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First-in-human study of a pharmacological duodenal exclusion therapy shows reduced postprandial glucose and insulin and increased bile acid and gut hormone concentrations

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Abstract

Aims: To address the need for noninvasive alternatives to metabolic surgery or duodenal exclusion devices for the management of type 2 diabetes (T2D) and obesity by developing an orally administered therapeutic polymer, GLY-200, designed to bind to and enhance the barrier function of mucus in the gastrointestinal tract to establish duodenal exclusion noninvasively.

Materials and Methods: A Phase 1, randomized, double-blind, placebo-controlled, single- (SAD) and multiple-ascending-dose (MAD) healthy volunteer study was conducted. In the SAD arm, four cohorts received a single dose of 0.5 g up to 6.0 g GLY-200 or placebo, while in the MAD arm, four cohorts received 5 days of twice-daily or three-times-daily dosing (total daily dose 2.0 g up to 6.0 g GLY-200 or placebo). Assessments included safety and tolerability (primary) and exploratory pharmacodynamics, including serum glucose, insulin, bile acids and gut hormones.

Results: No safety signals were observed; tolerability signals were limited to mild to moderate dose-dependent gastrointestinal events. In the MAD arm (Day 5), reductions in glucose and insulin and increases in bile acids, glucagon-like peptide-1, peptide YY and glicentin, were observed following a nonstandardized meal in subjects receiving twice-daily dosing of 2.0 g GLY-200 (N = 9) versus those receiving placebo (N = 8).

Conclusions: GLY-200 is safe and generally well tolerated at doses of ≤2.0 g twice daily. Pharmacodynamic results mimic the biomarker signature observed after Roux-en-Y gastric bypass and duodenal exclusion devices, indicating a pharmacological effect in the proximal small intestine. This study represents the first clinical demonstration that duodenal exclusion can be achieved with an oral drug and supports further development of GLY-200 for the treatment of obesity and/or T2D.

KEYWORDS
bariatric surgery, clinical trial, drug development, GLP-1, pharmacodynamics, type 2 diabetes

1 | INTRODUCTION

Metabolic surgery is recognized as having a profound impact on type 2 diabetes (T2D), obesity and related comorbidities. It can markedly improve glycaemic control and promote substantial and durable weight loss, remission of T2D, improved quality of life, improved cardiovascular outcomes, and reduced mortality.[1] Meta-analysis of 22 000 intestinal bypass patients documented complete remission of T2D in >80% of patients.[2,3] Given its profound effects, metabolic surgery was added to the American Diabetes Association treatment algorithm for T2D in 2017[4,5] as the only treatment known to substantially slow or even reverse the disease.

Notably, certain metabolic surgical procedures have been shown to induce an immediate and major improvement in glycaemic control well in advance of any substantial weight loss[6-9] or even in the absence of weight loss.[10,11] One such procedure is Roux-en-Y gastric bypass (RYGB), in which the stomach is made smaller and attached more distally to the jejunum. The surgically excluded distal stomach and duodenum are removed from the path of nutrient flow. This exclusion of the duodenum from contact with intraluminal chyme ("duodenal exclusion") may, in part, explain the profound and sustained reduction in blood glucose and body weight observed with this procedure.

The immediate improvements in glucose control observed after bariatric surgery may reflect several mechanisms, including reduced nutrient intake and/or absorption, enhanced L-cell secretion of gut peptides such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), changes in the levels and composition of bile acids, and potentially decreased secretion of unidentified duodenal factors that may promote insulin resistance and/or have detrimental effects on ß-cell secretion. While there is currently no consensus on which mechanisms are most important, bypassing some or all of the duodenum may account for much of the observed effect of RYGB.[9] While some metabolic surgeries that do not exclude the foregut (eg, sleeve gastrectomy) can substantially improve metabolic control,[12] duodenal-jejunal bypass liner (DJBL) devices that simply exclude a portion of duodenum are also effective,[13] suggesting that different metabolic interventions may work predominantly through different mechanisms. DJBL devices most directly validate the clinical relevance of duodenal exclusion in RYGB surgery as they lead to robust effects on glucose and body weight without the confounding effects of the more invasive procedures that also involve alterations to the stomach. A meta-analysis by Jirapinyo et al of 17 clinical DJBL studies in patients with obesity and T2D found that DJBL resulted in a glycated haemoglobin (HbA1c) decrease of 1.3%, total weight loss of 18.9% and excess weight loss of 36.9%.[13] In addition, a significant improvement in homeostatic model assessment of insulin resistance was noted, along with increases in GLP-1 and PYY. However, the DJBL device currently in development (Endobarrier™) has been delayed in the United States because of safety concerns, including gastrointestinal bleeding, abdominal pain, device migration, and hepatic abscesses attributed to the device's metallic anchor.[14]

The cost and risks associated with metabolic surgical procedures and devices continue to restrict their widespread use in treating T2D. Moreover, many patients do not meet National Institute of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) guidelines for metabolic surgery and, for those who do, fewer than 1% undergo surgery due to its invasiveness and potential complications.[15] Less invasive and safer alternatives to metabolic surgery or duodenal exclusion devices that still leverage the duodenal exclusion mechanism of action remain an unmet need in overweight, obese and T2D populations.

Accordingly, we have investigated whether we could enhance the barrier function of mucus in the gastrointestinal tract as a less invasive means of establishing duodenal exclusion. We developed an orally administered, pH-dependent, gut-restricted therapeutic polymer, GLY-200, that irreversibly crosslinks with mucin, a major component of the mucus layer that lines the gastrointestinal tract. Specifically, upon delivery to the stomach, GLY-200 dissolves rapidly in the low pH environment (pH < 5.5). As the dissolved polymer passes through the pylorus, the higher pH environment of the duodenum (pH > 5.5) facilitates rapid crosslinking of the polymer with endogenous mucin. When GLY-200 complexes with mucin, it enhances the mucus barrier in the duodenum to achieve reversible pharmacological duodenal exclusion. It is expected that the polymer-mucus complex would be gradually shed and eliminated in the faeces through the continual turnover of the intestinal mucus layer within 24 hours.[16]

Here, we report results from a Phase 1 study in healthy adult volunteers showing that (i) GLY-200 was safe and generally well tolerated at doses up to 2.0 g twice daily, and (ii) exploratory pharmacodynamic results are consistent with a duodenal exclusion mechanism of action.

2 | MATERIALS AND METHODS

2.1 | Phase 1 study design

A Phase 1, single-centre, placebo-controlled, randomized, double-blinded study was conducted to assess the safety and tolerability of oral GLY-200 in 64 healthy volunteers. The study was conducted at CMAX Clinical Research Pty Ltd in Adelaide, Australia, and consisted of two parts. Part 1 (N = 32) was a single-ascending-dose (SAD) escalation (four dose levels), with eight healthy individuals per cohort, randomized 3:1 to receive GLY-200 (a polymer of poly[allylamine] hydrochloride amide with 3-fluoro-4-carboxyphenylboronic acid) or placebo (microcrystalline cellulose, Avicel PH-105). Participants

received GLY-200 or placebo on Day 1, remained in the clinic for a total of 3 days, and had a follow-up visit on Day 10. As the study site was unable to offer standardized meals because of COVID-19 pandemic-related resource limitations, nonstandardized meals were provided three times a day, approximately 6 hours apart. Sentinels (1:1 active: placebo) were used for all SAD cohorts and were observed for 48 hours prior to study continuation, as determined by the principal investigator and medical monitor.

Progression to Part 2 of the study occurred after review of all available safety and tolerability data in the SAD cohorts. The multiple-ascending-dose (MAD) escalation component of the study involved four additional cohorts. MAD Cohorts 1, 2 and 3 each consisted of two dose groups, with each group consisting of four healthy individuals per group randomized 3 active: 1 placebo. Cohort 4 was an "expansion group", in which one dose group underwent a cohort expansion by another eight healthy individuals (randomized 3 active: 1 placebo). Participants received GLY-200 or placebo for 5 days, with a total of 7 days in clinic and a follow-up visit on Day 14. Nonstandardized meals were provided three times a day, approximately 6 hours apart. The decision to proceed to the next cohort was based on review of the available safety data by the Safety Review Committee. The Safety Review Committee made decisions to increase the dose, lower the dose, or expand previously studied doses. The group selected for expansion was determined based on safety and tolerability data.

For nonstandardized meals, all participants were offered the same menu for a given study day, but the lunch and dinner menus differed between each day of the study. The postprandial effects of GLY-200 (see Study Endpoints and Assessments) were assessed after the breakfast meal. The breakfast menu provided options for types of bread (two slices), milk, single-serve packets of butter and spreads, and packets of cereals for participants to choose from (participants could choose one bread, one milk, two butters, two spreads and two cereals). Whether an entire meal was consumed was up to each individual and the amount consumed was not documented.

The study was approved by an appropriate human research ethics committee and was conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) E6 (R2) (2016) and the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007, incorporating all updates). The study was registered at the Australian New Zealand Clinical Trials Registry (ACTRN12621000800820).

2.2 | Participants

Eligible participants were male or female adults aged ≥18 and ≤65 years at the time of screening, with body mass index (BMI) ≥ 18.0 and < 32 kg/m^2. Participants were to be in good general health with fasting blood glucose levels 3.0 to 5.4 mmol/L and HbA1c <42.1 mmol/mol at screening. Table S1 provides a summary of the study demographics. All participants provided written informed consent before any study procedure.

2.3 | Drug administration

Participants self-administered GLY-200 (500-mg capsules) or placebo capsules orally with water as required. In Part 1 (SAD), participants received a single dose of GLY-200 at doses of 0.5, 2.0, 4.0 and 6.0 g (N = 6 each) or placebo (N = 8). In Part 2 (MAD), participants received GLY-200 dose regimens of 1.0 g twice a day (N = 3), 1.0 g three times a day (N = 3), 2.0 g twice daily (expansion dose; N = 9), 2.0 g three times daily (N = 6), 3.0 g twice daily (N = 3), or placebo (N = 8). For each dose level, participants were randomized 3:1 active versus placebo and the same number of placebo and active capsules were administered to maintain the blind. Participants were required to fast for at least 2 hours prior to dosing and for at least 1 hour after dosing.

2.4 | Study endpoints and assessments

The primary objective of this study was the safety and tolerability of GLY-200 after single- and multiple-ascending oral doses in healthy volunteers. Safety and tolerability were assessed by incidence, type and severity of adverse events (AEs), dose-limiting toxicities, and changes from baseline in vital sign measurements, body weight, physical examination findings, clinical laboratory variables, and electrocardiogram (ECG) variables. The severity of each AE was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 five-point scale.

An exploratory objective was to evaluate preliminary pharmacodynamic (PD) characteristics. Exploratory PD analyses in Part 2 (MAD) were performed in the morning on Days 1 and 5, with PD samples collected at baseline (fasting/pre-dose) and 1, 2 and 4 hours post-dose. Dosing occurred at Hour 0 and a nonstandardized meal (breakfast) was consumed at 1 hour post-dose. The 1-hour post-dose PD sample was collected just prior to meal consumption. PD analyses included serum analysis of glucose (Atellica CH Glucose Hexokinase-3) and bile acids (Randox Total Bile Acids 5th Generation; Australian Clinical Labs, Adelaide, Australia) and of insulin, total GLP-1, glicentin, total glucose-dependent insulinotropic polypeptide (GIP) and glucagon (Mercodia ELISA), and PYY total and ghrelin total (Mesoscale Discovery U-PLEX; Mercodia, Uppsala, Sweden). Aside from glucose and bile acids, PD analyses were only performed for the groups that had larger participant numbers (2.0 g twice daily, N = 9; placebo, N = 8).

2.5 | Statistical methods

As is usual, the sample size for this Phase 1 study was not based on statistical considerations. Safety data are presented for all participants who were randomized and received at least one dose of study drug (ie, safety population) and are summarized using descriptive statistics. Exploratory PD endpoints were analysed using available data from the safety population. For PD measures, a mixed model with fixed effects for treatment, hour, and the interaction between treatment and hour and an unstructured within-subject covariance matrix was used to

TABLE 1 Related treatment-emergent adverse events of at least moderate severity, by treatment (multiple ascending dose)

System organ class	Number (%) of participants with related[a] moderate TEAEs[b] [Number of related TEAEs reported]							
Preferred term	1.0 g twice daily N = 3	1.0 g three times daily N = 3	2.0 g twice daily N = 9	2.0 g three times daily N = 6	3.0 g twice daily N = 3	All active subjects N = 24	Placebo N = 8	All subjects N = 32
Any TEAE	1 (33) [2]	1 (33) [1]	-	5 (83) [11]	1 (33) [1]	8 (33) [15]	-	8 (25) [15]
Metabolism and nutrition disorders	-	-	-	1 (17) [1]	-	1 (4) [1]	-	1 (3) [1]
Decreased appetite	-	-	-	1 (17) [1]	-	1 (4) [1]	-	1 (3) [1]
Nervous system disorders	-	-	-	1 (17) [1]	-	1 (4) [1]	-	1 (3) [1]
Headache	-	-	-	1 (17) [1]	-	1 (4) [1]	-	1 (3) [1]
Gastrointestinal disorders	1 (33) [2]	1 (33) [1]	-	5 (83) [9]	1 (33) [1]	8 (33) [13]	-	8 (25) [13]
Nausea	1 (33) [1]	1 (33) [1]	-	4 (67) [5]	1 (33) [1]	7 (29) [8]	-	7 (22)
Vomiting	1 (33) [1]	-	-	2 (33) [2]	-	3 (13) [3]	-	3 (9) [3]
Constipation	-	-	-	1 (17) [1]	-	1 (4) [1]	-	1 (3) [1]
Retching	-	-	-	1 (17) [1]	-	1 (4) [1]	-	1 (3) [1]

Abbreviation: TEAE, treatment-emergent adverse event.
[a]Related, relationship to study drug of possibly, probably or definitely related.
[b]Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), and data summarized by system organ class and preferred term.

analyse incremental concentration values at the 2-hour and 4-hour timepoints on days 1 and 5 (Pharmapace, Inc., San Diego, California). Additionally, a mixed model with treatment as a fixed effect was used to analyse area under the curve (AUC) values on Day 1 and Day 5; this is equivalent to a two-sample *t*-test (Pharmapace, Inc.). In keeping with the exploratory nature of the outcomes, *P* values were not adjusted for multiple comparisons.

3 | RESULTS

3.1 | Safety and tolerability of GLY-200 in healthy volunteers

A total of 64 participants were enrolled in the study, with 32 enrolled in Part 1 (SAD) (N = 32, 18-63 years, BMI 25.6 ± 2.52 kg/m^2 [min = 20, max = 30]) and 32 enrolled in Part 2 (MAD) (N = 32, 19-61 years, BMI 26.2 ± 3.20 kg/m^2 [min = 20, max = 31]).

Of the 32 participants enrolled in Part 1 (SAD), 31 completed the study. A total of 24 participants received GLY-200, with six participants in each of the cohorts. All participants receiving GLY-200 completed the study. Seven of the eight participants who received placebo completed the study, with one participant withdrawn due to difficulty swallowing capsules. There were no serious AEs (SAEs) and no dose-limiting toxicities in the SAD study. Treatment-emergent AEs (TEAEs) were primarily dose-dependent gastrointestinal events, with most (93%) being mild. The TEAEs with the highest incidences on active treatment were nausea (33%) and decreased appetite (33%).

In Part 1 (SAD), there were no changes in weight over the duration of the study. Overall, single doses of up to 6 g GLY-200 administered in Part 1 (SAD) were generally well tolerated.

All 32 participants enrolled in Part 2 (MAD) completed the study. Twenty-four participants received active study drug, with three participants each in the 1.0-g twice-daily, 1.0-g three-times-daily and 3.0-g twice-daily cohorts, nine participants in the 2.0-g twice-daily cohort, and six participants in the 2.0-g three-times-daily cohort. Eight participants received placebo. There were no SAEs or severe TEAEs in Part 2 (MAD), and most (90%) of the TEAEs were mild dose-dependent gastrointestinal events. The TEAEs with the highest incidences on active treatment were nausea (58%), vomiting (50%), and decreased appetite (46%). Related TEAEs of at least moderate severity are shown in Table 1. In six participants, there were study drug interruptions due to gastrointestinal TEAEs, the majority of which (four participants) were in the 2.0-g three-times-daily group.

In Part 2 (MAD), there was a small dose-dependent decrease in weight over time. The mean (SD) change in weight from baseline on Day 6 was 0.1 kg (0.2), −0.7 kg (0.5), −1.4 kg (0.7), −1.7 kg (1.6) and −1.7 kg (0.4) for the 1.0-g twice-daily, 1.0-g three-times-daily, 2.0-g twice-daily, 2.0-g three-times-daily and 3.0-g twice-daily groups, respectively. The placebo groups had a slight weight gain over this time, with a mean weight increase of 0.5 kg (1.1) on Day 6.

In Part 2 (MAD), tolerability signals were limited to dose-dependent mild gastrointestinal events (nausea and vomiting) that resolved quickly on withholding a scheduled dose. The data suggest that twice-daily administration was better tolerated than three-times-daily administration.

There were no safety signals identified in either Part 1 (SAD) or Part 2 (MAD) based on AEs, vital signs, ECGs, and physical examination. There were no changes in urine phosphate, urate or oxalate over the 5 days of dosing. Doses of 0.5 to 2.0 g GLY-200 were well tolerated in the SAD/MAD study when administered twice daily.

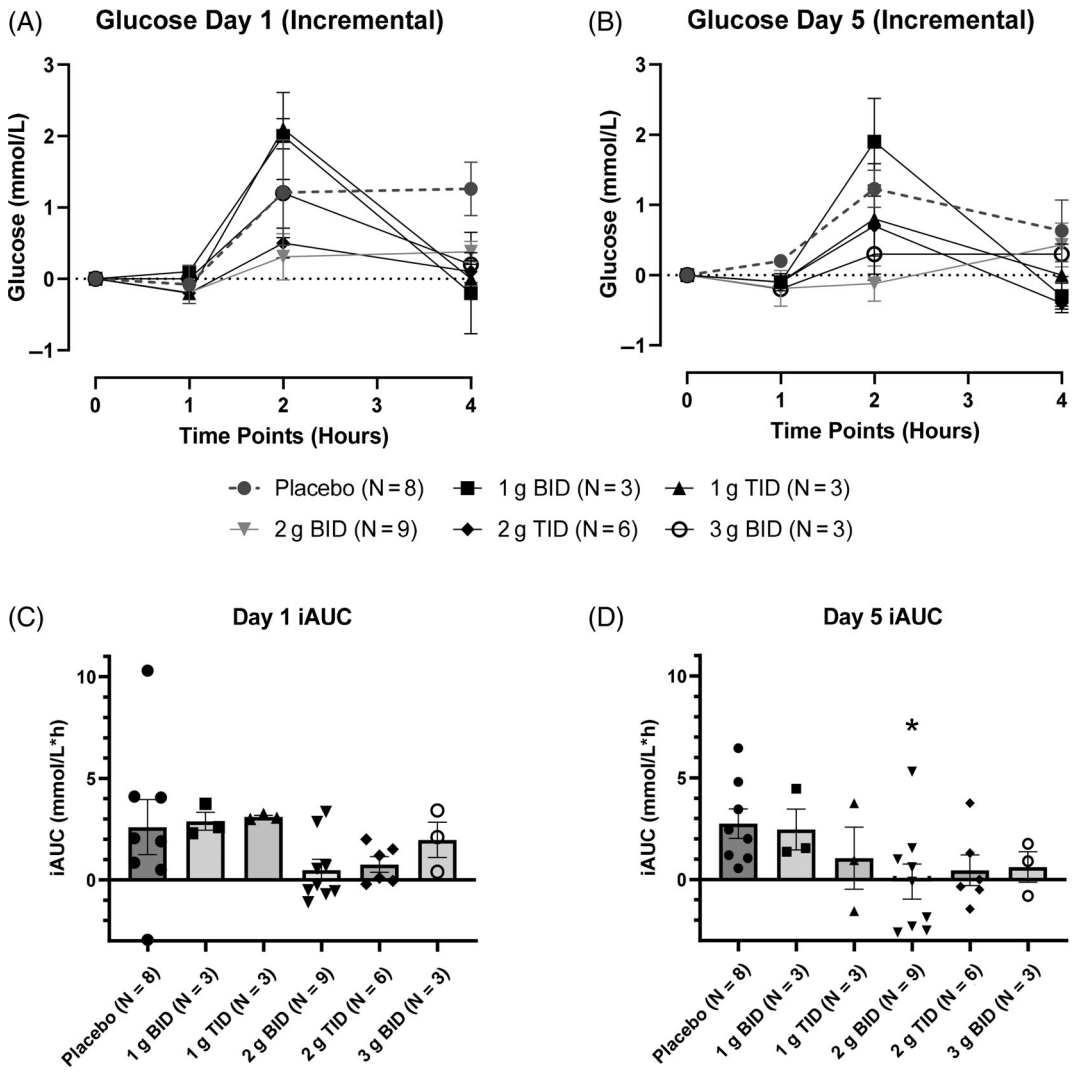

FIGURE 1 Effect of GLY-200 treatment on postprandial serum glucose. Mean incremental change from baseline in serum glucose following a meal on A, Day 1 and B, Day 5 of placebo or GLY-200 administration. GLY-200 dosing occurred at Hour 0 and a nonstandardized meal was consumed at Hour 1. Mean ± SEM. Incremental area under the curve (0-4 h) on C, Day 1 and D, Day 5. Mean ± SEM. *$P < 0.05$. Refer to Table S2 for mean observed values at baseline

3.2 | Effect of GLY-200 administration on glucose, insulin, bile acids and gut hormones

Although meals were not standardized, as discussed in the Materials and Methods above, serum glucose was assessed in response to the breakfast meal, which was provided 1 hour post-dose, on Day 1 and Day 5 of the MAD study for all doses. Other PD biomarkers were only assayed for the groups that underwent expansion and therefore had larger participant numbers (2.0 g twice daily, N = 9; placebo, N = 8). Table S2 shows the fasting values prior to dose on Day 1 and Day 5.

In the placebo group, serum glucose concentration increased in response to the meal, peaking at 4 hours post-dose or 3 hours post-meal on Day 1 (1.26 mmol/L incremental change from baseline; Figure 1A) and peaking at 2 hours post-dose or 1 hour post-meal on Day 5 (1.23 mmol/L incremental change from baseline; Figure 1B). The postprandial peak was blunted in the 2.0-g twice-daily group (N = 9) on Day 1 (0.38 mmol/L incremental change from baseline at 4 hours post-dose; Figure 1A), with a corresponding 82% reduction in incremental AUC (iAUC; Figure 1C). Similar results were seen on Day 5, when the blunted postprandial peak (0.43 mmol/L incremental change from baseline) was observed at 4 hours post-dose (Figure 1B) with a corresponding 104% reduction in iAUC ($P < 0.05$ compared to placebo; Figure 1D). The higher dose groups (2.0 g three times daily and 3.0 g twice daily) also tended to have blunted postprandial curves but were more variable, possibly reflecting the smaller sample sizes (N = 3-6). In the lower dose groups (1.0 g twice daily and 1.0 g three times daily), postprandial glucose was similar to placebo.

Similar to glucose, serum insulin concentration increased in response to the Day-1 and Day-5 meal in the placebo group, peaking at 2 hours post-dose or 1 hour post-meal (49.02 and 55.79 mU/L incremental change from baseline, respectively; Figures 2A and 3A). In

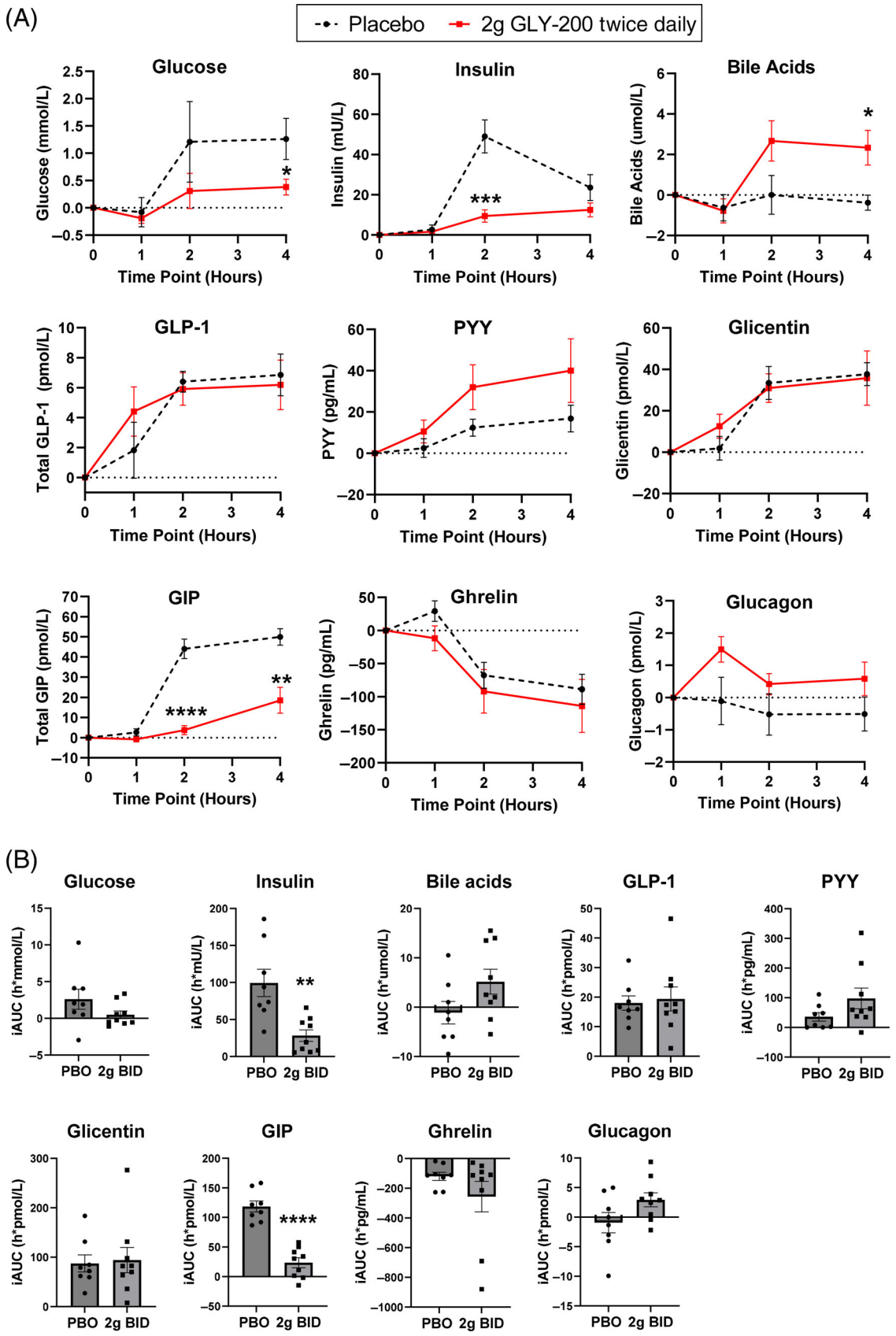

FIGURE 2 Postprandial biomarker profile following a single 2.0-g dose of GLY-200 compared to placebo. A, Mean incremental change from baseline in serum glucose, insulin, bile acids and gut hormones following a meal after the first dose of placebo (PBO; N = 8) or 2.0 g GLY-200 (N = 9) on Day 1. PBO or GLY-200 dosing occurred at Hour 0 and a nonstandardized meal was consumed at Hour 1. Mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. B, Incremental area under the curve (iAUC; 0-4 h) calculated from graphs in A. Mean ± SEM. **$P < 0.01$, ****$P < 0.0001$. Glucose panels in A, and B, are adapted from Figure 1A, C. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY

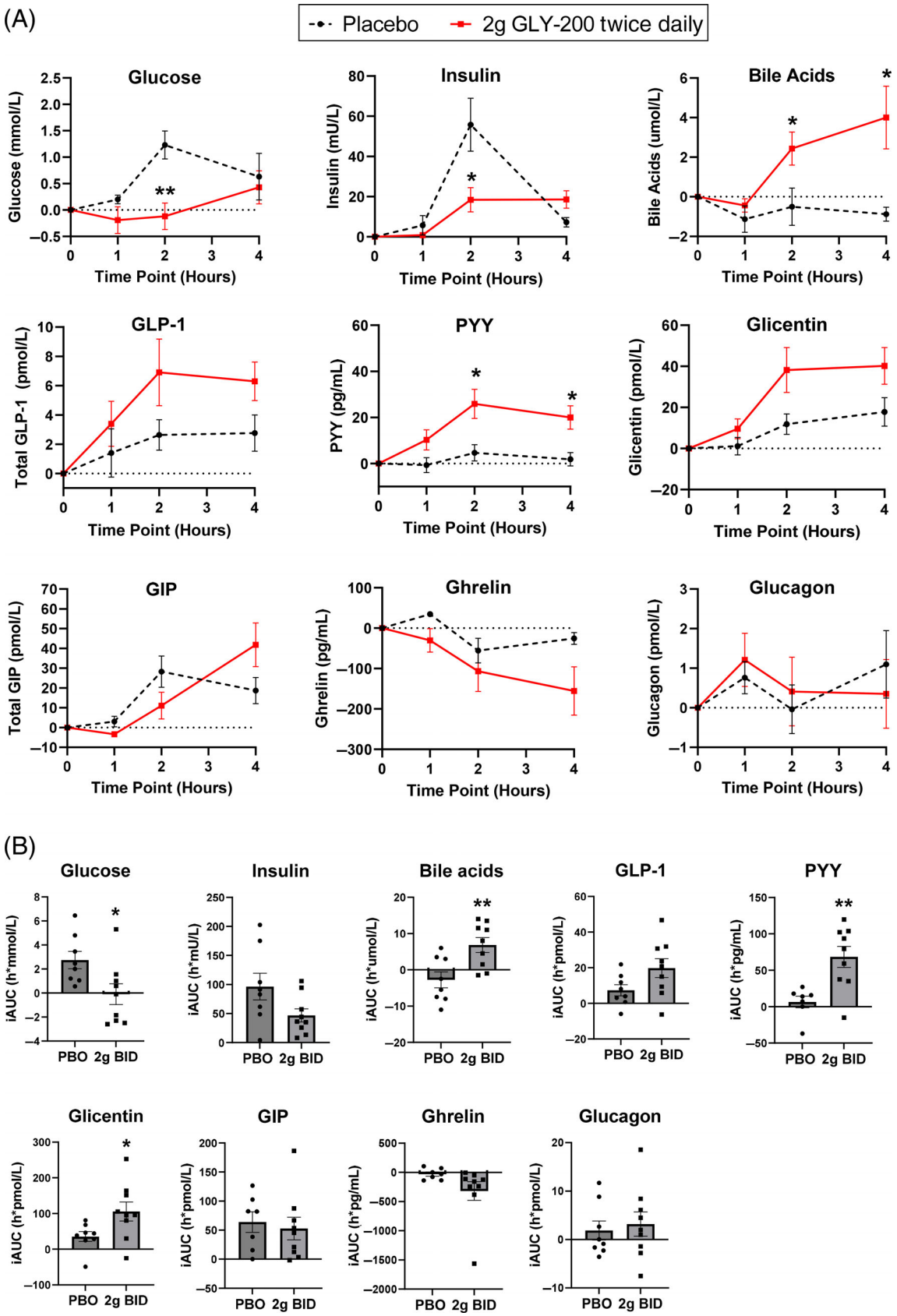

FIGURE 3 Postprandial biomarker profile on Day 5 of 2.0-g twice-daily GLY-200 treatment compared to placebo. A, Mean incremental change from baseline in serum glucose, insulin, bile acids and gut hormones following a meal after the morning dose of placebo (PBO; N = 7 for peptide YY [PYY], glucose-dependent insulinotropic polypeptide [GIP] and ghrelin, N = 8 for all others) or 2.0-g twice-daily GLY-200 (N = 9) on Day 5. PBO or GLY-200 dosing occurred at Hour 0 and nonstandardized meal was consumed at Hour 1. Mean ± SEM. *$P < 0.05$, **$P < 0.01$. B, Incremental area under the curve (iAUC; 0-4 h) calculated from graphs in A. Mean ± SEM. *$P < 0.05$, **$P < 0.01$. Glucose panels in A, and B, are adapted from Figure 1B, D

the 2.0-g twice-daily group, the increase in insulin in response to the Day-1 and Day-5 meals was smaller, with a significant reduction 2 hours post-dose ($P < 0.001$ and $P < 0.05$, respectively) and peaking at 4 hours post-dose (12.53 and 18.6 mU/L incremental change from baseline, respectively) (Figures 2A and 3A). On Day 1, there was a 72% reduction in mean iAUC ($P < 0.01$ compared to placebo) (Figure 2B) and on Day 5, there was a 51% reduction (Figure 3B).

The postprandial responses of bile acids and GLP-1, PYY and glicentin were greater in the 2.0-g twice-daily group compared to placebo, with the most robust differences observed on Day 5 (Figures 2 and 3). In the 2.0-g twice-daily group, GIP was reduced postprandially compared to placebo on Day 1, but not on Day 5. Mean ghrelin was slightly lower postprandially in the 2.0-g twice-daily group compared to placebo on both Day 1 and Day 5, but these differences were not statistically significant. The postprandial response of glucagon was more variable, with a slight postprandial increase in the 2.0-g twice-daily group compared to placebo on Day 1 that was not observed on Day 5. Significant differences between groups are noted in Figures 2 and 3.

4 | DISCUSSION

This clinical study is the first to explore duodenal exclusion physiology via a noninvasive (oral) pharmacological approach. It is also the first to show that the duodenal exclusion biomarker signature (elevations in bile acids and L-cell gut hormones) observed in patients with diabetes and/or obesity is also present in healthy volunteers. Due to the invasive nature of bariatric surgery and duodenal exclusion devices, no studies have been conducted on these interventions in this population. The ability of GLY-200 to lower postprandial glucose and insulin and increase postprandial gut hormones in healthy individuals highlights the physiological importance of duodenal signalling in maintaining normal weight and glycaemic homeostasis.

The importance of the gastrointestinal tract in the regulation of metabolism has been previously underscored by the profound effects of metabolic surgery on glycaemia and body weight through changes in several signalling pathways. Notably, RYGB results in several metabolic changes that are distinct from what occurs with caloric restrictive diets, suggesting that reduced nutrient absorption is not the main effect of the surgery.[17] These changes include an increase in energy expenditure, enhanced secretion of glucoregulatory and satiety-inducing gut hormones such as GLP-1, PYY and glicentin, reduced appetite, changes in food preference, increases in circulating total bile acids, and changes to the luminal bile acid pool and the gut microbiota.[10,11,18-20] These combined actions may explain the durability of effect observed with surgery that is rarely observed with sustained caloric restriction.

The trend towards lower postprandial glucose and insulin levels in participants receiving GLY-200 (2.0 g twice daily and 2.0 g three times daily) versus placebo and the dose-dependent trend towards a decrease in mean weight over time observed in Part 2 (MAD) may be reflective of reduced caloric intake, consistent with TEAEs that were reported by some participants (reduced appetite, nausea and vomiting). However, postprandial increases in bile acids, GLP-1, PYY and glicentin, while fasting levels remained generally unchanged, strongly suggest a pharmacological effect (ie, not a consequence of eating less) that mimics the effects of RYGB. Notably, we observed robust changes in glucose, insulin, bile acids and PYY with just a single dose on Day 1, and greater increases in GLP-1 and glicentin on Day 5. These data constitute a biomarker signature suggesting that 5 days of GLY-200 dosing modulates intestinal signalling in healthy participants through direct effects on the gastrointestinal environment. Interestingly, our GLP-1 results are consistent with those of Kirwan et al, who showed enhanced postprandial GLP-1 secretion after RYGB with oral meal administration but not when administered via a tube placed in the gastric remnant to deliver nutrients through the excluded proximal small bowel.[21]

In this first-in-human study of GLY-200, no treatment- or dose-related safety signals were observed. Tolerability signals were limited to dose-dependent mild and moderate gastrointestinal events consistent with the mechanism of action. The 2.0-g twice-daily dose regimen was well tolerated, with no moderate or severe AEs being reported and no dose holidays needed. The 3.0-g dose and three-times-daily regimens appeared to be less well tolerated. Notably, reduced appetite was a commonly reported TEAE in this Phase 1 safety study but would be considered a positive effect, as described above, in studies focused on efficacy. Not surprisingly, the gastrointestinal AE profile observed in this trial, including observations of nausea, is similar to healthy volunteer studies of GLP-1 receptor agonists.[22-24] Importantly, it is well known that dose titration improves the tolerability of higher-dose GLP-1 receptor agonism,[25] and a similar strategy may be useful for GLY-200 when exploring higher doses in chronic studies.

This Phase 1 study has several limitations, including the 5-day duration of treatment, which is insufficient to evaluate the impact of GLY-200 on HbA1c and body weight. An additional limitation is that meals consumed by the participants were not standardized and caloric intake was not documented during the study. Therefore, reduced food consumption and effects of varied meal contents could be confounders in the interpretation of postprandial responses. Additionally, postprandial PD samples were only collected over a duration of 3 hours, making it difficult to rule out the possibility that the observed reduction in postprandial glucose was due to a delay in absorption. Despite these limitations, however, significant increases in bile acids and gut hormones were observed in the postprandial period compared to placebo and the differences would likely be greater with standardized meals. Lastly, although the exploratory PD results in this healthy population suggest an acute effect on normal physiology, it remains to be seen how this will translate to patients with T2D and/or obesity. It would be reasonable to speculate, however, that the glucose-lowering and weight loss effect would be greater in these groups. Despite these limitations, the safety, tolerability and preliminary PD results support further development of GLY-200, a non-absorbed, orally administered polymer drug, in subjects with diabetes and/or obesity.

AUTHOR CONTRIBUTIONS

Kevin Colbert, Thomas H. Jozefiak, John S. Petersen, Michael Horowitz, Jiten Vora, Christopher K. Rayner, Paul Wabnitz, and Ashish Nimgaonkar were involved in the conception, design, and conduct of the study and the interpretation of the results. Mark S. Fineman and Christine L. N. Bryant were involved in the conduct of the study and the analysis and interpretation of the results and wrote the initial draft of the manuscript. All authors edited, reviewed, and approved the final version of the manuscript. Mark S. Fineman and Ashish Nimgaonkar are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

Mark S. Fineman, Christine L. N. Bryant, Kevin Colbert, Thomas H. Jozefiak, John S. Petersen, and Ashish Nimgaonkar are employees of Glyscend Therapeutics and own stock in the company. Ashish Nimgaonkar receives royalties or licences from Johns Hopkins University. Michael Horowitz has received honoraria for lectures from Eli Lilly and iNova; he is a Glyscend Therapeutic and Satiogen shareholder. Christopher K. Rayner has received consulting fees and/or honoraria for participation in a Data Safety Monitoring Board and/or honoraria for lectures paid to his institution by Glyscend Therapeutics and Eli Lilly; he received research funding paid to his institution by Sanofi, Novartis, National Health and Medical Research Council of Australia, and support from International Diabetes Federation for travel/meeting attendance. No other potential conflicts of interest relevant to this article were reported.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15066.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed in the current study are available from the corresponding authors upon reasonable request.

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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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