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RESEARCH LETTER

The novel GIP, GLP-1 and glucagon receptor agonist retatrutide delays gastric emptying

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1 | INTRODUCTION

Delayed gastric emptying (GE) is a well-known effect of glucagon-like peptide-1 (GLP-1).[1,2] Similarly, glucagon (GCG) has been shown to slow GE in rodents and humans,[3,4] while glucose-dependent insulinotropic polypeptide (GIP) does not appear to impact GE.[1,2]

Retatrutide (LY3437943) is a novel GIP/GLP-1/GCG receptor agonist (RA) under investigation for chronic weight management and its complications. It is more potent at the human GIP receptor and less potent at GCG and GLP-1 receptors versus the native hormones, with a half-life of approximately 6 days supporting once-weekly dosing.[5] In adults with type 2 diabetes, retatrutide reduced glycated hemoglobin (HbA1c) and body weight versus placebo and dulaglutide 1.5 mg after 12 weeks of treatment, with mild or moderate gastrointestinal events being the most common treatment-emergent adverse events.[6]

GE is a major determinant of glycemic response after food intake.[7] Delayed GE may reduce food intake and subsequently impact weight loss.[8] While GLP-1 RAs and the GIP/GLP-1 RA tirzepatide transiently delay GE, the effects of retatrutide are unknown.

We investigated the effect of retatrutide versus selective GLP-1 RAs on GE in non-clinical and clinical studies.

2 | METHODS

2.1 | Non-clinical methodology

C57/B16 male obese mice (Jackson) were singly housed and maintained on a standardized diet (TD95217; Teklad) with ad libitum water; 16 h before the assessment of acute GE, mice were fasted overnight and treated subcutaneously with either vehicle (10 ml/kg; 40 mM Tris pH 8), long-acting GCG RA (Table S1), semaglutide, retatrutide, or combined semaglutide and long-acting GCG RA. Mice were administered 0.5 ml of semi-liquid by oral gavage and GE was subsequently assessed (Additional Methods S1). GE delay, body weight, and food intake were also assessed following chronic (daily for 10 days) treatment with vehicle, semaglutide, long-acting GCG RA, retatrutide, or combined semaglutide and long-acting GCG RA. The mice were studied and maintained in accordance with the Institutional Animal Care and Use Committee of Eli Lilly and Company and the Guide for the Use and Care of Laboratory Animals by the National Institutes of Health.

2.2 | Clinical study design and participants

GE was assessed within a phase 1b, randomized, multiple-ascending dose study in adults with type 2 diabetes who received once-weekly

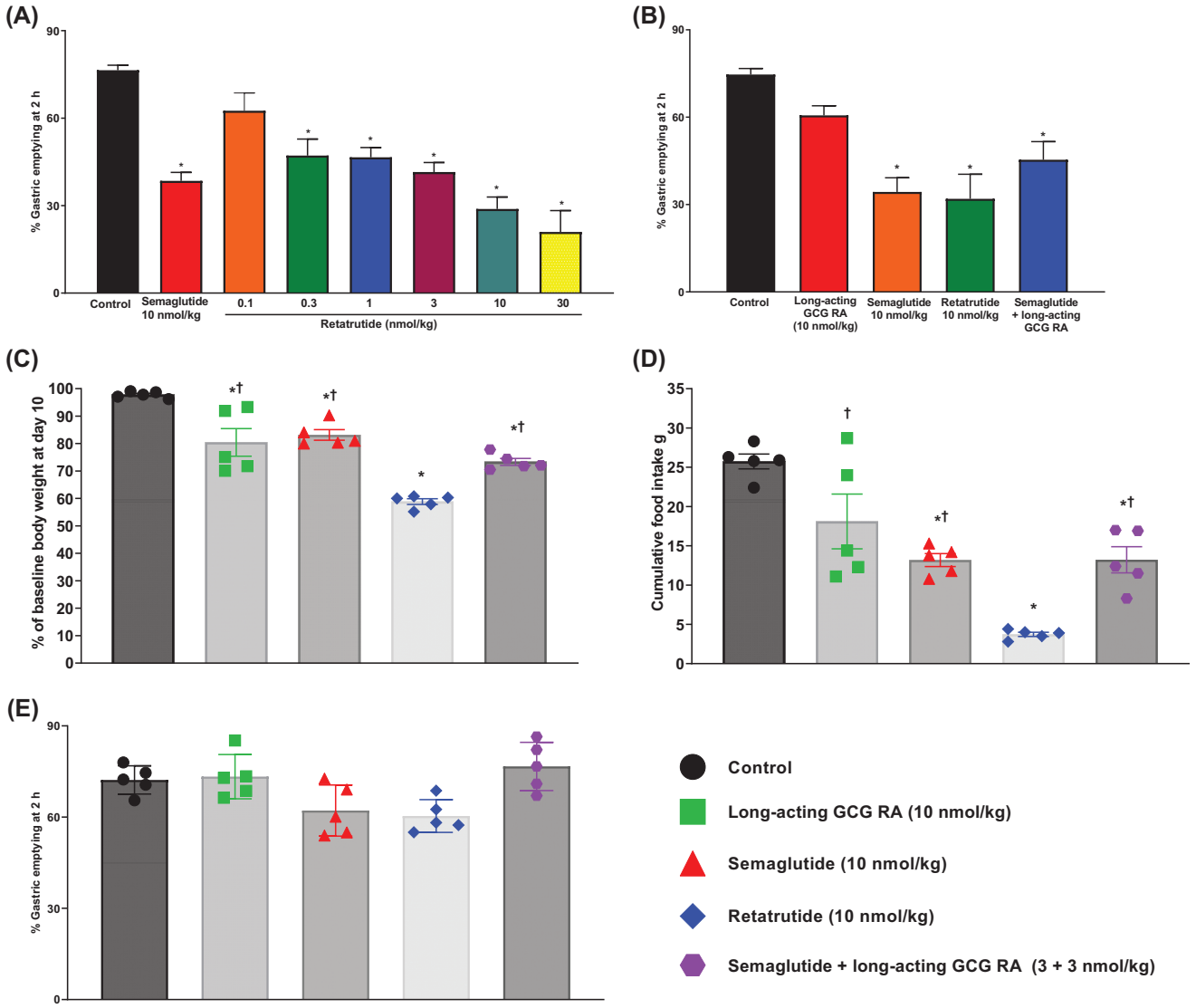

FIGURE 1 Acute and chronic effects of retatrutide, semaglutide and long-acting GCG RA on GE in mice. Data are mean ± SE with five mice per group. Gastric emptying data are percentage emptied from the stomach at 2 h. (A) Acute effect of ascending doses of retatrutide on GE. (B) Acute effect of long-acting GCG RA, semaglutide, retatrutide, or semaglutide combined with long-acting GCG RA on GE. (C) Percentage of baseline body weight at Day 10 after chronic (daily for 10 days) treatment with long-acting GCG RA, semaglutide, retatrutide, or semaglutide combined with long-acting GCG RA. (D) Cumulative food intake after chronic treatment. (E) Chronic effect on gastric emptying. $^{*}p < .05$ versus control and $^{\dagger}p < .05$ versus retatrutide. GCG, glucagon; GE, gastric emptying; RA, receptor agonist; SE, standard error.

retatrutide (0.5, 1.5, 3, 3/6 and 3/6/9/12 mg), placebo, or dulaglutide 1.5 mg, with study design and primary results published previously.[6] Retatrutide 0.5, 1.5 and 3 mg were fixed dose regimens for 12 weeks. The 3/6 mg group received 3 mg for Weeks 1-4, then 6 mg for Weeks 5-12. The 3/6/9/12 mg group received 3 mg for Weeks 1-2, 6 mg for Weeks 3-4, 9 mg for Weeks 5-8 and 12 mg for Weeks 9-12. GE was assessed pre-treatment at Day −2, and approximately 24 h after dose at Day 2, Day 30 and Day 79 using acetaminophen (Additional Methods S1 and Figure S1). The acetaminophen maximum concentration (C_{max}), time to C_{max} (T_{max}), and area under the concentration versus time curve from time 0 to the last time point with a measurable concentration (24 h) ($AUC_{0\text{-}t\ last}$) were key variables.

The trial (NCT04143802) was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained and all participants provided written informed consent before their participation.

2.3 | Statistical methods

In the non-clinical studies, between-group data were analysed using one-way analysis of variance followed by Tukey's multiple comparison test. The effects on body weight were calculated as the percentage of baseline body weight at Day 10. In the clinical study, the impact of retatrutide on GE was compared with dulaglutide 1.5 mg and placebo using the ratio of acetaminophen C_{max} and $AUC_{0\text{-}t\ last}$ estimated on

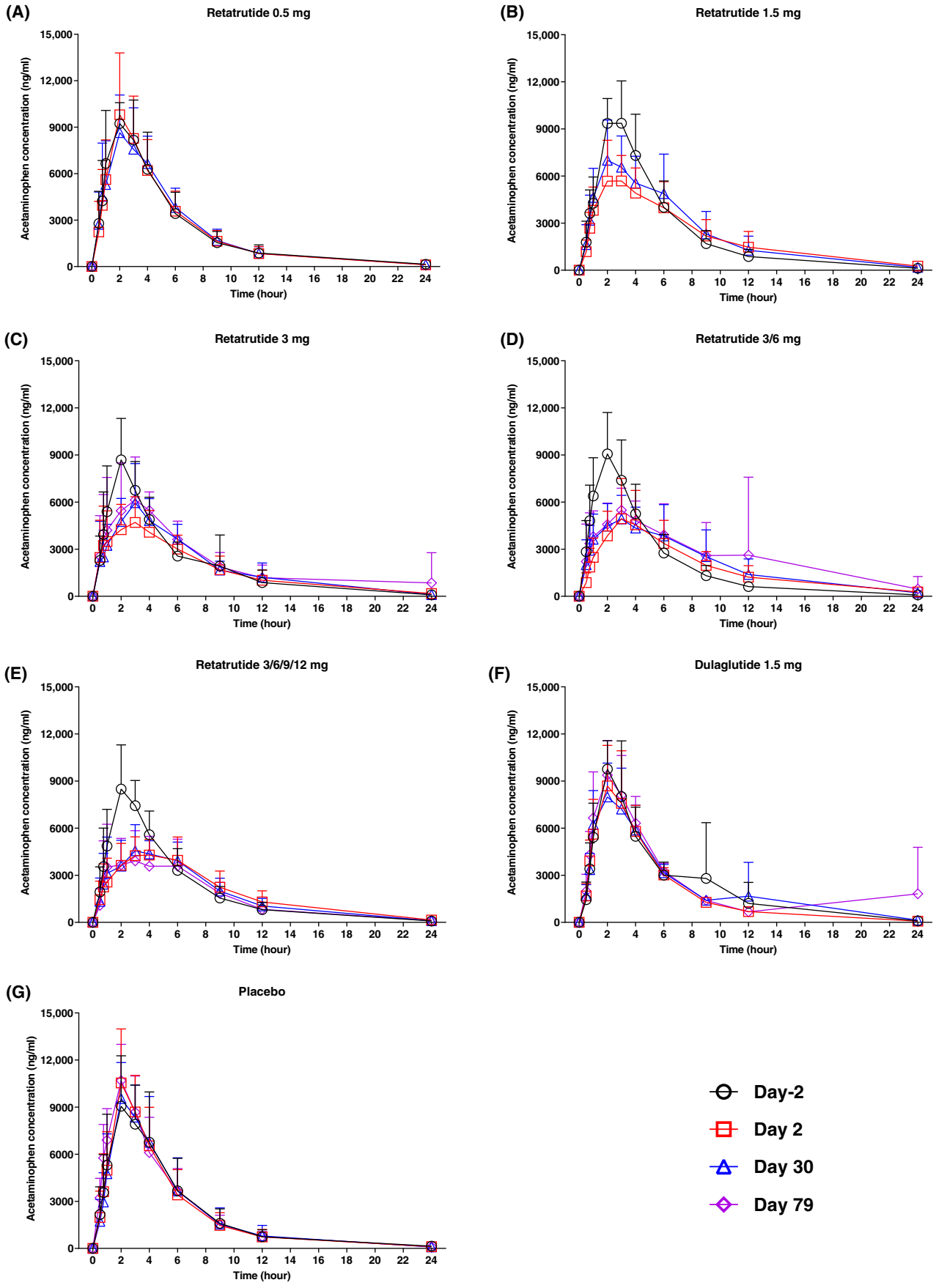

FIGURE 2 Legend on next page.

Days 2, 30 and 79 over baseline (Day −2). A mixed-model repeated measure with responses of log-transformed postbaseline C_{max} and $AUC_{0\text{-t last}}$ was performed using treatment, day, and treatment-by-day interaction as fixed effects, participant as random effect, and log-transformed baseline as covariate. The Wilcoxon rank-sum test was used to analyse and compare the acetaminophen T_{max} across treatment groups.

3 | RESULTS

3.1 | Acute and chronic effects of retatrutide on GE in mice

While a long-acting GCG RA had no statistically significant effect on GE (Figure S2), retatrutide dose-dependently delayed GE in mice (Figure 1A,B). Semaglutide also delayed GE (Figure 1A,B). The effects of acute combination treatment with semaglutide plus long-acting GCG RA on GE did not differ statistically from retatrutide (Figure 1B).

Over 10 days, retatrutide 10 nmol/kg reduced body weight and these decreases were greater than with semaglutide, long-acting GCG RA, and combined semaglutide plus long-acting GCG RA (Figure 1C). The combination dose of semaglutide 3 nmol/kg and long-acting GCG RA 3 nmol/kg was selected to achieve a similar body weight reduction to semaglutide 10 nmol/kg alone ($p = .0825$). Similarly, the largest decreases in food intake were observed with retatrutide treatment (Figure 1D). Effects of retatrutide on GE were attenuated after chronic treatment for 10 days (Figure 1E).

3.2 | Effects of retatrutide on GE in humans

In the clinical study, 72 participants were enrolled and received ≥1 dose of study drug and 43 completed the study. The COVID-19 pandemic was the most common reason for study discontinuation, which impacted the two lowest dose cohorts (retatrutide 0.5 mg and 1.5 mg) (Figure S3).[6] The mean (standard deviation) age was 58.4 (7.4) years, body mass index 32.1 (5.1) kg/m^2, HbA1c 8.66 (0.92)% [71 (10) mmol/mol], and 51% were women.[6]

On Day −2, before study treatment, the acetaminophen pharmacokinetic profiles were similar among groups (Figure 2 and Table S2). Within retatrutide-treated participants, the acetaminophen C_{max} generally decreased during treatment. The magnitude of decrease was greatest following the first retatrutide dose (Day 2) in the >1.5 mg groups. In the fixed dose 1.5 and 3 mg groups, the acetaminophen C_{max} did not decrease further following subsequent doses, but rather appeared to be increasing, although it did not reach pre-treatment levels by the last measurements. Similarly, in the 3/6 and 3/6/9/12 mg groups at Day 30, despite ongoing dose escalation (to the first 6 and 9 mg dose, respectively), the magnitude of acetaminophen C_{max} decrease was not greater than that noted at Day 2 and appeared to trend upwards to Day 79, when GE was measured after the last 6 and 12 mg dose, respectively. In the dulaglutide group, C_{max} decreased somewhat from Day −2 to Day 2, with little change thereafter.

The T_{max} appeared unaffected in the dulaglutide 1.5 mg group but was delayed by approximately 1 h at Day 2 in the ≥3 mg retatrutide groups and remained delayed at Days 30 and 79. $AUC_{0\text{-t last}}$ was not affected.

4 | DISCUSSION

The effect of GLP-1 receptor agonism on GE delay has been extensively studied, while corresponding data with GIP and GCG are limited.[1–4] While GIP appears to have no impact,[1,2] GCG may acutely delay GE and intestinal transit.[3,4,9–11] We investigated the impact of the GIP/GLP-1/GCG RA retatrutide on GE.

We examined the effects of long-acting GCG RA in mice to investigate the contribution of GCG RA in retatrutide to GE. We used a long-acting GCG RA that had similar molecular properties (C20 fatty acid moiety to enable albumin binding), in vitro functional receptor activity, and pharmacokinetic properties as retatrutide.[5] The long-acting GCG RA had no apparent effect on GE in mice, although it has been shown that short-acting GCG could delay GE in humans.[10] Semaglutide and retatrutide both inhibited GE to a similar extent at the 10 nmol/kg dose; however, retatrutide effectively delayed GE at 0.3 nmol/kg, at which dose semaglutide had no effect.[12] Chronic retatrutide treatment resulted in tachyphylaxis of the GE effect in mice.

In our clinical study, the greatest effect on GE occurred after the first retatrutide dose. The maximum extent of GE delay observed with retatrutide was similar to that previously noted with tirzepatide.[12] The magnitude of GE inhibition was lower following subsequent retatrutide doses and appeared to be diminishing at Days 30 and 79, despite ongoing dose escalation in the two highest dose retatrutide groups. Similar reports of tachyphylaxis of GE delay have been reported for liraglutide based on assessments at 16 weeks versus an earlier time point of 5 weeks.[13]

Limitations include the small sample size and our use of an acetaminophen test, rather than scintigraphy or breath tests to assess GE, as these methods were not feasible in this study.[14] Confirming our findings on the effects of retatrutide on GE following a solid meal may be of interest. The GE delay observed with dulaglutide was smaller than previously observed,[12,15] which may reflect cohort-specific features.

FIGURE 2 Effects of retatrutide, dulaglutide, and placebo on gastric emptying in participants with type 2 diabetes. Data are mean (standard deviation) acetaminophen concentration over time with (A) retatrutide 0.5 mg, (B) retatrutide 1.5 mg, (C) retatrutide 3 mg, (D) retatrutide 3/6 mg, (E) retatrutide 3/6/9/12 mg, (F) dulaglutide 1.5 mg, and (G) placebo. Largely because of COVID-19 related pandemic restrictions, no participants in the 0.5 mg retatrutide group and only one participant in the 1.5 mg retatrutide group completed the study. In these groups participants received treatment for an average of 10 weeks and 5 weeks, respectively.

These data suggest that the maximum extent of GE delay following initial retatrutide treatment is similar to observations with selective GLP-1 and GIP/GLP-1 RAs. The time course of tachyphylaxis of GE delay may be longer with retatrutide compared with previously studied incretins.[12,13]

AUTHOR CONTRIBUTIONS

Libbey O'Farrell and Tamer Coskun were responsible for the nonclinical work. Hongchang Qu and Jorge Alsina-Fernandez developed and characterized the peptides. Shweta Urva, Zvonko Milicevic, Mei Teng Loh, Axel Haupt and Tamer Coskun were involved in the clinical trial, and Zvonko Milicevic, Axel Haupt and Tamer Coskun provided medical oversight during the trial. Tamer Coskun, Libbey O'Farrell and Yu Du were responsible for statistical analyses. Andrea Hemmingway wrote the initial draft of the manuscript and all authors participated in data interpretation, authoring and critical review. All authors approved of the final version the manuscript for submission.

CONFLICT OF INTEREST STATEMENT

All authors 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.15167.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, 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.

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SUPPORTING INFORMATION

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

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