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Adaptive infusion of a glucagon-like peptide-1/glucagon receptor co-agonist G3215, in adults with overweight or obesity: Results from a phase 1 randomized clinical trial

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Abstract

Aims: To determine whether a continuous infusion of a glucagon-like peptide receptor (GLP-1R)/glucagon receptor (GCGR) co-agonist, G3215 is safe and well tolerated in adults with overweight or obesity.

Methods: A phase 1 randomized, double blind, placebo-controlled trial of G3215 in overweight or obese participants, with or without type 2 diabetes.

Results: Twenty-six participants were recruited and randomized with 23 completing a 14-day subcutaneous infusion of G3215 or placebo. The most common adverse events were nausea or vomiting, which were mild in most cases and mitigated by real-time adjustment of drug infusion. There were no cardiovascular concerns with G3215 infusion. The pharmacokinetic characteristics were in keeping with a continuous infusion over 14 days. A least-squares mean body weight loss of 2.39 kg was achieved with a 14-day infusion of G3215, compared with 0.84 kg with placebo infusion ($p < .05$). A reduction in food consumption was also observed in participants receiving G3215 and there was no deterioration in glycaemia. An improved lipid profile was seen in G3215-treated participants and consistent with GCGR activation, a broad reduction in circulating amino acids was seen during the infusion period.

Conclusion: An adaptive continuous infusion of the GLP-1/GCGR co-agonist, G3215, is safe and well tolerated offering a unique strategy to control drug exposure. By allowing rapid, response-directed titration, this strategy may allow for mitigation of adverse effects and afford significant weight loss within shorter time horizons than is presently possible with weekly GLP-1R and multi-agonists. These results support ongoing development of G3215 for the treatment of obesity and metabolic disease.

KEYWORDS
glucagon, glucagon-like peptide-1, multi-agonist, obesity, weight loss

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1 | INTRODUCTION

Obesity is associated with developing several non-communicable diseases, including cardiovascular, musculoskeletal, neurological and metabolic disease, in addition to certain types of cancer.[1] Bariatric surgery has been the frontrunner intervention as it achieves long-term and sustainable weight loss with clear benefits for mortality.[2] Advances in peptide biochemistry coupled with our increasing understanding of the biology of various gut hormones, has paved the way for pharmacotherapeutics with moderate weight-loss efficacy such as the glucagon-like peptide-1 (GLP-1) analogue semaglutide.[3] The quest for improved safety and efficacy over these existing options has driven the discovery and development of multi-agonists.[4] These act on several hormone receptors involved in energy balance, for example the co-agonist tirzepatide, which targets the GLP-1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide receptor (GIPR).[4,5]

In animal models of obesity, diabetes and metabolic-associated fatty liver disease, GLP-1R and glucagon receptor (GCGR) co-agonism leads to enhanced weight loss, loss of hepatic fat and improvements in glycaemia over targeting GLP-1R alone.[6–8] This strategy leverages GLP-1R-mediated reduction in food intake in addition to GCGR-mediated enhanced energy expenditure and hepatic lipid catabolism. Co-agonism of GLP-1R and GCGR has also been shown to be viable in humans where the hyperglycaemic effects of GCGR activity are mitigated by GLP-1R, and activation of the GCGR promotes energy expenditure and food intake suppression.[9,10] Subsequently, several GCGR-targeted multi-agonists have progressed to early phase clinical trials and have shown promising initial results, including the GLP-1R/GCGR co-agonists LY3305677,[11] cotadutide[12] and BI 456906.[13] More recently, GLP-1R/GIPR/GCGR triple agonists such as SAR441255[14] and retatrutide/LY3437943[15,16] have been tested in clinical trials.

However, long-acting multi-agonists have faced some obstacles to their development. For example, there has been a high frequency of gastrointestinal side effects in some early human trials of GLP-1R/GCGR co-agonists, leading to study discontinuation.[17,18] Cardiovascular and metabolic safety concerns have also been reported.[19] The biological effects of multi-agonists may also vary with chronicity of treatment, with the possibility that chronic treatment may lead to receptor de-sensitization.[20] Therefore, a multi-agonist with an initially optimal balance of receptor activities may become suboptimal with continued treatment. Another caveat of GCGR-targeted multi-agonists is the consistent finding of reduced circulating amino acids,[14,19,21,22] in keeping with the known stimulatory action of glucagon on hepatic amino acid catabolism.[23,24] The consequence of protracted action at the GCGR may lead to undesired side effects such as prolonged hypoaminoacidaemia and possible lean mass loss.[25,26] Lastly, the protocols for weekly injection long-acting GLP-1R mono- and GLP-1R/GCGR co-agonists have employed slow titration regimens to improve tolerability for the majority but at the cost of obtaining relatively slower weight loss. Hence, exploration of more flexible dosing strategies of this class of drug is warranted. A subcutaneous infusion could be titrated upwards over a shorter time frame, potentially leading to more rapid weight loss; this may be desired in certain circumstances, e.g. when weight loss is required for patients to undergo life-saving surgery.

We have designed a unimolecular GLP-1R/GCGR co-agonist, G3215, which, following pre-clinical evaluation, was tested in first-in-human (FIH) trials (NCT02692040). As part of these FIH trials, G3215 was delivered as a continuous infusion to healthy adults over 72 h and was shown to be safe. We report herein the subsequent randomized, double-blind, placebo-controlled phase 1 trial in overweight/obese adults where we assessed the safety and tolerability of a 14-day continuous infusion of G3215, given in an adaptive protocol.

2 | METHODS

2.1 | Study design and population

This single-centre, randomized, double-blind, placebo-controlled phase 1 trial was carried out at the NIHR Imperial Clinical Research Facility, Imperial Centre for Translational and Experimental Medicine, Hammersmith Hospital, London, UK. The trial was conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines. Ethical review and approval were granted by the MHRA (UK) and the UK Health Research Authority (HRA) National Research Ethics Service (NRES).

Eligible participants included adult males aged 18-65 years with a body mass index between 25 and 45 kg/m^2, with or without or type 2 diabetes (WHO 2006 and 2011 criteria[27,28]). A full list of eligibility criteria is available (Supplementary Appendix S1).

2.2 | Peptide and preparation

G3215 is a peptide analogue of oxyntomodulin (OXM), an endogenous gut hormone with activity at both the GLP-1R and GCGR. G3215 was selected by screening over 2000 analogues for GLP-1R and GCGR binding and cAMP accumulation. The primary peptide sequence of G3215 is characterized by amino acid deletions or substitutions predicting enhanced activity at both the GLP-1R and GCGR compared with native oxyntomodulin. The peptide did not contain a half-life enhancing group, therefore resulting in a predicted circulatory half-life of minutes in humans. Biological activity was assessed in rodent models showing enhanced satiety and weight loss effects (data not shown). G3215 was manufactured according to Good Manufacturing Practice (GMP) requirements by Almac Sciences and Symbiosis Pharmaceutical Services Limited. The Investigative Medicinal Product (IMP) was manufactured by Imperial College Healthcare NHS Trust Pharmacy where G3215 was reconstituted and diluted in sterile 0.9% saline solution. Sterile 0.9% saline was used as placebo and visually matched the G3215 product, both of which were provided to the blinded study team.

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2.3 | Randomization

Once randomization had been activated by the study investigator using the Oracle Inform data capture system, participants were automatically allocated to their treatment arm. Participants were allocated into three sequential cohorts of eight participants. Within each cohort, two participants received placebo and six participants received G3215. A sentinel pair of study participants were randomly allocated 1:1 to either G3215 or placebo. Following the sentinel pair, study participants were randomly allocated to G3215 or placebo, in a 5:1 ratio. In the event of participant withdrawal from the study, replacement participants were recruited and randomized within the same cohort.

2.4 | Study protocol and procedures

Participants underwent a 14-day continuous subcutaneous infusion of G3215 or placebo (Figure 1). On day −1, participants underwent a 75 g oral glucose tolerance test followed by an ad libitum food intake study for lunch and dinner. On day 1, following an ad libitum food intake study for breakfast, a subcutaneous infusion set (Advanced Therapeutics, UK) was attached to the lower right abdominal area and a Dana Rs infusion pump (Advanced Therapeutics, UK) containing the allocated treatment vial was attached. The infusion site, set and treatment vial were changed every 24-72 h throughout the 14-day infusion period. All participants remained in the Clinical Research Facility

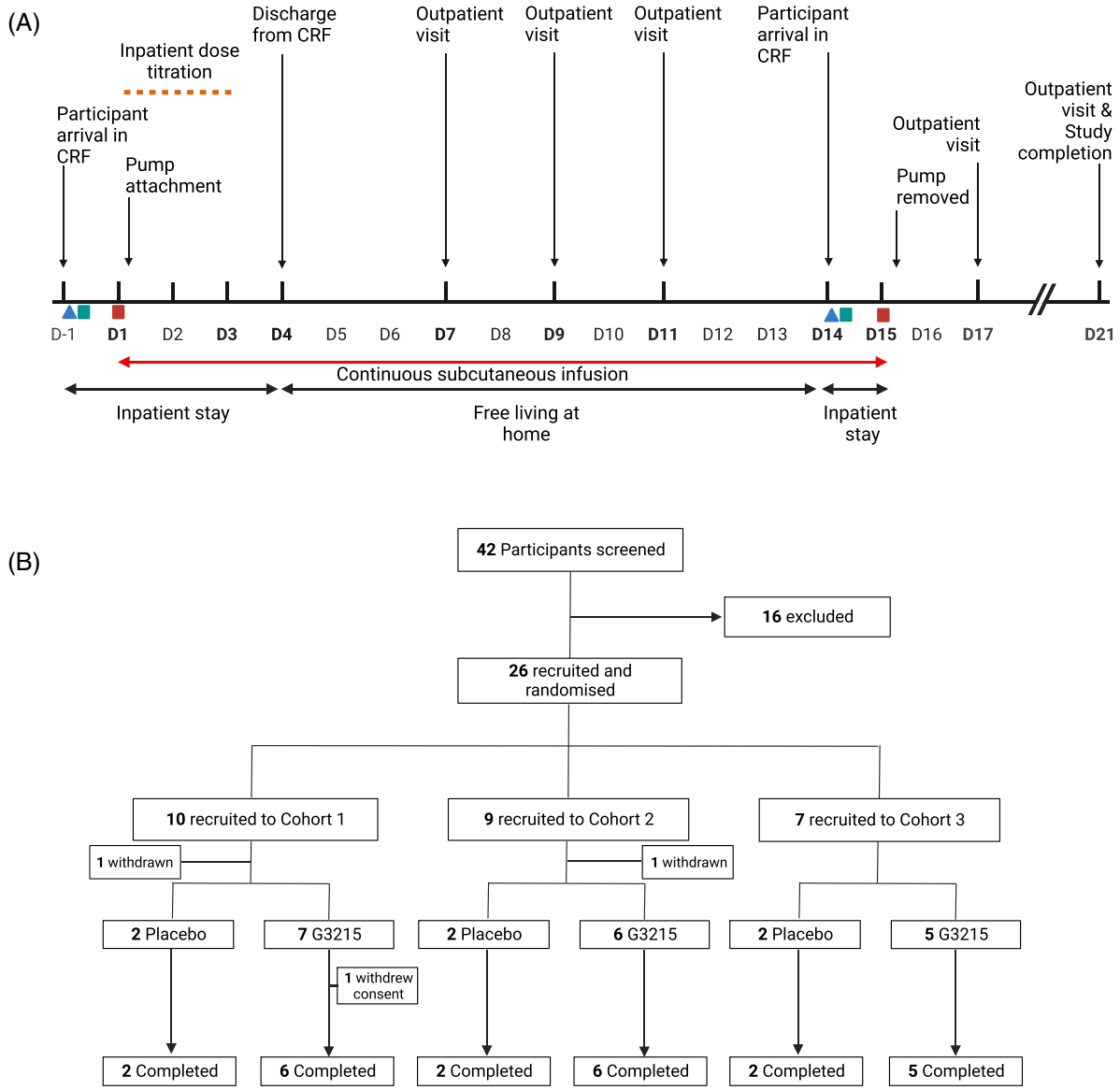


FIGURE 1 Timeline and recruitment of participants to the 14-day subcutaneous infusion of G3215 phase 1 trial. (A) Study timeline with participants arriving in the Clinical Research Facility (CRF) on day −1. Pump attachment on day 1 for continuous subcutaneous administration over 14 days. Pump infusion set and allocated treatment vial changed on each study day (in bold). Blue triangle, 75 g oral glucose tolerance test; green square, lunch and dinner food intake study; red square, breakfast food intake study. (B) Participant recruitment and randomization to study cohort groups.

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for dose uptitration during the first 3 days before discharge home on day 4 with pump self-care instructions. Participants returned on days 7, 9 and 11 for pharmacokinetic (PK), safety and pharmacodynamic (PD) assessments. If there is an adverse event (AE), a pre-determined adjustment of dose was made. On day 14, participants returned to the Research Facility for a repeat oral glucose tolerance test and ad libitum food intake study for lunch and dinner meals (Figure 1). Following an ad libitum breakfast food intake study on day 15, the infusion pump was permanently discontinued. Participants returned for final visits on day 17 and day 21. For the 24-h ad libitum food intake studies, a choice of meals of similar caloric density (Sainsbury's Supermarkets Ltd) were offered and meals were kept the same for both studies; participants were asked to eat until comfortably full. Nausea was subjectively assessed using visual analogue scales and participants were also instructed to inform the study team if there was an onset of symptoms at any time during the infusion period. Body weight was measured using a Tanita weighing scale (Tanita, MC-780MA P). Vital signs including heart rate and blood pressure were measured in the fasting state each morning.

The study aimed to include participants with normoglycaemia in cohort 1, whereas participants with or without type 2 diabetes could be recruited in subsequent cohorts. Participants with type 2 diabetes were stably treated and temporarily discontinued their diabetes treatment during the study period.

The primary outcome was the safety and tolerability of the 14-day subcutaneous infusion of G3215. The secondary outcome was the PK profile of G3215. Exploratory PD outcomes included body weight, food intake, glycaemic control and circulating levels of lipids and amino acids.

2.4.1 | Subcutaneous pump dose titration

The infusion rate for the allocated treatment was changed using the Dana Rs pump unit and translated to pre-determined doses. In each cohort, different dose titration strategies were used during the first 3 days of the initial inpatient stay of the study. These variations were designed to establish whether changes in starting dose and initial titration affected tolerability. In cohort 1 we typically aimed to commence G3215 at a dose of 0.2 mg/day, increasing by 0.1 mg/24 h each day for the first 3 days. For cohort 2, we aimed to commence G3215 at a dose of 0.4 mg/24 h, increasing by 0.2 mg/24 h each day for the first 3 days. For cohort 3, we aimed to commence G3215 at a dose of 0.2 mg/24 h, increasing by 0.2 mg/24 h each day for the first 3 days. In each cohort, following discharge on study day 4 we aimed to increase the dose of G3215 by 0.1 mg/24 h at each outpatient visit until the final study day 15. As the change in pump setting was made for infusion rate for both treatment groups, G3215 and placebo, this rate applied to the dose of G3215 administered and the rate of saline infusion (placebo). A specific dose-reduction protocol was implemented in response to a treatment-emergent AE (TEAE); this was pre-programmed into the pump unit and participants were educated on how to access this change. For example, during the infusion period if the participants experienced nausea, the infusion rate and, therefore G3215 dose was reduced by 50%. Once nausea dissipated, the infusion was recommenced at 75% and then 100% of the original rate in 2-h intervals if tolerated. In the event of vomiting, the infusion was stopped and restarted in the same way an hour after any nausea had dissipated. In some cases, the infusion rate did not return to the original rate, and this was based on the discretion of the principal investigator.

2.5 | Quantification and statistical analysis

The study design planned to recruit a total of 24 subjects into three cohorts, consistent with other phase 1 exploratory studies.[29] AEs were summarized as the frequency of TEAEs including severity and relationship to the study drug. PK analysis was performed in participants who received at least one dose of the study drug. PK parameters were derived by non-compartmental analysis using Phoenix WinNonlin Version 8.3 (Certara Inc.). $AUC_{0\text{-}t}{}^{\#}$ represents the area under the concentration versus time curve from time 0 to the time of the last PK sample, calculated from extrapolated values which were below limits of quantification and by the mixed linear/log trapezoid rule. As plasma concentrations for most measurements were below the limit of quantification, the AUC was calculated using extrapolated values from peak areas ratios and therefore interpreted with caution. Individual amino acids were measured using gas chromatography/mass spectrometry (WellChild laboratory, Evelina Children's Hospital, St Thomas's Hospital, London, UK). A complete-cases analysis was performed for PD outcomes. For body weight, energy intake and metabolic parameters, the least squares mean change from baseline and timepoint-specific group differences are reported with 95% confidence intervals. Statistical analysis was carried out using Stata software release 17 (StataCorp LLC).

3 | RESULTS

3.1 | Participants and demographics

Between November 2020 and August 2021, 42 individual subjects were screened for entry into the phase 1 trial (ISRCTN67889041). Of the 42 participants screened, 26 met the eligibility criteria, 24 received study infusion and 23 participants completed a 14-day continuous infusion of G3215 or placebo (Figure S1 in Appendix S1). Ten participants were recruited to cohort 1, nine participants to cohort 2 and seven participants to cohort 3. Two participants were withdrawn from the study before commencing on the allocated treatment infusion, one with ECG changes and another with hypoglycaemia. One participant in the G3215 group withdrew consent on day 2 because of nausea and vomiting (Figure 1). All participants were male and the majority were from a white ethnic group (Table 1). Mean age, body weight, height, body mass index and glycated haemoglobin were similar across cohorts.

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TABLE 1 Baseline demographics of trial participants.

Cohort	Placebo (aggregated)	1	2	3
Number	7	7	7	5
Age, years	50.7 (10.5)	51.3 (9.4)	51.0 (11.6)	44.0 (17.1)
Weight, kg	92.1 (18.3)	95.9 (19.4)	100.8 (15.2)	95.2 (13.0)
Height, cm	173.4 (8.3)	174.7 (5.4)	179.4 (7.0)	178.4 (7.7)
BMI, kg/m^2	30.4 (4.2)	31.2 (4.6)	31.4 (5.2)	29.8 (2.3)
Waist circumference, cm	106.8 (19.5)	105.9 (16.2)	101.8 (9.9)	101.4 (5.9)
SBP, mmHg	120.3 (15.0)	122.7 (7.1)	138.3 (17.7)	121.6 (10.5)
DBP, mmHg	70.4 (5.5)	77.4 (11.0)	85.0 (10.3)	75.6 (15.4)
Triglycerides, mmol/L	1.1 (0.5)	1.8 (0.8)	1.4 (0.5)	1.8 (0.8)
Total cholesterol, mmol/L	4.2 (1.5)	4.8 (1.1)	4.6 (1.1)	4.5 (1.2)
Fasting glucose, mmol/L	6.0 (1.4)	6.0 (1.0)	5.9 (1.5)	5.1 (0.9)
HbA1c, mmol/mol	44.6 (13.4)	41.3 (6.42)	42.2 (10.3)	37.6 (4.5)
Ethnicity, White/Asian/Black/Mixed/Other	5:1:1:0:0	4:1:1:0:1	5:0:1:1:0	3:2:0:0:0

Note: Including all enrolled male participants allocated to placebo (aggregated across all cohorts) and G3215 treatment cohorts 1-3. Demographic parameters including age, weight, height, BMI, waist circumference, SBP, DBP, triglycerides, total cholesterol, fasting plasma glucose, HbA1c and ethnicity. Data presented as mean (SD).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; SBP, systolic blood pressure.

3.2 | Pharmacokinetics

Despite the differences in the initial titration regimens between cohorts, the maximum infusion dose reached at day 3 and throughout the study varied within cohorts because of differences in individual sensitivity to the infusion (Table S1 in Appendix S1). The highest cumulative doses were achieved in cohort 2 where the starting and initial titration dose was highest (Table S1 in Appendix S1). In some participants, the day 3 dose achieved was lower than expected because of individual sensitivity, and this guided a more cautious titration at subsequent outpatient visits and hence the maximum infusion dose achieved. This adaptive dosing strategy naturally entailed high between-subject variability in systemic exposures of G3215. The traditional PK values of a fixed-dose, periodic dosing strategy cannot be presented, and terminal half-life was not estimable. Cumulative doses given ranged up to approximately 12 mg (Table S1 in Appendix S1), 1/10th of the safe and tolerated maximum cumulative dose given in the FIH trial (NCT02692040). Area under the curve (AUC) data representing exposure is available in the supplementary data (Table S2 in Appendix S1).

3.3 | Safety and adverse events

G3215 was well tolerated across the three cohorts (Table 2). The most common TEAE was nausea or vomiting. In cohort 1, seven of seven participants who received G3215 experienced a TEAE and all events (13 of 13 events, 100%) were mild in severity. Of these mild events, six of 13 (46%) were gastrointestinal including nausea, vomiting or dyspepsia (Table S3 in Appendix S1). One participant from cohort 1 withdrew consent following pump infusion commencement because of nausea and vomiting. In cohort 1, seven of 13 (54%) AEs were related to the study treatment (Table S4 in Appendix S1). In cohort 2, five of six participants who received G3215 experienced a TEAE and most of these events (10 of 12 events, 83%) were mild in severity (Table 2). Of these mild severity events, nine of 10 (90%) comprised of gastrointestinal, including nausea, vomiting or dyspepsia (Table S3 in Appendix S1). There were two moderate TEAEs (two of 12 events, 17%) including nausea and vomiting. In cohort 2, 11 of 12 (92%) AEs were related to the study treatment (Table S4 in Appendix S1). In cohort 3, four of five participants who received G3215 experienced a TEAE and most of these events (nine of 10 events, 90%) were mild in severity (Table 2). Of these mild events, five of nine (56%) were gastrointestinal, including nausea, vomiting or constipation (Table S3 in Appendix S1). There was one moderate TEAE (one of 10 events, 10%) in an individual reporting headache. In cohort 3, five of 10 (50%) of AEs were related to the study treatment (Table S4 in Appendix S1). Despite the minor changes in initial dose titration regimens, the increased frequency of gastrointestinal adverse effects that were related to study treatment in cohort 2 is relevant as the starting and daily increment doses were higher than other cohorts (Table S1 and Table 2). No adverse cardiovascular signs were noted from clinical assessment or electrocardiography (Tables S5 and S6 in Appendix S1). A sustained reduction in systolic blood pressure was evident in G3215-treated participants over the course of the study (Table S5 in Appendix S1).

3.4 | Body weight, food intake and metabolic parameters

An exploratory analysis was carried out to determine both change in body weight and 24-h food intake over the 14-day subcutaneous infusion period. In the participants treated with G3215, the cohort-

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TABLE 2 TEAEs by systems organ classification.

	Placebo	Cohort 1	Cohort 2	Cohort 3
Participants	6	7	6	5
Reporting TEAEs	3	7	5	4
With SAEs	0	0	0	0
Discontinuation	0	1	0	0
SOC: no. of subjects (no. of AE)				
Gastrointestinal[a]				
Nausea	0	1 (1)	3 (5)	1 (1)
Vomiting	0	1 (1)	3 (5)	2 (3)
Constipation	0	0	0	1 (1)
Dyspepsia	0	2 (4)	1 (1)	0
General/admin site[b]	0	0	0	0
Immune system[c]	1 (1)	1 (1)	0	1 (1)
Infections/infestations[d]	0	0	1 (1)	1 (1)
Injury/poisoning/procedural[e]	0	1 (1)	0	0
Musculoskeletal/connective tissue[f]	0	1 (2)	0	0
Nervous system[g]	2 (2)	1 (2)	0	1 (2)
Respiratory/thoracic/mediastinal[h]	0	0	0	1 (1)
Skin/subcutaneous tissue[i]	1 (1)	1 (1)	0	0
Severity classification				
Total number of AE	4	13	12	10
Mild	4	13	10	9
Moderate	0	0	2	1
Severe	0	0	0	0
Relationship to drug/placebo administration (no. of AE)				
Not related	3	2	1	1
Unlikely related	0	4	0	4
Possibly related	1	4	2	1
Probably related	0	1	2	3
Definitely related	0	2	7	1

Note: Data presented for participants receiving placebo aggregated across cohorts, and G3215-treated participants in cohorts 1-3. Most common AE associated with each SOC are as follows. Data presented as no. of subjects (no. of AE).
Abbreviations: AE, adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.
[a]Gastrointestinal: nausea, vomiting, dyspepsia, constipation.
[b]General or administration site: injection site reactions, erythema, pain.
[c]Immune system: local reaction to adhesive.
[d]Infections/infestations: skin infections, urinary tract infections.
[e]Injury/poisoning/procedural.
[f]Musculoskeletal/connective tissue: joint pain, joint swelling.
[g] Nervous system: headaches.
[h]Respiratory/thoracic/mediastinal: cough.
[i]Skin/subcutaneous tissue: pruritic rash, eczema.

combined least-squares mean change in body weight from baseline at day 15 of infusion was −2.39 kg (95% confidence interval −2.98, −1.79; $p < .001$) compared with a −0.84 kg (−1.86, 0.17; $p = .104$) change from baseline in the participants treated with placebo (Figure 2); the mean placebo-subtracted body weight change at day 15 was −1.54 kg (−2.73, −0.36; $p < .05$). The mean placebo-subtracted weight change in the G3215-treated participants at day 15 in cohort 1 to 3 was −1.58 kg (−2.60, −0.56; $p < .01$), −1.85 kg (−3.34, −0.35; $p < .05$) and 0.95 kg (−2.23, 0.33; $p = .145$), respectively. Body weight loss over the infusion period was negatively correlated with the cumulative dose of G3215 received (Figure S2 in Appendix S1). The response to G3215 in terms of energy consumption mirrored the change in body weight (Figure 2). The mean placebo-subtracted energy intake in the cohort-combined G3215

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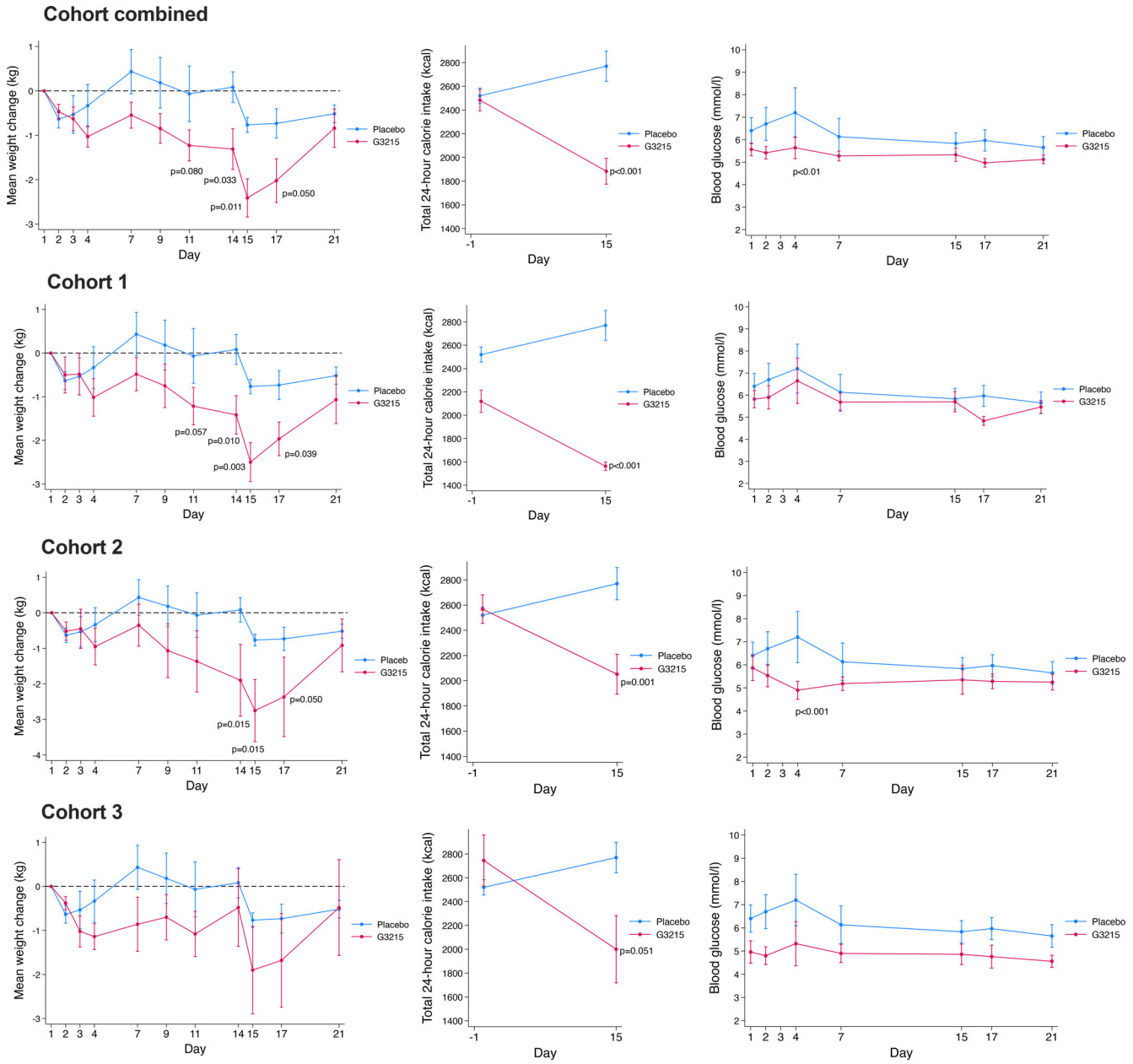


FIGURE 2 Change in body weight (kg), total 24-h food intake (kcal) and fasting blood glucose (mmol/L) in response to a continuous infusion of G3215 (red line) or placebo (blue line) over 15 days. Data presented for combined cohorts and individual cohorts for G3215; data for participants receiving placebo are aggregated from all cohorts. Mean plotted and error bars represent the SEM, *p*-values calculated for contrast of G3215 and placebo groups at the specified day of study (analysed by repeated measured mixed linear model analysis with baseline value as a covariate).

group at day 15 was −855.37 kcal (95% confidence interval −1155.82, −554.92; $p < .001$).

There was no evidence of a hyper- nor hypoglycaemic response to G3215 infusion (Figure 2, Figures S3 and S4 in Appendix S1). In the participants treated with G3215 across all cohorts, there was a significant reduction in total and LDL cholesterol at day 14, which returned to baseline at day 21 (Table 3). A reduction in triglycerides was observed in both groups, which was more pronounced in the G3215-treated participants. There was a broad reduction in circulating amino acids in G3215-treated participants, which plateaued between study days 7 and 14 and recovered by day 21, a week after the infusion was permanently discontinued (Table 4). Consistent with this, serum urea levels were significantly reduced in G3215-treated participants (Table 3). Alanine and aspartate transaminases were not adversely affected during the infusion period (Table 3) and in two participants there was a mild rise at day 21 after G3215 had been discontinued. A minor rise in C-reactive protein was observed in G3215-treated participants. Lipase levels were found to be mildly raised on average by day 15 of the study in G3215-treated participants and inspection of the data showed that two participants

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TABLE 3 Changes in lipid, liver and pancreatic markers in participants treated with placebo or G3215.

	Placebo (N = 6)	G3215 (N = 17)
Total cholesterol mmol/L		
Baseline	4.48	4.52
CFB Day 14	0.14 (−0.20, 0.48)	−0.81 (−1.01, −0.61)***
CFB Day 21	0.18 (−0.16, 0.51)	−0.11 (−0.32, 0.09)
LDL cholesterol mmol/L		
Baseline	2.59	2.60
CFB Day 14	0.27 (0.03, 0.51)*	−0.30 (−0.44, −0.15)***
CFB Day 21	0.17 (−0.07, 0.41)	−0.01 (−0.16, 0.13)
HDL cholesterol mmol/L		
Baseline	1.47	1.28
CFB Day 14	−0.30 (−0.52, −0.08) **	−0.26 (−0.39, −0.14)***
CFB Day 21	−0.26 (−0.48, −0.05)*	−0.18 (−0.31, −0.06)**
Triglycerides mmol/L		
Baseline	1.36	1.57
CFB Day 14	−0.32 (−0.65, −0.01)*	−0.61 (−0.81, −0.42)***
CFB Day 21	−0.11 (−0.44, 0.21)	0.11 (−0.08, 0.31)
Alanine transaminase U/L		
Baseline	31.17	33.35
CFB Day 7	0.89 (−10.86, 12.63)	−0.84 (−7.79, 6.11)
CFB Day 15	−4.11 (−15.86, 7.63)	−0.31 (−7.26, 6.64)
CFB Day 21	−6.28 (−18.02, 5.47)	11.10 (4.15, 18.05)**
Aspartate transaminase U/L		
Baseline	26.92	28.41
CFB Day 7	−0.59 (−7.17, 5.99)	−2.54 (−6.43, 1.35)
CFB Day 15	−5.42 (−12.00, 1.15)	−2.32 (−6.31, 1.66)
CFB Day 21	−4.59 (−11.17, −1.99)	5.58 (1.69, 9.47)**
Amylase U/L		
Baseline	74.88	74.42
CFB Day 7	5.18 (−9.33, 19.68)	−2.94 (−11.54, 5.65)
CFB Day 15	4.35 (−10.16, 18.85)	3.19 (−5.62, 12.00)
CFB Day 21	−4.49 (−18.99, 10.02)	2.53 (−6.07, 11.12)
Lipase U/L		
Baseline	36.27	37.31
CFB Day 7	12.17 (−12.77, 37.10)	6.50 (−8.31, 21.31)
CFB Day 15	12.17 (−12.77, 37.10)	30.75 (15.18, 46.33)***
CFB Day 21	−7.75 (−34.67, 19.16)	13.59 (−2.00, 29.17)
Urea mmol/l		
Baseline	5.05	5.18
CFB Day 7	0.79 (0.00, 1.59)*	−0.36 (−0.83, 0.11)
CFB Day 15	0.28 (−0.51, 1.07)	−1.08 (−1.55, −0.61)***
CFB Day 21	0.31 (−0.48, 1.10)	−0.62 (−1.08, −0.15)*
CRP mg/L		
Baseline	4.30	4.00
CFB Day 7	−0.02 (−1.72, 1.76)	1.37 (0.35, 2.39)**
CFB Day 15	−0.46 (−2.20, 1.28)	2.52 (1.49, 3.54)***
CFB Day 21	1.70 (−0.03, 3.44)	−0.04 (−1.06, 0.99)

Note: Data are presented for combined cohorts for participants receiving G3215; data for participants receiving placebo are aggregated from all cohorts. Data are presented as mean (95% confidence interval). Analysed by repeated measured mixed linear model analysis with baseline value as a covariate. *p*-Values calculated for change from baseline at the specified day of study.
Abbreviation: CFB, change from baseline.
*$p < .05$; **$p < .01$; ***$p < .001$.

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TABLE 4 Changes in circulating amino acids in participants treated with placebo or G3215.

	Placebo (N = 6)	G3215 (N = 10)
Alanine μmol/L		
Baseline	290.98	289.56
CFB Day 7	18.37 (−34.16, 70.91)	−110.80 (−151.46, −70.15)***
CFB Day 14	−17.74 (−70.27, 34.79)	−126.60 (−167.26, −85.95)***
CFB Day 21	17.86 (−34.67, 70.39)	120.68 (80.02, 161.33)***
Arginine μmol/L		
Baseline	73.42	74.75
CFB Day 7	20.14 (10.38, 29.90)***	−36.20 (−43.76, −28.65)***
CFB Day 14	−1.36 (−11.12, 8.40)	−39.97 (−47.53, −32.42)***
CFB Day 21	7.16 (−2.60, 16.92)	24.22 (16.66, 31.77)***
Asparagine μmol/L		
Baseline	33.50	34.09
CFB Day 7	5.62 (0.44, 10.79)*	−9.91 (−13.91, −5.91)***
CFB Day 14	1.92 (−3.26, 7.09)	−11.53 (−15.53, −7.53)***
CFB Day 21	4.87 (−0.31, 10.04)	5.66 (1.66, 9.66)**
Cysteine μmol/L		
Baseline	50.00	48.91
CFB Day 7	−0.32 (−4.52, 3.88)	−18.61 (−21.85, −15.37)***
CFB Day 14	0.38 (−3.82, 4.58)	−20.29 (−23.53, −17.05)***
CFB Day 21	1.20 (−3.00, 5.40)	3.48 (0.24, 6.72)*
Glutamate μmol/L		
Baseline	48.89	47.79
CFB Day 7	2.92 (−7.64, 13.48)	−23.19 (−31.37, −15.02)***
CFB Day 14	1.65 (−8.90, 12.21)	−24.43 (−32.61, −16.26)***
CFB Day 21	9.15 (−1.40, 19.71)	−3.70 (−11.88, 4.47)
Glutamine μmol/L		
Baseline	381.42	379.77
CFB Day 7	19.75 (−13.14, 52.65)	−127.62 (−153.09, −102.15)***
CFB Day 14	12.45 (−20.44, 45.35)	−152.90 (−178.37, −127.43)***
CFB Day 21	11.24 (−21.66, 44.13)	87.06 (61.59, 112.53)***
Glycine μmol/L		
Baseline	161.22	161.84
CFB Day 7	8.01 (−14.87, 30.90)	−55.66 (−73.37, −37.94)***
CFB Day 14	−7.72 (−30.61, 15.17)	−46.18 (−63.89, −28.46)***
CFB Day 21	3.81 (−19.07, 26.70)	71.61 (53.90, 89.33)***
Histidine μmol/L		
Baseline	63.00	63.62
CFB Day 7	5.60 (0.33, 10.87)*	−3.94 (−8.01, 0.13)
CFB Day 14	4.10 (−1.17, 9.37)	−9.33 (−13.40, −5.26)***
CFB Day 21	3.17 (−2.11, 8.44)	−3.54 (−7.61, 0.53)
Isoleucine μmol/L		
Baseline	57.48	56.30
CFB Day 7	17.40 (3.94, 30.87)*	−4.01 (−14.41, 6.38)
CFB Day 14	8.89 (−4.58, 22.35)	−6.62 (−17.02, 3.77)
CFB Day 21	3.30 (−10.16, 16.77)	2.20 (−8.20, 12.59)

(Continues)

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TABLE 4 (Continued)

	Placebo (N = 6)	G3215 (N = 10)
Leucine μmol/L		
Baseline	112.74	109.44
CFB Day 7	30.01 (8.83, 51.19)**	−8.58 (−24.96, 7.81)
CFB Day 14	10.59 (−10.58, 31.77)	−8.54 (−24.92, −7.85)
CFB Day 21	2.99 (−18.18, 24.17)	−2.13 (−18.51, 14.26)
Lysine μmol/L		
Baseline	190.20	191.94
CFB Day 7	59.78 (28.14, 91.42)***	−52.37 (−76.87, −27.87)***
CFB Day 14	29.47 (−2.17, 61.11)	−54.36 (−78.86, −29.86)***
CFB Day 21	40.80 (9.16, 72.44)*	35.58 (11.08, 60.08)**
Methionine μmol/L		
Baseline	18.34	18.26
CFB Day 7	6.23 (2.59, 9.87)**	−3.88* (−6.70, −1.06)**
CFB Day 14	2.75 (−0.89, 6.39)	−4.31 (−7.13, −1.49)**
CFB Day 21	1.68 (−1.96, 5.32)	2.10 (−0.72, 4.92)
Phenylalanine μmol/L		
Baseline	48.35	48.30
CFB Day 7	4.10 (−1.02, 9.21)	−0.86 (−4.82, 3.10)
CFB Day 14	6.23 (1.12, 11.35)*	−0.81 (−4.77, 3.15)
CFB Day 21	2.01 (−3.10, 7.13)	−1.72 (−5.68, 2.24)
Proline μmol/L		
Baseline	176.19	177.47
CFB Day 7	33.19 (−1.92, 68.30)	−102.03 (−129.22, −74.84)***
CFB Day 14	12.89 (−22.22, 48.00)	−100.82 (−128.01, −73.63)***
CFB Day 21	−0.75 (−35.86, 34.36)	30.00 (2.81, 57.19)*
Serine μmol/L		
Baseline	94.23	94.08
CFB Day 7	5.81 (−6.17, 17.79)	−24.58 (−33.86, −15.30)***
CFB Day 14	2.47 (−9.52, 14.44)	−28.19 (−37.47, 18.91)***
CFB Day 21	2.41 (−9.57, 14.39)	20.91 (11.63, 30.19)***
Threonine μmol/L		
Baseline	108.57	106.60
CFB Day 7	21.30 (0.68, 41.91)	−51.08 (−67.02, −35.14)***
CFB Day 14	1.86 (−18.75, 22.47)	−46.03 (−61.97, −30.09)***
CFB Day 21	1.55 (−19.07, 22.16)	78.66 (−62.72, 94.60)***
Tryptophan μmol/L		
Baseline	39.42	39.97
CFB Day 7	2.10 (−1.93, 6.13)	−3.93 (−7.05, −0.81)*
CFB Day 14	−0.91 (−4.94, 3.12)	−3.50 (−6.62, −0.38)*
CFB Day 21	−1.73 (−5.76, 2.30)	−1.12 (−4.24, 2.00)
Tyrosine μmol/L		
Baseline	50.63	51.40
CFB Day 7	10.85 (2.79, 18.91)**	−12.41 (−18.65, −6.17)***
CFB Day 14	7.77 (−0.29, 15.83)	−9.88 (−16.12, −3.64)**
CFB Day 21	4.05 (−4.01, 12.11)	6.04 (−0.20, 12.28)

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TABLE 4 (Continued)

	Placebo (N = 6)	G3215 (N = 10)
Valine μmol/L		
Baseline	157.31	157.25
CFB Day 7	32.32 (10.90, 53.74)**	−26.24 (−42.83, −9.65)**
CFB Day 14	13.52 (−7.90, 34.94)	−20.79 (−37.38, −4.20)*
CFB Day 21	4.72 (−16.70, 26.14)	−1.29 (−17.88, 15.30)

Note: Data are presented for combined cohorts for participants receiving G3215; data for participants receiving placebo are aggregated from all cohorts. Data are presented as mean (95% confidence interval). Analysed by repeated measured mixed linear model analysis with baseline value as a covariate. *p*-Values calculated for change from baseline at the specified day of study.
Abbreviation: CFB, change from baseline.
*$p < .05$; **$p < .01$; ***$p < .001$.

exhibited elevated lipase levels, which declined to baseline by the follow-up day 21 study visit. No significant changes in amylase levels were seen in G3215-treated participants (Table 3). Similar changes in lipase have been observed in trials of GLP-1 analogues and have been shown to be of low predictive value for acute pancreatitis.[30]

4 | DISCUSSION

In this phase 1 trial, a continuous infusion of G3215 over 14 days was found to be safe and well tolerated. Across the three cohorts, most TEAEs were gastrointestinal and mild in severity. As the infusion rate was adjusted based on sensitivity to the infusion and any TEAEs, this allowed the study team to respond to these in real time, enabling responsive and tailored therapy. By following a standard dose reduction protocol in participants who identified nausea, this mitigated more severe or prolonged effects. This flexible dosing strategy takes account for the interindividual variation in drug sensitivity, particularly for the GLP-1 component.[31] This approach contrasts with conventional trials of fixed interval dosing of long-acting GLP-1R/GCGR co-agonists, some of which have led to high frequencies of AEs and study discontinuation.[17,18]

A rapid weight loss was observed in G3215-treated participants with mean body weight loss of 2.39 kg over 15 days in the cohort-combined G3215 group, compared with 0.84 kg in the placebo group. This magnitude of body weight loss should be contrasted with other co-agonists over a longer time frame, for example cotadutide, which achieved 3.41 kg over double the time, 32 days.[21] More recently, a GLP-1R/GCGR/GIPR triple agonist led to a body weight reduction of up to 3.52 kg over three times the time, 43 days.[22] A continuous infusion dosing strategy tailored to the individual may more easily allow for titration to the maximum tolerated dose and may therefore translate to faster weight loss. The reduction in energy intake mirrored the weight loss effects observed, consistent with the known pharmacological actions of both GLP-1 and glucagon on appetite suppression.[32,33] Limitations in our study, however, were standardization of meal studies to similar caloric content between participants and the small sample size. This trial did not measure energy expenditure as part of its protocol: GLP-1 does not have any significant effects on energy expenditure,[9,10,32,34] but concurrent GCGR-driven thermogenesis may contribute to the weight loss observed,[35] which will need confirming in subsequent studies.

As seen with other GLP-1 receptor agonists,[36] G3215 led to a sustained reduction in systolic blood pressure during the infusion period. However, a sustained chronotropic effect of G3215 was not observed, in contrast to reports with semaglutide treatment[37,38] and the GLP-1R/GCGR co-agonist NN1177.[19] A small rise in C-reactive protein was observed in G3215-treated participants and longer-term studies are required to determine changes in markers of inflammation. Semaglutide reduces C-reactive protein levels, although this was over a longer period.[39]

G3215 did not lead to hyperglycaemia and there was no evidence of impaired glucose tolerance in G3215-treated participants. The balance of GLP-1R and GCGR action is thought to be critical to glycaemic control in response to GCGR-targeted multi-agonists, whereby GLP-1R agonism may mitigate against unwanted GCGR-driven hyperglycaemia.[9,40] However, the differential effects of GLP-1R and GCGR action in a unimolecular co-agonist on glucose control are not easily predictable, highlighted by NN1177,[19] which led to impaired glucose tolerance in phase 1 testing. Several factors may contribute to this differential effect, including compound exposure, study duration and differences in physiological response between species.[20] Further clinical studies will therefore be required to establish the long-term effect of G3215 on glycaemia in humans, in addition to any potential sex differences that may exist.[41]

G3125 led to an improved lipid profile, which may be a combined effect of reduced energy intake, in addition to GCGR activity on hepatic lipid catabolism.[42,43] Indeed, the glucagon-mediated effects on lipid metabolism have positioned other GCGR-targeted co-agonists as potential therapeutics for metabolic-associated hepatic steatosis.[12,44]

G3215 also led to a broad reduction in circulating amino acids over the duration of the infusion. We found that the amino acid concentrations recovered after cessation of the infusion. G3215 had minor effects on branched chain and aromatic amino acids consistent with the individual amino acid changes in response to GCGR agonism.[23] This catabolic effect on amino acids has been reported in long-acting GCGR-targeted multi-agonists.[14,19,22] This is consistent with glucagon's physiological effect: normally, when protein is consumed there is a rise of plasma amino acids, this triggers glucagon secretion and hepatic GCGR activation, hence increasing hepatic amino acid breakdown in a negative feedback loop.[24,45–47] This raises the

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possibility that long-acting GCGR agonists may cause loss of muscle mass over time, but further studies are required to confirm this. The mechanism of glucagon-mediated energy expenditure in humans is also unclear and it will be important to establish whether amino acid metabolism plays a role.[25,26] Further studies are required to determine whether strategies such as concomitant consumption of high protein diets or utilizing an intermittent infusion strategy can mitigate GCGR-driven hypoaminoacidaemia and potential muscle mass loss.

This study highlights the potential advantages with an adaptive continuous infusion of a GLP-1R/GCGR co-agonist. As the dose of G3215 could be modulated in real-time, a limitation was a high degree of variability of systemic exposures within and between cohorts. Future early phase studies of infusion-based therapy could include single cohorts with higher numbers of participants. A further limitation is that this study does not directly compare safety or efficacy outcomes to interval dosing of GLP-1R/GCGR co-agonists, for example once-weekly injections.

5 | CONCLUSIONS

Together, our findings suggest that an adaptive continuous infusion is a safe and effective strategy to deliver a multi-agonist targeting both the GLP-1 and GCG receptors. This individually tailored approach may offer several benefits, including mitigation of adverse effects and rapid weight loss. Further studies are required to compare infusion-based multi-agonist delivery to interval dosing of long-acting preparations.

AUTHOR CONTRIBUTIONS

Tricia M-M. Tan, Stephen R. Bloom and James Minnion performed the conceptualization and study design. Tricia M-M Tan, David C.D. Hope, Saleem Ansari, Sirazum Choudhury, Kleopatra Alexiadou, Yasmin Tabbakh, Ibiyemi Ilesanmi, Katharine Lazarus, Iona Davies, Lara Jimenez-Pacheco, Wei Yang, Beata Reglinska and Laura-Jayne Ball investigated and acquired the data. Bernard Khoo and David C.D. Hope conducted the formal analysis. Laura-Jayne Ball and Reshma Malviya performed the project administration. David C.D. Hope wrote the original draft. Tricia M-M. Tan and Bernard Khoo revised the draft. Tricia M-M. Tan and Stephen R. Bloom supervised and validated the project.

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CONFLICT OF INTEREST STATEMENT

RM, JM, TM-MT and SRB declare that they are shareholders in Zihipp Ltd, an Imperial College spin-out company developing new treatments for obesity and related metabolic disorders. All the other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author 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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