and $t_{1/2}$ were not impacted by the prandial state.
The observed effect of prandial status on pharmacokinetics is not likely to result in significant effects on the clinical safety and efficacy of orforglipron.
Orforglipron may therefore serve as a convenient oral treatment option for patients with type 2 diabetes or obesity owing to the lack of prandial restrictions for dosing.

INTRODUCTION

Glucagon-like peptide 1 receptor agonist (GLP-1 RA) therapies have demonstrated efficacy and safety in patients with type 2 diabetes (T2D) and in people with obesity [1–5]. These peptide-based treatments exert glycemic control by modulating nutrient-stimulated insulin secretion. In addition, these therapies reduce glucagon secretion and delay gastric emptying, facilitating weight reduction through a neuronally mediated satiety effect [1, 2]. Considering the added cardiovascular benefits conferred to patients with T2D, the American Diabetes Association and the European Association for the Study of Diabetes guidelines recommend treatment with GLP-1 RAs for adults with T2D who are at high risk of cardiovascular disease [6–8]. Obesity treatment guidelines also recommend adjunct treatment with pharmacotherapies such as GLP-1 RAs when initial treatment through lifestyle interventions (nutrition, physical activity, and behavioral modifications) are unsuccessful [9–12].

Most currently approved GLP-1 RA treatments for patients with T2D or obesity are administered once weekly by subcutaneous injection [1]. Adherence to antihyperglycemic and antiobesity medications is associated with improved glycemic control and weight reduction, respectively [13, 14], whereas treatment non-adherence leads to increased risk of diabetes-related macrovascular and microvascular complications [15]. Unrestricted oral GLP-1 RA therapies may prompt earlier treatment initiation and improve acceptance, adherence, and compliance for patients with T2D and obesity.

Currently, semaglutide is the only orally administered GLP-1 RA approved by the US Food and Drug Administration for the treatment of T2D; to date, there are no oral GLP-1 RAs approved for the treatment of obesity [16–18]. Orally administered semaglutide is formulated with an absorption enhancer to avoid enzyme- and pH-mediated hydrolysis of the peptide in the gastrointestinal tract, facilitating gastrointestinal absorption and ensuring sufficient bioavailability [1, 19–21]. However, patients are required to adhere to multiple intake requirements to ensure adequate absorption and efficacy. These include taking the medication at least 30 min before the first food, beverage, or other oral medications of the day, consuming no more than approximately 120 mL of water when taking the medication, and avoiding food or beverages for at least 30 min after taking the medication [22]. Restrictive conditions for the intake of oral medications may adversely affect treatment adherence and compliance and, consequently, patient outcomes [23, 24]. Therefore,

expanding the armamentarium of oral GLP-1 RAs to include pharmacotherapies with relatively simpler dietary requirements remains an important treatment goal.

Orforglipron (LY3502970) is a chemically synthesized, non-peptide, oral GLP-1 RA under development as an adjunct therapy to diet and exercise to improve glycemic control and promote weight reduction in adults with T2D and/or obesity [25–27]. In a previous report, treatment with orforglipron was found to promote glucose-dependent insulin secretion after a glucose challenge [25]. Additionally, orforglipron demonstrated a terminal half-life of 29–49 h in a phase 1b study in people with T2D, which allows once-daily oral dosing [25, 28]. Furthermore, orforglipron demonstrated a pharmacodynamic and safety profile similar to that of injectable GLP-1 RAs [28]. Here, we investigated the effect of a fasted versus fed state (food-effect) on the pharmacokinetics (PK), safety, and tolerability of single and multiple oral doses of orforglipron in healthy adults in two phase 1 studies (A and B).

METHODS

Study Design and Procedures

Study A (NCT03929744) and study B (NCT05110794) were phase 1, randomized, crossover studies in healthy participants.

Study A was a first-in-human study conducted at one study center in the USA from June 12, 2019 until November 2, 2020. The study had five parts (A–E). Parts A and B were single- and multiple-dose escalation placebo-controlled studies whose results have been published previously [28]. Here, we describe analyses of data from participants in part C of the study, which sought to assess food-effect. Figure 1a describes the study design. Briefly, following a 30-day screening period, participants received a single oral dose (3 mg) of orforglipron with approximately 240 mL of water in each of two treatment periods. Participants were randomly assigned to one of two treatment sequences with two treatment arms: (1) fasted treatment, where participants received the dose following an overnight fast of at least 10 h, and (2) fed or food-effect treatment, where participants received the dose following a standardized high-calorie meal consumed after an overnight fast of at least 10 h. The meal was approximately 500 kcal, composed of approximately 50% carbohydrates, 30% fat, and 20% protein. There was a washout period of at least 5 days between each dose. In each treatment period, participants remained in the clinical research unit until completion of assessments on day 4 and returned for an outpatient visit on day 5. Venous blood samples for PK measurements were collected at predose and at 0.5, 1, 2, 4, 8, 12, 16, 24, 48, 72, and 96 h postdose.

Study B was an open-label study conducted at one study center in Singapore from November 5, 2021 until February 10, 2022. Figure 1b describes the study design. Participants were first evaluated for eligibility during the screening period. In the dose titration period, participants received a daily dose of orforglipron with weekly dose titration of 2 mg, 4 mg, and 8 mg, before escalation to a dose of 16 mg once daily on day 22. There were no food or water restrictions during this "titration" period. Venous blood samples for PK measurements were collected on day 1 (predose and at 0.5, 1, 2, 4, 6, 8, 12, and 16 h postdose) and days 2, 8, and 15 (predose). On day 21, participants were randomly assigned to receive orforglipron orally under two administration conditions, i.e., fasted treatment and fed treatment. In the fed part of the test periods, participants received a pre-dose meal on the first 6 days and a standardized high-fat, high-calorie meal pre-dose on day 7, before PK assessment. The meal was approximately 800–1000 kcal, composed of approximately 50% fat, 25–30% carbohydrates, and 15–19% protein. In the fasted part of the test periods, participants receive the dose after fasting overnight for at least 10 h and no food was allowed for at least 4 h post-dose. Fluid was restricted 1 h prior to and 1 h after dosing, except for the water required for dose administration. During test period 1 (days 22–28), participants received 16-mg orforglipron capsules once daily either in the fed or fasted state as per their random assignment. Blood samples for PK measurements were collected on day 28 (predose and at 0.5, 1, 2, 4,

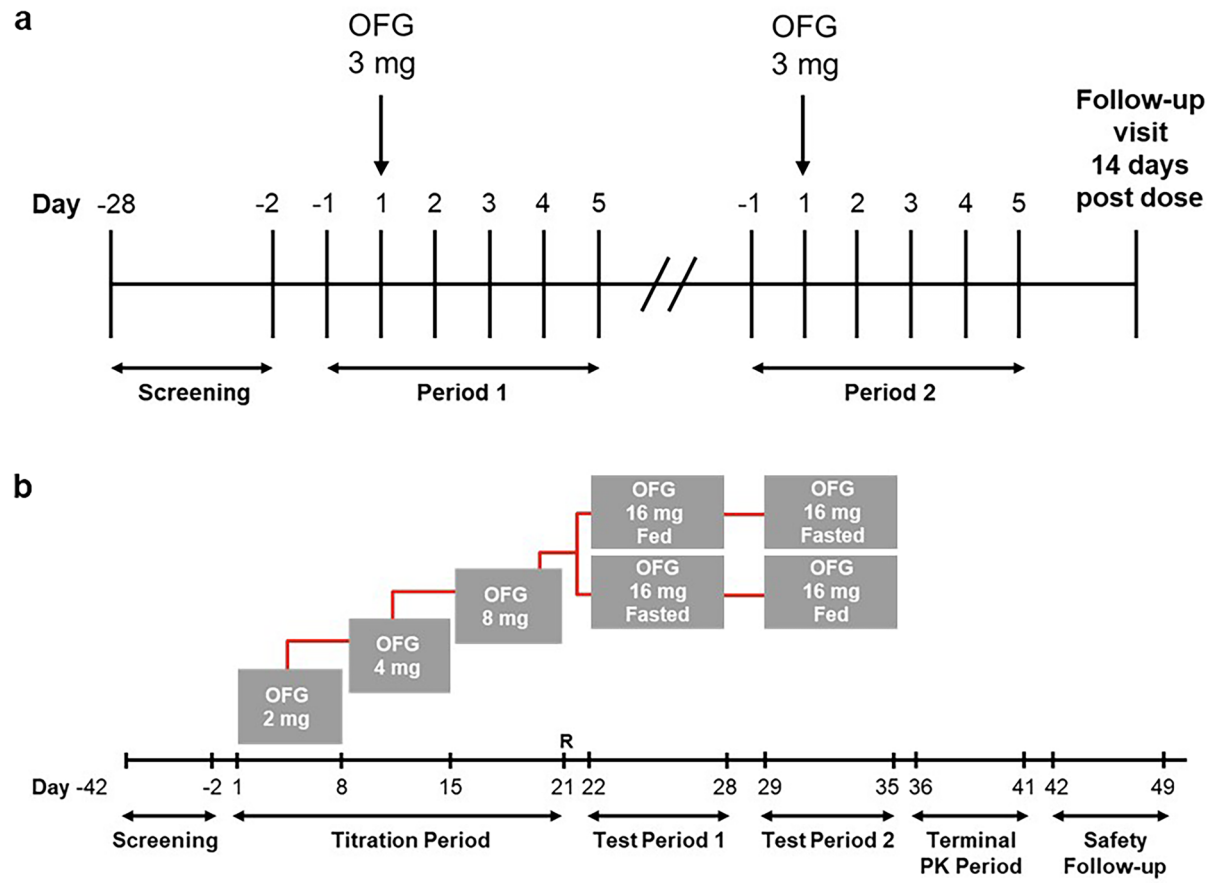


Fig. 1 **a** Study A design. There was a washout period of ≥ 5 days between each dose. In each treatment period, participants remained in the clinical research unit at least until completion of assessments on day 4 and returned for an outpatient visit on day 5. Participants were randomly assigned to one of two treatment sequences. Treatment sequence 1—Period 1: Fasted treatment; Period 2: Food-effect treatment or fed treatment. Treatment sequence 2—Period 1: Food-effect treatment or fed treatment; Period 2: Fasted treatment. *OFG* orforglipron. **b** Study B design. *PK* pharmacokinetic

6, 8, 12, and 16 h postdose) and day 29 (predose). During test period 2 (days 29–35), they received the dose under the other administration condition (i.e., if they received the dose in the fed state in test period 1, they would receive the dose in the fasted state in test period 2, and vice versa). Following the final dose on day 35, additional PK samples were collected from day 36 through the morning of day 41. Participants were discharged on day 36. Finally, participants underwent safety assessments at the safety follow-up visit that occurred between 7 and 14 days after the last dose.

In both studies, no food was allowed for at least 4 h after dosing. Fluids were restricted from 1 h before to 1 h after dosing, except for the fluid provided with the meals and water required for dose administration. Alcohol consumption and nicotine use were not permitted during the participants' stay at the clinical research unit. All participants were allowed to maintain regular caffeine consumption and levels of physical activity throughout the studies.

Study protocols and informed consent forms were approved by an ethics review board at each site (study A: ERB Midlands IRB, KS 66212, USA;

study B: National Healthcare Group Domain Specific Review Board, Singapore 138543). The study was conducted in accordance with ethical principles of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and the Declaration of Helsinki of 1964, and its later amendments. Written informed consent was obtained from each participant at study entry before any study procedures.

Study Participants

Both studies included overtly healthy men, as well as women who were not of child-bearing potential. Study A participants were aged 18–65 years, with body mass index (BMI) of 20–40 kg/m^2 and a glycated hemoglobin concentration less than 6.5%. Study B participants were aged 21–70 years, with a body weight of ≥ 45 kg, BMI of 18.5–35.0 kg/m^2, and a hemoglobin level of at least 11.4 g/dL for female participants and at least 12.5 g/dL for male participants.

Exclusion criteria for both studies were history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders; pancreatitis; or history of malignancy within 5 years prior to screening.

Outcomes

Food-effect was assessed by PK parameters following orforglipron administration in the fed and fasted states. The PK variables included the following: (i) area under the concentration–time curve (AUC) during the dosing intervals (study A: $AUC_{0-\infty}$ after a single dose of 3 mg orforglipron; study B: steady-state AUC_{0-24} following multiple doses of 16 mg orforglipron); (ii) maximum observed drug concentration (C_{max}); (iii) time of C_{max} (t_{max}); and (iv) half-life ($t_{1/2}$) associated with terminal rate constant.

The primary safety outcomes were incidence and severity of treatment-emergent adverse events (TEAEs), adverse events of special interest (nausea, vomiting, diarrhea, and acute pancreatitis), and serious adverse events (SAEs).

Statistical Analyses

For study A, a sample size of up to 12 participants was chosen to evaluate safety and PK parameters. For study B, the sample size was based on a calculation of precision of the estimated ratio of AUC_{0-24} between the 16-mg capsule dosed in the fasted state and the 16-mg capsule dosed in the fed state. Assuming a standard deviation (SD) of treatment difference of 0.444 in the log-scale in AUC_{0-24} (according to a preliminary analysis of the food-effect data in study A), a sample size of 24 participants was expected to provide approximately 80% coverage probability to get a 90% confidence interval (CI) for the ratio R of the geometric mean AUC_{0-24} between treatments within [0.841R, 1.189R].

Participants' demographic and baseline clinical characteristics were summarized descriptively, and included age, sex, race, ethnicity, height, weight, and BMI. Categorical variables (e.g., sex, race, ethnicity) were presented as number and percentage of participants; continuous variables (e.g., age, BMI) were presented as mean and SD.

PK analyses were conducted on data from all participants who received at least one dose of orforglipron and had evaluable PK data. Safety analyses were conducted for all enrolled participants, whether or not they completed all study procedures.

PK parameter estimates were calculated by standard non-compartmental methods and were summarized using descriptive statistics. PK parameters for subjects with an incidence of emesis that occurred within the two times median t_{max} period were excluded from summary statistics and statistical analysis. The C_{max} and AUC parameter estimates from treatment periods 1 and 2 for study A and from test periods 1 and 2 for study B were log-transformed and analyzed using a linear mixed-effects model. The model used treatment (fasted, fed), period, and sequence as fixed effects, and participant within sequence as a random effect. For both studies, the treatment differences were back-transformed to present the ratios of geometric least squares

means (GLSM) and the corresponding 90% CIs for the fed versus fasted arms. Through this linear mixed-effects model, missing data were handled under the missing-at-random (MAR) assumption. The parameter t_{max} was analyzed non-parametrically using the Wilcoxon signed-rank test. All tests of treatment effects were conducted at a two-sided alpha level of 0.1, unless otherwise stated. No multiplicity adjustments were made. PK parameters from participants who vomited within two times the median t_{max} period after dosing were excluded from analysis. Statistical analyses were conducted using SAS software Version 9.4 (2016; SAS Institute Inc., Cary, NC, US).

RESULTS

Participants' Baseline and Demographic Characteristics

Table 1 summarizes the participants' demographic and baseline characteristics. Study A included 12 participants with a mean (SD) age of 45.0 (10.9) years. The majority were male (66.7%) and White (66.7%). The mean (SD) BMI of the population was 27.9 (4.1) kg/m^2. Study B included 34 participants with a mean (SD) age of 42.8 (10.2) years. The majority were male (88.2%) and all participants were Asian (100.0%). The mean (SD) BMI of the population was 25.4 (3.1) kg/m^2.

Table 1 Participants' demographic and baseline characteristics

Parameter	Study A OFG 3 mg (N = 12)	Study B* OFG 16 mg (N = 34)
Age, years, mean (SD)	45.0 (10.9)	42.8 (10.2)
Sex, *n* (%)		
Male	8 (66.7)	30 (88.2)
Female	4 (33.3)	4 (11.8)
Ethnicity, *n* (%)		
Not Hispanic or Latino	8 (66.7)	–
Hispanic or Latino	4 (33.3)	–
Race, *n* (%)		
Asian	1 (8.3)	34 (100.0)
Black or African American	3 (25.0)	0 (0.0)
White	8 (66.7)	0 (0.0)
Weight, kg, mean (SD)	82.3 (9.8)	73.1 (10.4)
Height, cm, mean (SD)	172.0 (7.7)	169.4 (7.1)
BMI, kg/m^2, mean (SD)	27.9 (4.1)	25.4 (3.1)

BMI body mass index, *N* total number of participants, *n* number of participants, *OFG* orforglipron, *SD* standard deviation

*In study B, 29 (of the 34) participants completed titration through 2/4/8/16 mg to receive 16 mg orforglipron at steady state

Table 2 Pharmacokinetic parameters after oral administration of orforglipron (3 mg or 16 mg) in the fasted and fed states

Study	Parameter	Fasted ($N = 12$)	*n*	Fed ($N = 12$)	*n*
Study A OFG 3 mg	$AUC_{0-\infty}$, ng h/mL, GM (CV%)	362 (33.0)	11	260 (43.0)	12
	C_{max}, ng/mL, GM (CV%)	13.4 (44.0)	11	10.1 (44.0)	12
	t_{max}, hours, median (min–max)	8.0 (4.0–24.0)	11	8.0 (4.0–12.0)	12
	$t_{1/2}$, hours, GM (min–max)	29.5 (19.6–50.6)	11	27.9 (19.9–37.9)	12
	CL/F (L/h)	8.28 (33.0)	11	11.6 (43.0)	12
	Vz/F (L)	353 (41.0)	11	465 (48.0)	12
	Vss/F (L)	303 (43.0%)	11	423 (44.0)	12
	Parameter	**Fasted ($N = 28$)[a]**	***n***	**Fed ($N = 27$)[a]**	***n***
Study B OFG 16 mg	AUC_{0-24}, ng h/mL, GM (CV%)	1200[b] (58.0)	26	1050[b] (40.0)	25
	C_{max}, ng/mL, GM (CV%)	80.5 (64.0)	26	67.5 (40.0)	25
	t_{max}, hours, median (min–max)	8.0 (4.0–16.0)	26	8.0 (4.0–24.0)	25
	$t_{1/2}$, hours, GM (min–max)	26.0 (8.0–73.4)[c]	21	24.6 (8.7–87.1)[c]	22
	CL/F (L/h)	13.4 (58.0)	26	15.2 (40.0)	25
	Vz/F (L)	474 (84.0)	21	520 (73.0)	22

AUC_{0-24} area under the concentration versus time curve from time zero to 24 h postdose, *$AUC_{0-\infty}$* area under the concentration versus time curve from time zero to infinity, *CL/F* apparent total body clearance calculated after extravascular administration, *C_{max}* maximum observed drug concentration, *CV* coefficient of variation, *GM* geometric mean, *N* number of subjects, *n* number of observations, *OFG* orforglipron, *t* half-life associated with the terminal rate constant in non-compartmental analysis, *t_{max}* time of maximum observed drug concentration, *Vss/F* apparent volume of distribution at steady state after extravascular administration, *Vz/F* apparent volume of distribution during the terminal phase after extravascular administration

[a]Prior to starting treatment, one participant was discontinued because of an adverse event (urticaria); six participants were excluded from pharmacokinetic analysis because of emesis that impacted pharmacokinetic calculations on day 1 ($n = 5$) and day 35 ($n = 1$), which occurred within two times the median t_{max} period

[b]Steady-state AUC_{0-24}

[c]$t_{1/2}$ was not calculable for five participants in the fasted state and three participants in the fed state because of < 3 quantifiable OFG concentrations after C_{max} or poor R_{sq} adjusted value

Pharmacokinetics of Single and Multiple Oral Doses of Orforglipron in the Fasted and Fed States

Table 2 presents the PK parameters (AUC, C_{max}, t_{max}, and $t_{1/2}$) for orforglipron in study A (3 mg, single dose) and study B (16 mg, multiple doses) in the fasted and fed states. Following oral administration of 3 mg orforglipron in study A, the GLSM $AUC_{0-\infty}$ and C_{max} were 23.7% and 23.2% lower, respectively, in the fed state compared with the fasted state (Table 3, Fig. 2a). Similarly, following oral administration of 16 mg orforglipron in study B, the GLSM AUC_{0-24} and C_{max} were 17.6% and 20.9% lower, respectively, in the fed state than the fasted state (Table 3, Fig. 2b).

In both studies, $t_{1/2}$ values were comparable in the fasted and fed states (Table 2). In study A, geometric mean $t_{1/2}$ values were 29.5 and 27.9 h in the fasted and fed states, respectively. In study B, mean $t_{1/2}$ values were 26.0 and 24.6 h in the fasted and fed states,

Table 3 Statistical analysis of plasma pharmacokinetic parameters after orforglipron administration to healthy participants in fed versus fasted states

Study	Parameter	Treatment	*n*	GLSM	GLSM ratio, fed/fasted (90% CI lower–upper)
Study A OFG 3 mg	C_{max}, ng/mL	Fasted	11	13.1	0.768 (0.652–0.905)
	C_{max}, ng/mL	Fed	12	10.1	
	$AUC_{0-\infty}$, ng h/mL	Fasted	11	340	0.763 (0.698–0.833)
	$AUC_{0-\infty}$, ng h/mL	Fed	12	260	
Study B OFG 16 mg	C_{max}, ng/mL	Fasted	26	80.5	0.791 (0.674–0.928)
	C_{max}, ng/mL	Fed	25	63.7	
	AUC_{0-24}, ng h/mL	Fasted	26	1197	0.824 (0.725–0.937)
	AUC_{0-24}, ng h/mL	Fed	25	986	

AUC_{0-24} area under the concentration versus time curve from time zero to 24 h postdose, *$AUC_{0-\infty}$* area under the concentration versus time curve from time zero to infinity, *CI* confidence interval, *C_{max}* maximum observed drug concentration, *GLSM* geometric least squares mean, *n* number of observations, *OFG* orforglipron

respectively. There was no statistical difference in the median t_{max} between prandial states in both studies (Table 4).

Safety and Tolerability of Orforglipron

The majority of TEAEs in both studies were conditions related to the gastrointestinal tract. No SAEs or deaths were reported in either study (Table 5).

In study A, of the 12 participants who received at least one dose of 3 mg orforglipron, two participants (16.7%) experienced at least one TEAE in the fasted condition: two participants (16.7%) experienced nausea, one participant each (8.3%) experienced upper abdominal pain, dizziness, headache, oropharyngeal pain, sneezing, and vomiting (Table 5, Table S1 in Supplementary material). All TEAEs were mild in severity (data not shown). None of the participants reported TEAEs under the fed condition (Table 5). Overall, two participants (16.7%) reported treatment-related adverse events. Among the adverse events of special interest, two participants (16.7%) reported nausea, while one (8.3%) reported vomiting. None of the participants experienced acute pancreatitis.

In study B, 18 of 28 participants (64.3%) reported at least one TEAE under the fasted condition, of whom 12 participants (42.9%) reported at least one treatment-related adverse event. Twelve of 27 participants (44.4%) reported at least one TEAE under the fed condition, of whom seven participants (25.9%) reported at least one treatment-related adverse event (Table 5). All TEAEs were of mild-to-moderate severity (data not shown). The most common TEAEs under the fasted condition were nausea, headache, and abdominal distension (each reported by four participants [14.3%]), while the most common TEAEs under the fed condition were nausea (five participants [18.5%]), and abdominal distension and catheter site erythema (each reported by three participants [11.1%]; Table S1 in Supplementary material). One participant (3.6%) discontinued the study as a result of an adverse event (vomiting) under the fasted condition (Table 5). Among the adverse events of special interest, under the fasted condition, four participants (14.3%) reported nausea, and two participants each (7.1%) reported vomiting and diarrhea. Under the fed condition, five participants (18.5%) reported nausea, and

two participants each (7.4%) reported vomiting and diarrhea. None of the participants in either study experienced acute pancreatitis.

DISCUSSION

In this analysis of two phase 1 crossover clinical trials in healthy participants, the AUC and C_{max} were determined to be up to 24% lower when orforglipron was administered orally with food; t_{max} and $t_{1/2}$ were not impacted by the prandial state. The safety profile of orforglipron was consistent with previous reports and with the known safety profiles of other oral and injectable compounds in the GLP-1 RA pharmaceutical class [26, 28–31].

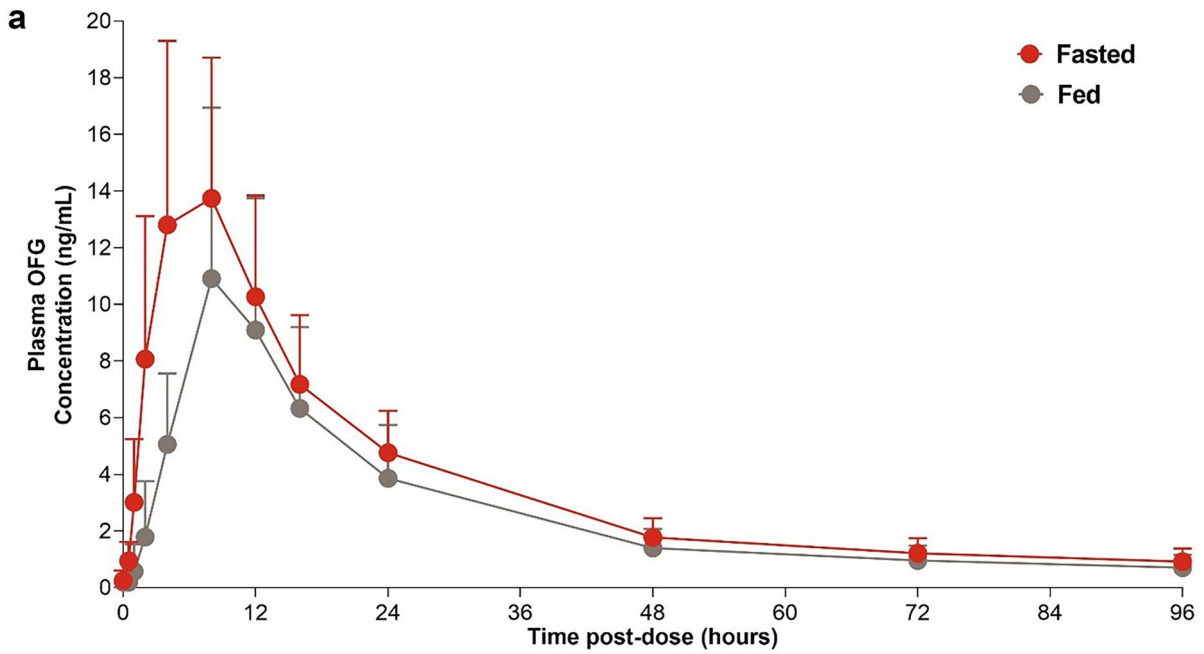
Single oral administration of 3 mg orforglipron in the fed state led to approximately 24% and 23% lower $AUC_{0-\infty}$ and C_{max}, respectively, versus the fasted state, with no differences in t_{max} between the prandial states. Following multiple once-daily oral doses of 16 mg orforglipron to healthy participants in the fed and fasted states, overall mean exposure to orforglipron based on AUC_{0-24} and C_{max} was approximately 18–21% lower when administered after a high-fat, high-calorie meal than in the fasted state, whereas median t_{max} was unaffected between the prandial states. In both studies, AUC and C_{max} reductions were similar after the first dose of 3 mg and at the steady-state 16-mg dose through titration. The observed effect of prandial status on PK was within variability of the PK and not expected to result in a clinically meaningful effect on safety and efficacy, and this effect may be consistent across the therapeutic dose range. On the basis of these results, two phase 2 randomized clinical trials were designed without food or water restrictions, wherein orforglipron treatment demonstrated robust glycemic control and body weight reduction in a 26-week study in participants with T2D and in a 36-week study in participants with obesity [26, 27].

Treatment adherence, particularly in the early stages of T2D, is important for augmenting the effectiveness of pharmaceutical therapy and improving glycemic outcomes [32]. Furthermore, evidence indicates a positive correlation between treatment adherence and weight reduction following treatment with the GLP-1 RA liraglutide [14]. However, patients with chronic conditions who are treated with long-term therapies are commonly non-adherent to their prescribed medications [33]. A study by Zhang et al. found that nearly 60% of patients with T2D were medication non-adherent [34].

Acknowledging patients' preferences during treatment-related decision-making could potentially improve treatment compliance and outcomes. Current treatment guidelines note the importance of considering patient-specific factors when evaluating a treatment regimen for T2D or chronic weight management [6, 9]. A key factor for consideration is the complexity of the treatment regimen to optimize medication use and reduce treatment discontinuation [6], and therefore, oral GLP-1 RA therapies with few intake requirements might help overcome this obstacle. The finding that the prandial state does not have a clinically significant effect on the PK of orforglipron offers dosing convenience to patients by removing the requirement of a fed or a fasted state and is anticipated to be a significant advantage for treatment adherence and thus therapeutic effectiveness. This important factor needs to be taken into consideration during patient–physician conversations when evaluating treatment options, enabling a patient-centered and personalized approach to disease management.

STRENGTHS AND LIMITATIONS

The strength of the current analysis is that, in both trials, the study intervention doses were administered in a clinical setting, ensuring participant compliance with the predefined treatment and dosing conditions. This allows for a robust understanding of food–drug interactions. Additionally, we assessed food-effect at the first treatment dose which can be impacted by gastric emptying as well as at the steady-state higher dose.


a
Fasted
Fed
Plasma OFG Concentration (ng/mL)
0
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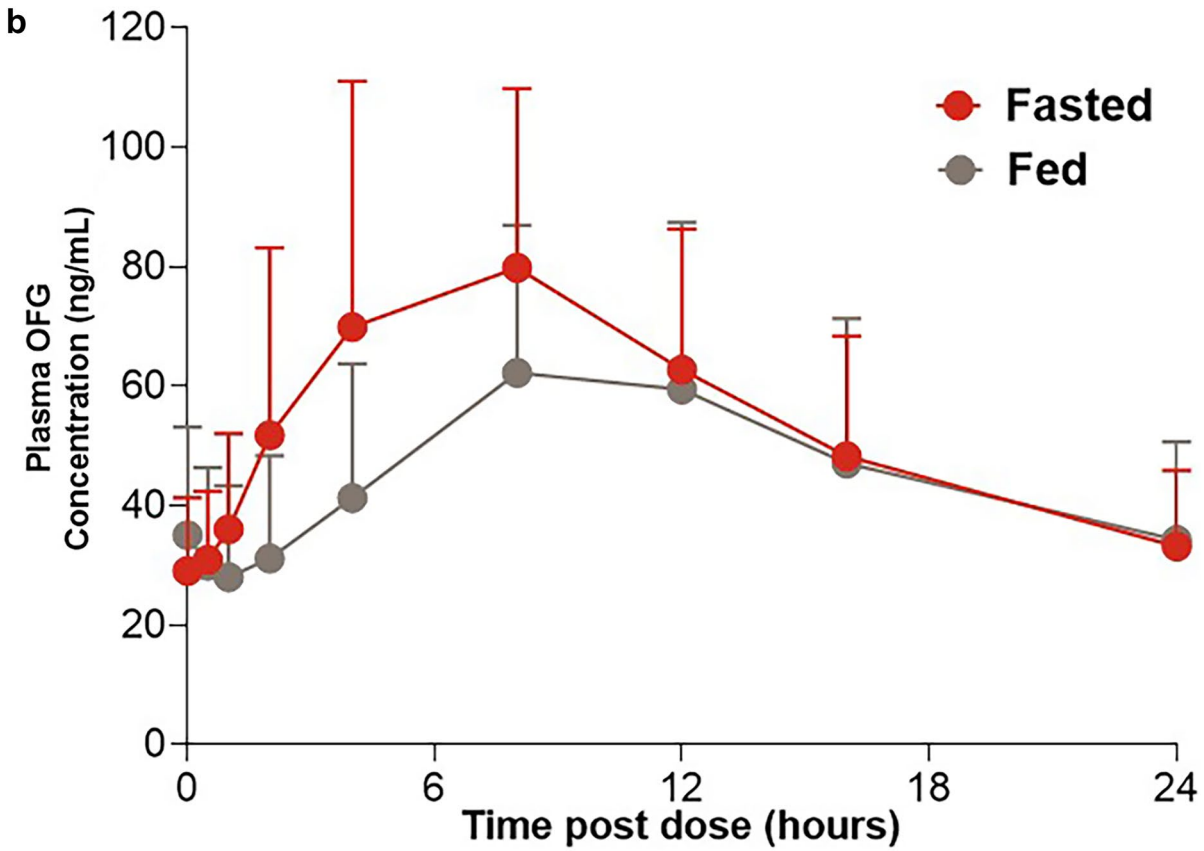
36
48
60
72
84
96
Time post-dose (hours)


b
Fasted
Fed
Plasma OFG Concentration (ng/mL)
0
20
40
60
80
100
120
0
6
12
18
24
Time post dose (hours)

◂**Fig. 2** **a** Plasma concentration profile of orforglipron (3 mg) after single oral administration to healthy subjects in the fasted and fed states in study A. **b** Plasma concentration profile of orforglipron (16 mg) after multiple oral administration to healthy participants in the fasted and fed states in study B. Data in graph are arithmetic mean (+ 1 SD). *OFG* orforglipron

However, we note the following limitations of the current investigation. The two phase 1 studies included overtly healthy people, of whom a majority were male. While both studies had small sample sizes, the results from these studies enabled phase 2 studies to be run outside the clinical setting, where compliance with dosing conditions cannot be fully ensured. In recently published articles, orforglipron demonstrated robust efficacy without strict control of the prandial state at the time of dosing [26, 27]. Ongoing studies ACHIEVE and ATTAIN phase 3 studies will aim to further demonstrate the safety and efficacy of orforglipron regardless of prandial state.

Table 4 Analysis of t_{max} after orforglipron administration to healthy participants in fed versus fasted states

Study	Treatment	*n*	Median t_{max} (h)	Median of differences (fed–fasted)	Approximate 90% CI for the difference (lower, upper)	*p* value
Study A OFG 3 mg	Fasted	11	8.0	0.0	(− 0.02 to 4.00)	0.6875
	Fed	11	8.0			
Study B OFG 16 mg	Fasted	25	8.0	0.0	(0.00 to 4.00)	0.0529
	Fed	25	8.0			

CI confidence interval, *h* hours, *n* number of observations, *OFG* orforglipron, t_{max} time of maximum observed drug concentration

Table 5 Summary of treatment-emergent adverse events reported in studies A and B

	Study A OFG 3 mg		Study B[a] OFG 16 mg	
	Fasted (*N* = 12)	Fed (*N* = 12)	Fasted (*N* = 28)	Fed (*N* = 27)
All TEAEs	2 (16.7)	0 (0.0)	18 (64.3)	12 (44.4)
Treatment-related AEs	2 (16.7)	0 (0.0)	12 (42.9)	7 (25.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
AEs of special interest				
Nausea	2 (16.7)	0 (0.0)	4 (14.3)	5 (18.5)
Vomiting	1 (8.3)	0 (0.0)	2 (7.1)	2 (7.4)
Diarrhea	0 (0.0)	0 (0.0)	2 (7.1)	2 (7.4)
Acute pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are *n* (%)

AE adverse event, *OFG* orforglipron, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event

[a]Safety population included participants who received ≥ 1 dose of study treatment (*N* = 33)

CONCLUSION

This analysis demonstrated that the overall mean exposure to orforglipron based on AUC and C_{max} was numerically lower when administered with food, while the effect on t_{max} and $t_{1/2}$ was negligible. In both studies, AUC and C_{max} reductions were similar after the first treatment dose and at the steady-state dose through titration. Based on the exposure–response property of orforglipron, these observed PK differences due to prandial state are unlikely to result in clinically meaningful differences in the safety and efficacy of orforglipron. Oral GLP-1 RAs without prandial restrictions may offer a desirable and convenient treatment option for patients with T2D and/or obesity who would like to achieve glycemic control or weight reduction without injectable therapy.

ACKNOWLEDGEMENTS

The authors thank the participants for their involvement in the study.

Medical Writing, Editorial, and Other Assistance. Richa Kapoor, PhD, an employee of Eli Lilly Services India Pvt. Ltd., provided medical writing support which was funded by Eli Lilly and Company.

Authorship. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Study design: Xiaosu Ma, Edward J Pratt, Shobha N. Bhattachar, Charles T. Benson. Data collection: Rong Liu. Interpretation: Xiaosu Ma, Rong Liu, Edward J Pratt, Kyle W. Sloop, Charles T. Benson, Shobha N. Bhattachar. Analysis: Xiaosu Ma, Rong Liu, Charles T. Benson.

Funding. This study and the journal's Rapid Service fee was sponsored by Eli Lilly and Company, Indianapolis, IN, USA.

Data Availability. 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 USA 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.

Declarations

Conflict of interest. Xiaosu Ma, Rong Liu, Edward J. Pratt, Charles T. Benson, Shobha N. Bhattachar, and Kyle W. Sloop are employees and shareholders of Eli Lilly and Company, Indianapolis, USA.

Ethical Approval. Study protocols and informed consent forms were approved by an ethics review board at each site (study A: ERB Midlands IRB, KS 66212, USA; study B: National Healthcare Group Domain Specific Review Board, Singapore 138543). The study was conducted in accordance with ethical principles of ICH GCP and the Declaration of Helsinki of 1964, and its later amendments. Written informed consent was obtained from each patient at study entry before any study procedures.

REFERENCES

1. Bailey CJ, Flatt PR, Conlon JM. An update on peptide-based therapies for type 2 diabetes and obesity. Peptides. 2023;161:170939.

2. 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.

3. Karagiannis T, Liakos A, Bekiari E, et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonists for the management of type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2015;17(11):1065–74.

4. Anam M, Maharjan S, Amjad Z, et al. Efficacy of semaglutide in treating obesity: a systematic review of randomized controlled trials (RCTs). Cureus. 2022;14(12):e32610.

5. Iqbal J, Wu HX, Hu N, et al. Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus-a systematic review and meta-analysis of randomized control trials. Obes Rev. 2022;23(6):e13435.

6. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. Diabetes Care. 2022;46(Suppl_1):S140–57.

7. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65(12):1925–66.

8. 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):653–62.

9. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract. 2016;22(Suppl 3):1–203.

10. Jensen MD, Ryan DH, Apovian CM, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol. 2014;63(25 Pt B):2985–3023.

11. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. CMAJ. 2020;192(31):E875–91.

12. Yumuk V, Tsigos C, Fried M, et al. European guidelines for obesity management in adults. Obes Facts. 2015;8(6):402–24.

13. Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. Clin Ther. 2011;33(1):74–109.

14. Tronieri JS, Wadden TA, Walsh O, Berkowitz RI, Alamuddin N, Chao AM. Measures of adherence as predictors of early and total weight loss with intensive behavioral therapy for obesity combined with liraglutide 3.0 mg. Behav Res Ther. 2020;131:103639.

15. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405–12.

16. Bækdal TA, Breitschaft A, Donsmark M, Maarbjerg SJ, Søndergaard FL, Borregaard J. Effect of various dosing conditions on the pharmacokinetics of oral semaglutide, a human glucagon-like peptide-1 analogue in a tablet formulation. Diabetes Ther. 2021;12(7):1915–27.

17. Anderson SL, Beutel TR, Trujillo JM. Oral semaglutide in type 2 diabetes. J Diabetes Compl. 2020;34(4):107520.

18. US Food & Drug Administration. FDA approves first oral GLP-1 treatment for type 2 diabetes. 2019. https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes. Accessed 29 Aug 2023.

19. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eear7047.

20. Mentlein R, Gallwitz B, Schmidt WE. Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7–36)amide, peptide histidine methionine and is responsible for their degradation in human serum. Eur J Biochem. 1993;214(3):829–35.

21. Pechenov S, Revell J, Will S, et al. Development of an orally delivered GLP-1 receptor agonist through peptide engineering and drug delivery to treat chronic disease. Sci Rep. 2021;11(1):22521.

22. US Food & Drug Administration. RYBELSUS prescribing information 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf. Accessed 29 Aug 2023.

23. Kvarnström K, Westerholm A, Airaksinen M, Liira H. Factors contributing to medication adherence in patients with a chronic condition: a scoping review of qualitative research. Pharmaceutics. 2021;13(7):1100.

24. Patel S, Abreu M, Tumyan A, Adams-Huet B, Li X, Lingvay I. Effect of medication adherence on clinical outcomes in type 2 diabetes: analysis of the SIMPLE study. BMJ Open Diabetes Res Care. 2019;7(1):e000761.

25. 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 USA. 2020;117(47):29959–67.

26. Frias JP, Hsia S, Eyde S, et al. Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study. Lancet. 2023;402(10400):472–83.

27. Wharton S, Blevins T, Connery L, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. N Engl J Med. 2023;389(10):877–88.

28. 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;25(9):2634–41.

29. 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):1079–87.

30. 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):781–91.

31. 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;25(9):2642–9.

32. Lin LK, Sun Y, Heng BH, Chew DEK, Chong PN. Medication adherence and glycemic control among newly diagnosed diabetes patients. BMJ Open Diabetes Res Care. 2017;5(1):e000429.

33. Cheen MHH, Tan YZ, Oh LF, Wee HL, Thumboo J. Prevalence of and factors associated with primary medication non-adherence in chronic disease: a systematic review and meta-analysis. Int J Clin Pract. 2019;73(6):e13350.

34. Zhang ZP, Premikha M, Luo M, Venkataraman K. Diabetes distress and peripheral neuropathy are associated with medication non-adherence in individuals with type 2 diabetes in primary care. Acta Diabetol. 2021;58(3):309–17.