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Safety and efficacy of an extended-release peptide YY analogue for obesity: A randomized, placebo-controlled, phase 1 trial

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Abstract

Aim: To report the results from a Phase 1 trial of an extended-release peptide YY analogue, Y14, developed for the treatment of obesity.

Methods: Y14 was evaluated in overweight/obese volunteers in a Phase 1 randomized placebo-controlled trial, conducted in a clinical trial unit in the United Kingdom. Part A was a blinded single-ascending-dose study evaluating doses up to 36 mg. Part B was double-blinded and tested multiple ascending doses between 9 and 36 mg, given at 7- to 14-day intervals, over the course of 28 days, with up to five doses given per participant. The primary outcome was safety and tolerability; the secondary outcome was assessment of pharmacokinetic (PK) characteristics. Exploratory outcomes included food intake, body weight change and glucose tolerance after multiple doses.

Results: Between April 11, 2017 and December 24, 2018, 53 participants were enrolled into Part A and 24 into Part B of the trial. The PK characteristics were compatible with administration every 7 to 14 days. The most common adverse events (AEs) were nausea, vomiting or administration site reactions, which were mild in most cases and settled with time. No serious AE occurred. Participants given multiple doses of Y14 lost between −2.87 and −3.58 kg body weight compared with placebo (P <0.0001) at

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31 days from the first dose, with profound reductions in food intake of 38% to 55% (P <0.0001, compared to placebo) and there was no evidence of tachyphylaxis.

Conclusions: Our results support the continued development of Y14 as a novel treatment for obesity.

KEYWORDS
clinical trial, obesity, peptide YY, pharmacokinetics, safety, weight loss

1 | INTRODUCTION

Obesity affects 13% of the world's adult population.[1] It is a key driver of cardiovascular disease, diabetes and cancer, three of the four major non-communicable diseases identified by the World Health Organization (WHO). Moreover, obesity is an important contributor to mortality from pandemic respiratory infections.[2,3] Although lifestyle change is effective in the short term, most people regain weight to baseline after 1 to 2 years.[4,5] Bariatric surgery leads to sustained weight loss and reductions in mortality,[6] but can have long-term complications such as post-bariatric hypoglycaemia,[7] it is limited in scalability, and patients need to be fit for surgery.[8] Conventional small-molecule drugs including orlistat, rimonabant, lorcaserin, sibutramine and bupropion/naltrexone are modestly effective in reducing weight but have adverse effects: most have been withdrawn from marketing.[9] Biological agents based on satiety hormones such as glucagon-like peptide-1 (GLP-1), oxyntomodulin, peptide YY (PYY) or melanocyte-stimulating hormone have emerged as potential treatments. They exploit natural satiety pathways to reduce food intake and body weight.[10] The GLP-1 analogues have primarily been developed for diabetes and secondarily developed for obesity, with liraglutide now being licensed for obesity therapy. Semaglutide is also currently being developed for this indication.[11] The melanocyte-stimulating hormone analogue setmelanotide has been recently approved for severe obesity caused by the rare genetic conditions of leptin or proopiomelanocortin deficiency.[12] These peptide therapeutics show that satiety hormone-based treatments for obesity are deliverable, safe and practical.

PYY is a peptide hormone that is cosecreted from enteroendocrine L cells with GLP-1 and oxyntomodulin in response to food intake. PYY has two major forms: full length $PYY_{1\text{-}36}$ that binds to neuropeptide Y1, Y2, Y4 and Y5 receptors, and $PYY_{3\text{-}36}$, which is derived from $PYY_{1\text{-}36}$ via processing by dipeptidyl peptidase-4. $PYY_{3\text{-}36}$ preferentially activates Y2 and Y5 receptors. It acts as a satiety hormone, suppressing food intake via activation of Y2 in the arcuate nucleus of the hypothalamus.[13] Infusion of $PYY_{3\text{-}36}$ in obese volunteers causes a 30% reduction in food intake[14] and short-term subcutaneous injections increase satiety and reduce hunger.[15] Early studies of nasal delivery of $PYY_{3\text{-}36}$ showed limited tolerability and dose-dependent nausea and vomiting,[16] as there was a rapid "burst" release of PYY to supraphysiological levels. When PYY levels are increased slowly, suppression of food intake is obtained, with better tolerability and less nausea even when combined with other satiety hormones.[13,17] Extended-release pharmacokinetic (PK) profiles are important to mitigate nausea and vomiting[18] and to enable weekly delivery of treatment, for example, Novo Nordisk's PYY analogue 1875, which is currently in development.[19] In the present study, we aimed to evaluate the safety, PK profile and preliminary efficacy of a novel analogue of PYY, formulated for extended release, in a Phase 1 trial.

2 | METHODS

2.1 | Preclinical summary

Y14 is a human PYY analogue based on human $PYY_{1\text{-}36}$, with the following features: composition wholly of natural L-amino acids without derivatization or cross linking, deletion of the first residue, and substitution of six other residues within the 35-residue peptide, with the receptor active sequence of PYY being unchanged. Y14 is a selective agonist of the human Y2 receptor, with equivalent binding affinity and functional activity to endogenous $PYY_{3\text{-}36}$. Y14 is at least 250-fold less selective for Y1 versus the endogenous ligand $PYY_{1\text{-}36}$, and 800-fold less selective for Y4 versus the endogenous ligand pancreatic polypeptide. An extended-release formulation was developed, whereby Y14 is given in a $ZnCl_2$ diluent to form a depot after subcutaneous injection, with a prolonged elimination half-life in the rat at 17.3 hours. Safety pharmacology and general toxicology studies in rats and nonhuman primates revealed that Y14 was well tolerated. A "no observable adverse effect limit" dose of 20 mg/kg was established in nonhuman primates. There were no findings in the preclinical evaluation that would preclude administration to humans. For further details on the preclinical evaluation, please see the Study Protocol p.21 (Supplementary Appendix).

2.2 | Study design, participants, procedures

The study was a randomized placebo-controlled Phase 1 clinical trial (ClinicalTrials.gov NCT03673111, EudraCT 2017-000380-33), conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. Approvals were obtained from the National Health Service Health Research Agency North West-Greater Manchester Central Research Ethics Committee (17/NW/0084) and the UK Medicines and Healthcare Products Regulatory Agency. All volunteers gave written consent to participate. A substantial amendment to the protocol (Supplementary Appendix: version 2, dated August 22, 2017) was approved, principally to expand the eligibility criteria for Part B to include participants with normal glucose tolerance in

addition to those diagnosed with diabetes or prediabetes. The amended protocol also included a prescreening visit to allow for assessment of participant glycaemic status, the intention being to improve recruitment rates. The trial was conducted at Covance Clinical Research Unit, Leeds, UK (first participant, first visit date April 11, 2017 to last participant, last visit date December 24, 2018) and ended as planned as all participants had completed trial procedures.

Adult males aged 18 to 65 years inclusive, with body mass index between 25.0 and 38.0 kg/m^2 inclusive, were recruited. In Part A only, participants were verified to have normal glucose tolerance. In Part B, participants with type 2 diabetes, impaired glucose tolerance or impaired fasting glucose according to the WHO 2006 and 2011 criteria were additionally eligible. If identified as being prediabetic or diabetic, participants were only included if stably treated either with diet only, or single, dual or triple therapy with a sulphonylurea, metformin, and/or a sodium-glucose cotransporter-2 inhibitor. Participants identified as being prediabetic or diabetic were included if their glycated haemoglobin (HbA1c) concentration at screening was 42 to 69 mmol/mol (6%-8.5%) and < ±11 mmol/mol (±1.0%) from a previous HbA1c reading within the last 6 months, where available. Exclusion criteria included: positive testing for hepatitis B, hepatitis C and human immunodeficiency virus (HIV) I and II at screening; positive testing for drugs of abuse and alcohol at screening and at admission; smoking within the 3 months preceding screening; and being unable to use medically acceptable methods of contraception for at least 3 months after study drug administration.

The trial was conducted in two parts: Parts A and B. Part A was a randomized, placebo-controlled, single-ascending-dose study. Twenty-eight eligible participants were planned to be enrolled in five sequential cohorts. Cohort A1 comprised four participants (three active and one placebo): each volunteer was dosed in three treatment periods (TPs) with three ascending dose levels (doses 1, 2, 6 mg Y14), with minimum washouts of 1 week between Day 1 of each TP. Within each TP three participants were given the study drug and one was given placebo (sterile 0.9% [w/v] saline). The first two participants in Cohort A1 were randomized such that one participant received Y14 and one received placebo. This sentinel pair was dosed first and observed for 48 hours before the remainder of the cohort was dosed. Because of the design, the 3rd and 4th injections were guaranteed to contain Y14 and so the participants in this cohort were considered partially blinded. Cohort A2 onwards comprised six participants (five active and one placebo) for each cohort, given in a double-blinded design. Each volunteer in Cohort A2 onwards was dosed only once. A follow-up visit was conducted 14 days after the dose was given. Up to eight additional cohorts comprising six participants each could be enrolled if recommended by the trial safety committee.

Part B was a double-blind, randomized, placebo-controlled, multiple-ascending-dose study in sequential cohorts of eight participants each. Twenty-four eligible participants were planned to be enrolled in three cohorts (B1 to B3), with an additional three cohorts if recommended by the trial safety committee. Participants received five doses of Y14/placebo by subcutaneous injection given during short inpatient stays, each separated by 7 days, that is, on Day 1 (visit 1), Day 8 (visit 2), Day 15 (visit 3), Day 22 (visit 4) and Day 29 (visit 5). Participants undertook a standardized food intake study on Days −1, 2 and 30, and a 75-g oral glucose tolerance test (OGTT) on Days −2 and 31. Seven days after the last dose was given, on Day 37, participants underwent a further OGTT. On Days 70 to 73 there was a follow-up outpatient visit.

Randomization lists were generated using SAS® by a study centre statistician who was not otherwise involved with the trial. Treatment codes were provided to the study centre pharmacist who prepared labelled syringes containing either placebo or study drug; these were identical in appearance. All clinical and nonclinical staff (except for the PK scientist) remained blinded to treatment assignment until database lock.

2.3 | Outcomes

The primary outcomes of the study were to investigate the safety and tolerability of single and multiple doses of Y14. Secondary outcomes were to assess the PK profile of single and multiple ascending doses of Y14. The exploratory outcomes of the study were to investigate the pharmacodynamic (PD) effects of multiple doses of Y14 on food consumption, body weight, enteropancreatic hormone changes and glucose tolerance. The analytical performance of the Imperial College radioimmunoassay for Y14 was also compared with the liquid chromatography/tandem mass spectrometry (LC/MS-MS) assay. Only the exploratory data for body weight, food intake and glucose tolerance are presented in this publication.

2.4 | Safety and tolerability assessments

The procedure for recording adverse events (AE) and for their classification is found in the Study Protocol p.53 (Supplementary Appendix). In brief, AEs were coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA), together with onset time and date, offset time and date, description of event, severity, relationship to investigational product, action taken, and outcome. Measurement of antidrug antibodies (ADAs) in participants receiving repeat doses was conducted by Pharmaron Inc. Briefly, serum from Day 1 (prior to dosing), Day 14 after final dosing (Part A, Cohort A1) and Day 70 after first dosing (Part B) was analysed using an electrochemiluminescent bridging assay utilising Biotinylated Y14 and Sulfo-Tag-labelled Y14. A three-tiered approach was taken. Those samples at 1:2 dilution with response above the cut-off point on screening were taken forward to a confirmation assay. If found positive in the confirmation, the samples were diluted and tested in a titre assay, and the reciprocal highest dilution tested with a response above the threshold was reported as the titre.

2.5 | LC-MS/MS method for measurement of Y14

The bioanalytical assay for Y14 was developed by LGC (Fordham, UK). In brief, an assay, utilizing samples of human plasma (K_3EDTA) stabilized with aprotinin, based on solid phase extraction and LC/MS-MS,

was developed and validated according to applicable European Medicines Agency and US Food and Drug Administration guidance. The lowest limit of quantification (LLOQ) was 0.2 ng/mL and the highest limit of quantification 100 ng/mL. The mean precision (coefficient of variation [CV]) of the assay with quality control samples spanning 0.3 to 80 ng/mL was ≤9.3% and the accuracy was within −1.3% to 5.3% relative error. The selectivity of the assay for Y14 alone was verified prior to approval for bioanalysis.

2.6 | PK sampling and analysis

Following a single dose (Part A), blood samples were collected at pre-dose and at 0.5 to 144 hours post-dose, at the follow-up (Day 14; 312 hours post-dose) visit and, for Cohort A8, at 336 hours (Week 3) and 504 hours (Week 4) post-dose. In addition, for Cohort A2, there was a Day 36 sample (840 hours) and for Cohorts A3 to A9 there was sampling on Days 22 (504 hours) and 36 (840 hours). Following the first dose of multiple dosing (Part B), blood samples were collected at pre-dose and at 0.5 to 72 hours post-dose. Blood samples were also collected at pre-dose and post-dose at 4 to 12 hours on Days 8, 15, 22 and 29. Following the final dose, blood samples were collected on Days 30 to 37 and were collected subsequently on Days 43 to 63, and a follow-up on Day 70. PK parameters were derived by standard noncompartmental methods using WinNonlin Phoenix Version 8.1 (Certara USA, Inc.). The following parameters were derived, where appropriate, from the individual plasma concentration versus time profiles obtained: C_{max}, $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}\tau}$ (area-under-concentration curve, calculated by mixed linear/log trapezoidal rule, respectively, from dosing to 72 hours after dosing and from dosing to 168 hours), apparent terminal rate constant λ_z, apparent terminal half-life $t_{½}$ and R_0 (extent of accumulation, calculated as C_{max} repeat dose/C_{max} single dose or $AUC_{0\text{-}\tau}$ repeat dose/$AUC_{0\text{-}\tau}$ single dose). Three or more points were required within the terminal phase for λ_z and corresponding $t_{½}$ to be estimated. Estimates were considered reliable if the period over which λ_z was calculated was greater than twice the half-life itself. Actual blood sampling times were used for the PK analysis. Plasma concentrations below the LLOQ of the assay were taken as zero for calculation of concentration summary statistics and all PK parameters. Between-participant variability was based on geometric mean CVs.

2.7 | Standardized food intake study

While resident in the clinical unit during 24-hour food intake assessment days, participants were individually provided meals in a designated area. Meals were presented with an excess of food and participants asked to eat until they felt "comfortably full" within a period of 30 minutes. If a volunteer required more time to eat, an extra 15 minutes was to be allowed, and this was recorded as a deviation from protocol. Food was weighed pre- and postmeal to determine consumption and energy intake calculated from summing the energy value of each component of the meal.

2.8 | Statistical analysis

The following datasets are presented: the all-participants population (comprising any participants who enrolled in the study and had study assessments recorded in the database as per the protocol), the safety population (consisting of all participants who received study drug, Y14 or placebo), the PK population (consisting of all participants who received Y14 and had data from at least one PK blood draw), and the PD population (consisting of all participants who received study drug, Y14 or placebo, and who had data from at least one PD blood draw or measurement, as appropriate). As this was a first-in-human Phase 1 study, the sample sizes were determined based on previous experience in Phase 1 studies. Continuous data were summarized as mean (SD) or geometric mean (geometric CV%) as indicated. Statistical analysis was performed using STATA 15.1 (STATACorp, LLC). A repeated-measures mixed linear model was used to analyse weight changes, percentage food intake changes and changes in glucose total area under the curve (AUC) after 75-g OGTT as a measure of glucose tolerance. Q-Q plots of standardized residuals were used to verify that residuals were normally distributed. No imputation was made for missing data, which were assumed to be "missing at random".

3 | RESULTS

3.1 | Participant disposition and characteristics

Supplementary Figure S1 shows the numbers of volunteers screened, enrolled, randomized, followed up and analysed in the trial. Three additional cohorts of six participants each were enrolled in Part A of the trial per protocol to allow for investigation of the PK effect of varying the zinc:peptide ratio. This was to increase the scientific value of the study. One participant in Part A, Cohort A1 discontinued the intervention and was replaced with a back-up volunteer. One participant in Part B, Cohort B1 (who received placebo) was withdrawn due to a protocol violation (positive test for alcohol during study visit) on Day 4 of the study. This participant's data are included in the all-participants, safety and PD populations. Table 1 summarizes the baseline characteristics of the all-participants populations for Parts A (n = 53) and B (n = 24) of the study, respectively. Of note, only two participants in Part B had impaired glucose tolerance based on the 120 minutes value from their baseline 75-g OGTT and no participants were diabetic. The doses and zinc:peptide ratios of Y14 given to each cohort are also summarized in Table 1. Although the protocol allowed for maximal doses of up to 96 mg, the maximal dose eventually given in the study was limited to 36 mg, based on the emerging AE profile from Part A (see Safety and adverse events).

3.2 | Pharmacokinetics

3.2.1 | Part A

For the doses given to cohorts A1, A2 and A3, Y14 was below the LLOQ (<0.2 ng/mL) in most samples, so the data for cohort 4 onwards are presented (Supplementary Figure S2 and Table 2). It was not possible to estimate an unambiguous t_{max} due to the extended PK profile of Y14. For a doubling in dose from 18 to 36 mg (1:1), C_{max} and $AUC_{0-\tau}$ increased 1.6 and 2.6-fold, respectively. For a doubling in dose from 9 to 18 mg (0.5:1), C_{max} and $AUC_{0-\tau}$ increased 1.5 and 2.4-fold, respectively. Between-participant variability in systemic exposure (C_{max} and $AUC_{0-72\,h}$) to Y14 was considered generally high (geometric CVs of 44% to 111%).

Comparing the concentration-time profiles for Cohorts A5 and A7 (18 mg, 1:1 and 0.5:1 zinc:peptide ratios, respectively), it was noted that the lower zinc:peptide ratio led to a more acute release of Y14 over the first 48 hours. Comparing Cohorts A6 and A8 (36 mg, 1:1 and 0.7:1, respectively) a marked "acute release" effect was not noted. The concentration-time profiles of Cohorts A8 and A9 (both 36 mg, 0.7:1, 100 and 200 mg/mL solutions, respectively) were similar. Geometric mean apparent terminal half-lives of Y14 could not be reliably estimated as a terminal monoexponential phase could not be unambiguously identified in most participants. However, the PK of Y14 was considered compatible with weekly administration.

3.2.2 | Part B

Supplementary Figure S3 and Table 2 present the PK of Y14 when given as repeated weekly doses. Of note, in Cohorts B2 and B3, participants assigned to Y14 were not given the drug on day 22. Systemic exposure to Y14, as measured by $AUC_{0-\tau}$, increased after weekly dosing of 9 to 26 mg (0.5:1), 9 to 36 mg (0.7:1) and 12 to 36 mg (1:1); the extent of accumulation on Day 29 was 5.80, 10.5 and 13.3-fold, respectively (unadjusted for different doses). Overall (except for $AUC_{0-\tau}$ for Day 1), between-participant variability in systemic exposure (C_{max} and $AUC_{0-\tau}$) to Y14 was moderate (geometric CVs of 16.2% to 76.1%).

Examination of the concentration-time profiles suggested that, with the 0.5:1 formulation (Cohort B1), Y14 levels decline more rapidly between weekly doses in comparison to 0.7:1 (Cohort B2) and 1:1 (Cohort B3). Geometric mean apparent terminal half-lives of Y14 of 8 to 12 days were estimated on Day 29 in eight participants and were considered reliable in only three participants. Overall, the PK of Y14 in the 0.5:1 and 0.7:1 formulations were considered compatible with weekly dosing and in the 1:1 formulation compatible with dosing every 10 to 14 days.

3.3 | Safety and adverse events

In general, Y14 was well tolerated, with the most common treatment-emergent adverse event (TEAE) reported being dose-related gastrointestinal AEs (nausea, vomiting, abdominal distension, constipation) or AEs related to the administration site (injection site mass, pain, erythema; Tables 3 and 4). The frequency of TEAEs was dose-related. At the maximal 36 mg dose in Part A (aggregated across all zinc:peptide ratios) 13/15 participants reported gastrointestinal AEs (43/113 reports, 38%) and 14/15 participants reported administration site AEs (37/113, 33%). For comparison, two of eight

TABLE 1 Characteristics of the participants in Part A (n = 53) and Part B (n = 24): all-participants population

Part	Cohort	Dose given (zinc: peptide)	N	Age, years	Weight, kg	Height, cm	BMI, kg/m^2	HbA1c, mmol/mol
A	A1	1, 2, 6 mg (1:1)	5	49.2 (13.4)	89.0 (12.4)	175 (8.6)	29.2 (2.1)	
	A2	9 mg (1:1)	5	28.2 (5.02)	101.6 (12.7)	184 (4.0)	30.0 (2.7)	
	A3	9 mg (0.7:1)	5	47.8 (10.8)	100.4 (11.3)	180 (6.9)	30.8 (1.9)	
	A4	9 mg (0.5:1)	5	41.2 (13.3)	86.2 (11.78)	177 (6.2)	27.6 (2.4)	
	A5	18 mg (1:1)	5	45.6 (14.9)	101.6 (9.6)	182 (5.2)	30.6 (1.8)	
	A6	36 mg (1:1)	5	47.8 (1.5)	93.3 (5.60)	180 (8.2)	28.8 (1.87)	
	A7	18 mg (0.5:1)	5	40.4 (13.3)	87.4 (13.3)	179 (9.2)	27.0 (2.9)	
	A8	36 mg (0.7:1)	5	44.2 (12.5)	92.4 (16.7)	174 (5.4)	30.6 (4.2)	
	A9	36 mg (0.7:1)[a]	5	37.0 (12.2)	88.6 (7.4)	182 (5.2)	26.6 (0.9)	
	A2-A9	Placebo	8	44.8 (11.5)	97.5 (14.9)	180 (7.1)	30.1 (2.9)	
B	B1	9-26 mg (0.5:1)	6	36.7 (10.0)	97.5 (14.0)	180 (7.6)	30.2 (3.9)	30.8 (7.0)
	B2	9-36 mg (0.7:1)	6	42.3 (9.6)	95.2 (9.8)	178 (3.9)	30.2 (2.9)	39.3 (11.0)
	B3	12-36 mg (1:1)	6	40.8 (9.7)	92.0 (8.1)	177 (5.0)	29.5 (2.1)	35.3 (1.9)
	B1-3	Placebo	6	49.5 (11.9)	93.2 (14.8)	177 (7.1)	29.7 (3.1)	38 (5.7)

Note: Mean (SD) listed. Doses indicated also include the zinc:peptide molar ratio in brackets.

[a]200 mg/mL solution tested. In Cohort A1, an additional participant was recruited to replace one participant who discontinued the intervention for a total of five participants. For Cohorts A2 to A9, six participants were recruited: five received Y14 and one received placebo ($ZnCl_2$ diluent). All the participants in Cohorts A2 to A9 who received placebo are aggregated together in a placebo cohort (all participants in Cohort A1 received study drug at some point during the trial). For Cohorts B1 to B3, eight participated in each cohort: six received Y14 and two placebo. All the participants who received placebo in Cohorts B1 to B3 are aggregated (including a participant who was withdrawn from the trial for a protocol violation).

[a]Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin.

TABLE 2 Geometric mean (CV%) pharmacokinetic parameters following single doses (Part A) and multiple doses of Y14 (Part B)

Part	Cohort	Day dose given	Dose, mg (zinc:peptide)	C_{max}, ng/mL (%)	$AUC_{0\text{-}72h}$, ng·h/mL (%)	$AUC_{0\text{-}\tau}$, ng·h/mL (%)	$t_{½}$, hours (%)	R_O[b] C_{max} (%)	R_O[b] $AUC_{0\text{-}\tau}$ (%)
A	A4	1	9 (0.5:1)	0.459 (44)	16.4 (83%)	NC	NC		
	A5	1	18 (1:1)	0.383 (46)	NC	64.0 (105)	NC		
	A6	1	36 (1:1)	0.607 (111)	24.4 (21)	164 (199)	NC		
	A7	1	18 (0.5:1)	0.677 (66)	26.3 (105)	65.2 (126)	NC		
	A8	1	36 (0.7:1)	0.908 (81)	34.0 (50)	78.2 (47)	NC		
	A9	1	36 (0.7:1)[a]	0.704 (59)	33.4 (51)	59.2 (84.6)	NC		
B	B1	1	9 (0.5:1)	0.640 (39)	19.7 (89.7)	24.8 (127)			
		8	12 (0.5:1)	0.870 (26)	53.2 (21)	108 (18.7)		1.36 (29)	4.33 (96)
		15	16 (0.5:1)	1.32 (35)	76.7 (26)	139 (17)		2.06 (62)	5.60 (151)
		22	20 (0.5:1)	1.64 (19)	89.6 (17)	153 (16)		2.56 (27)	6.15 (110)
		29	26 (0.5:1)	1.48 (49)	81.2 (45)	144 (53)	277 (106)	2.31 (66)	5.80 (183)
	B2	1	9 (0.7:1)	0.389 (41)	10.1 (303)	15.6 (598)			
		8	24 (0.7:1)	0.702 (52)	38.1 (34)	107 (31)		2.18 (85)	7.86 (906)
		15	36 (0.7:1)	1.40 (21)	82.1 (21)	159 (25)		4.17 (52)	12.1 (590)
		29	36 (0.7:1)	1.10 (66)	63.6 (76)	154 (76)	294 (46)	2.61 (110)	10.5 (859)
	B3	1	12 (1:1)	0.355 (37)	9.67 (165)	17.0 (298)			
		8	24 (1:1)	0.787 (35)	40.4 (36)	106 (28)		2.41 (33.6)	6.55 (259)
		15	36 (1:1)	1.35 (20)	86.6 (22)	193 (19)		4.00 (40)	11.8 (323)
		29	36 (1:1)	1.54 (41)	87.2 (34)	225 (48)	190 (28)	4.43 (61.3)	13.3 (263)

Abbreviation: NC, not calculable.
[a]200 mg/mL solution tested.
[b]Not adjusted for different doses administered.

participants given placebo in cohorts A2 to A9 reported a gastrointestinal AE (5/11 reports, 45%) and two of eight reported an administration site AE (3/11, 27%). Only one participant in Part A (TP2 of Cohort A1) discontinued participation due to gastrointestinal and administration site AE. In Part B, a similar pattern was seen with 16/18 participants given Y14 reporting a gastrointestinal AE (72/287 reports, 25%) and 18/18 participants reporting an administration site AE (123/287, 43%). For comparison, three of six participants given placebo reported a gastrointestinal AE (4/11 reports, 36%) and one of six reported an administration site AE (1/11, 9%). None in Part B discontinued participation in the trial due to AE. In both Parts A and B, participants also noted the expected effect of decreased appetite (recorded under the System Organ Classification of Metabolism/Nutrition). Most TEAEs were assessed as being mild in severity, with a few being assessed as moderate and none being assessed severe.

Focusing on the 72 gastrointestinal AE reports in Part B in those who received Y14, 33 were for nausea and eight for vomiting, reported by 14 and five out of 18 participants, respectively. The median (interquartile range) time of onset after dosing for either nausea or vomiting was 12 (1, 35) hours and the duration 10 (4, 58) hours. All reports of nausea/vomiting were graded as mild. Supplementary Figure S4 shows the duration of individual reports of nausea/vomiting AEs plotted with the day of the start of the AE. As the zinc:peptide ratio was increased from 0.5:1 (Cohort B1) to 0.7:1 (B2) and 1:1 (B3) the frequency of nausea/vomiting AEs decreased (23 reports in Cohort B1, seven reports in B3) and the duration of nausea/vomiting decreased from a median of 23 (9, 69) hours in Cohort B1 to 5 (1, 10) hours in B3 (Kruskal-Wallis test, $P = 0.0398$). Increasing the zinc:peptide ratio (Supplementary Figure S3) was therefore associated with fewer and significantly shorter nausea/vomiting AEs despite the higher cumulative drug dose (108 mg in Cohort B3, 83 mg in B1).

With regard to ADAs, of the five participants who received multiple doses in Cohort A1, only one developed detectable ADAs at a low titre. In the 24 participants in Part B, 17 developed detectable ADAs, most of which were at a low titre and only two had high titre ADAs of >320. No discernible relationship to AE frequency nor efficacy in terms of body weight reduction was found. No systemic hypersensitivity reactions were reported. Overall, Y14 was considered well tolerated during this trial.

3.4 | Y14 reduces body weight and food intake

An exploratory analysis showed dose-related reductions in weight in response to single doses of Y14 (Supplementary Figure S5). When

TABLE 3 Treatment-emergent adverse events reported during part A of the trial in the safety analysis population, summarized by cohort, dose, zinc:peptide ratio

Cohort(s)	A1				A2-A9	A2	A3	A4	A5	A6	A7	A8	A9	A2,3,4	A5,7	A6,8,9
Dose, mg	**Pbo**	**1**	**2**	**6**	**Pbo**	**9**	**9**	**9**	**18**	**36**	**18**	**36**	**36***	**9**	**18**	**36**
(zinc: peptide)		(1:1)	(1:1)	(1:1)		(1:1)	(0.7:1)	(0.5:1)	(1:1)	(1:1)	(0.5:1)	(0.7:1)	(0.7:1)	All	All	All
Participants	3	3	3	3	8	5	5	5	5	5	5	5	5	15	10	15
Reporting TEAEs	2	2	1	3	3	1	4	5	5	5	5	4	5	10	10	14
With SAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Discontinuation	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
SOC: No. subj (no. AEs)																
Gastrointestinal[a]	1(2)	1(3)	1(1)	0	2(5)	1(1)	1(1)	3(10)	4(5)	5(20)	4(10)	4(12)	4(10)	5(12)	8(15)	13(42)
Nausea	1(1)	0	0	0	2(3)	1(1)	1(1)	3(3)	4(5)	5(13)	4(4)	4(5)	3(3)	5(5)	8(9)	12(21)
Vomiting	0	0	0	0	0	0	0	2(2)	0	1(2)	3(3)	3(4)	2(2)	2(2)	3(3)	6(9)
General/admin site[b]	1(1)	0	1(2)	3(4)	2(3)	1(1)	4(7)	2(2)	5(7)	5(9)	5(7)	4(7)	5(21)	7(10)	10(14)	14(37)
Immune system[c]	1(1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infections/infestations[d]	0	0	0	0	0	0	0	1(2)	0	4(4)	1(1)	1(1)	2(3)	1(2)	1(1)	7(8)
Injury/poisoning/procedural[e]	0	0	0	0	1(1)	0	0	0	0	0	0	0	0	0	0	0
Metabolism/nutrition[f]	0	1(1)	1(1)	0	0	0	0	1(1)	4(4)	0	1(1)	1(1)	5(5)	1(1)	5(5)	6(6)
MSK/conn tissue[g]	0	0	0	0	1(1)	0	1(2)	0	0	0	0	1(1)	1(1)	1(2)	0	2(2)
Nervous system[h]	0	0	1(1)	0	0	0	0	2(2)	0	2(6)	2(2)	3(7)	1(3)	2(2)	2(2)	6(16)
Resp/thoracic/mediastinal[i]	0	0	0	1(1)	0	0	0	1(1)	0	0	0	0	1(1)	1(1)	0	1(1)
Skin/subcut tissue[j]	0	1(2)	0	0	1(1)	0	0	0	0	0	0	0	0	0	0	0
Ear/labyrinth[k]	0	0	0	0	0	0	0	0	1(1)	0	0	0	0	0	1(1)	0
Severity: No. AEs																
Total number of AEs	4	6	5	5	11	2	10	18	17	39	21	29	44	30	38	112
Mild	4	6	5	5	10	2	9	16	17	35	20	26	40	27	37	101
Moderate	0	0	0	0	1	0	1	2	0	4	1	3	4	3	1	11
Severe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Relation to drug																
Not related	1	1	0	1	1	0	2	5	1	5	3	6	5	7	4	16
Unlikely related	1	0	1	0	2	0	0	1	0	7	0	5	2	1	0	14

(Continues)

TABLE 3 (Continued)

Cohort(s)	A1				A2-A9	A2	A3	A4	A5	A6	A7	A8	A9	A2,3,4	A5,7	A6,8,9
Dose, mg	Pbo	1	2	6	Pbo	9	9	9	18	36	18	36	36*	9	18	36
Possibly related	2	6	3	2	8	2	8	12	16	21	18	18	37	22	34	76
Definitely related	0	0	1	2	0	0	0	0	0	6	0	0	0	0	0	6

Abbreviations: admin, administration; AE, adverse events; conn, connective; MSK, musculoskeletal; Pbo, placebo; resp, respiratory; SAE, severe adverse event; SOC, System Organ Classification; subcut, subcutaneous.

*200 mg/mL solution.

Note: Most common AEs for each SOC are:

[a]nausea, vomiting, abdominal distension: nausea and vomiting are separately reported as well; [b]injection site mass, erythema, pain, fatigue; [c]seasonal allergy; [d]viral upper respiratory tract and oral herpes infection; [e]confusion in one case; [f]decreased appetite; [g]back pain and musculoskeletal pain; [h]headache, dizziness and dysgeusia; [i]cough and nasal congestion; [j]cold sweat; [k]ear discomfort.

For the SOC sub-table, number of participants reporting (number of AEs reported) is shown unless it is zero.

participants were given multiple doses of Y14, this was associated with significant weight loss relative to placebo treatment (Figure 1). Using a repeated-measures linear mixed model with adjustment for the baseline weight as a covariate, in cohort B1 on Day 31 the mean weight change for Y14 versus placebo was −2.92 kg (95% confidence interval [CI] −3.99, −1.87; P <0.0001), in cohort B2 this was −2.87 kg (95% CI −3.89, −1.86; P <0.0001) and in cohort B3 this was −3.58 kg (95% CI −4.55, −2.61). This was associated with a profound reduction in food intake; in cohort B1, the Day 30 mean percentage change in food intake for Y14 versus placebo was −45% (95% CI −64, −25; P <0.0001), in cohort B2 this was −38% (95% CI −56, −20; P <0.0001) and in cohort B3 this was −55% (95% CI −72, −38; P <0.0001). The reductions in food intake observed on Day 2 were similar in magnitude to those recorded at Day 30, indicating no evidence of tachyphylaxis with multiple dosing. There were significant negative correlations between the percentage change in 24-hour food intakes on Days 2 and 30 and measures of drug exposure: Pearson ρ with the C_{max} after the doses on Day 1 and 29 was −0.54 (P = 0.0008), $AUC_{0\text{-}72h}$ −0.49 (P = 0.0026) and $AUC_{0\text{-}\tau}$ −0.47 (P = 0.0042; Supplementary Figure S6).

In terms of glucose tolerance in response to an oral 75-g glucose load, no significant changes from baseline (Day −2) to Day 31 (2 days after the last Y14 dose) and Day 37 (follow-up) were seen between placebo- and Y14-treated participants in Cohorts B2 and B3 (data not shown). It was noted that in Cohort B1, the participants given Y14 displayed, on average, slightly better glucose tolerance than the placebo-treated participants at baseline (Day −2), with a mean difference in $AUC_{0\text{-}180}$ for glucose of −225 mmol·min/L (95% CI −376, −74; P = 0.0036), and also at Day 37 (follow-up): −188 mmol·min/L (95% CI −339, −36; P = 0.015), probably as a result of the fact that this cohort, by chance, were on average younger than the placebo-treated participants (Table 1).

4 | DISCUSSION

In this Phase 1 trial we have shown that Y14, a novel analogue of PYY, is well tolerated in human subjects. To our knowledge, this is the first publication to report on a clinical trial of an extended-release PYY analogue. The TEAEs recorded were to be anticipated from the mechanism of action, with nausea, vomiting and reduced appetite being reported. Injection site reactions were also reported. Only one participant withdrew due to a TEAE, and no severe AEs were reported. Although ADAs were detected in 17/24 participants given multiple-dose Y14 in Part B, these were mostly of low titre. No systemic hypersensitivity was noted in the trial. ADAs against gut hormone analogues are more common in extended-release than immediate-release formulations, tend to wane with time, and, in most cases, do not seem to affect the desired PD effects nor to cause systemic hypersensitivity reactions as shown with extended-release exenatide.[20]

Using a zinc-based extended-release formulation we also saw PK characteristics compatible with weekly/fortnightly administration.

TABLE 4 Treatment-emergent adverse events during Part B of the trial in the safety analysis population, summarized by cohort, zinc:peptide ratio and dose given

Cohort	B1-3	B1						B2				B3				B1,2,3
(zinc:peptide)		(0.5:1)						(0.7:1)				(1:1)				All
Dose, mg	Pbo	9	12	16	20	26	All	9	24	36	All	12	24	36	All	All
Participants	6	6						6				6				18
Reporting TEAEs	3	5	6	6	6	6	6	4	6	5	6	5	5	6	6	18
With SAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Discontinuation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SOC: No. subj (no. AEs)																
Gastrointestinal[a]	2(3)	4(14)	3(6)	5(8)	3(5)	4(5)	6(38)	2(3)	6(12)	3(3)	6(18)	0	1(2)	3(14)	4(16)	16(72)
Nausea	0	4(7)	2(2)	4(5)	3(3)	2(2)	5(19)	1(2)	3(5)	2(2)	5(9)	0	1(1)	3(4)	4(5)	14(33)
Vomiting	0	2(2)	0	1(1)	0	1(1)	2(4)	0	2(2)	0	2(2)	0	0	1(2)	1(2)	5(8)
General/admin site[b]	1(1)	4(7)	4(5)	5(11)	3(6)	6(12)	6(41)	2(2)	6(10)	4(22)	6(34)	5(7)	5(9)	6(32)	6(48)	18(123)
Immune sys disorders[c]	1(1)	0	0	0	0	0	0	0	0	1(1)	1(1)	0	0	0	0	1(1)
Infections/infestations[d]	2(2)	1(1)	1(1)	0	0	1(1)	3(3)	0	0	1(2)	1(2)	0	0	2(2)	2(2)	6(7)
Injury/poisoning/procedural[e]	0	0	0	0	0	0	0	0	0	1(1)	1(1)	0	0	2(3)	2(3)	3(4)
Metabolism/nutrition[f]	0	2(2)	0	2(2)	3(3)	0	3(7)	2(2)	2(2)	1(1)	4(5)	0	0	3(4)	3(4)	10(16)
MSK/conn tissue[g]	1(1)	0	0	0	1(1)	0	1(1)	1(1)	0	0	1(1)	0	0	0	0	2(2)
Nervous system[h]	2(2)	3(10)	4(5)	3(6)	3(6)	3(5)	5(32)	2(4)	4(7)	2(5)	5(16)	0	1(1)	1(2)	2(3)	12(51)
Resp/thoracic/mediastinal[i]	0	2(4)	1(1)	0	1(1)	2(3)	3(9)	0	0	0	0	0	0	0	0	3(9)
Surg/med procedures[j]	0	0	0	0	0	1(1)	1(1)	0	0	0	0	0	0	0	0	1(1)
Investigations[k]	0	1(1)	0	0	0	0	1(1)	0	0	0	0	0	0	0	0	1(1)
Severity: No. AEs																
Total number of AEs	10	39	18	27	22	27	133	12	31	35	78	7	12	57	76	287
Mild	10	36	16	26	21	27	126	11	29	34	74	7	12	54	73	273
Moderate	0	3	2	1	1	0	7	1	2	1	4	0	0	3	3	14
Severe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Relation to drug																
Not related	4	2	0	1	2	3	8	4	0	5	9	0	1	3	4	21
Unlikely related	3	1	1	1	0	7	10	1	1	2	4	0	2	2	4	18

(Continues)

TABLE 4 (Continued)

Cohort	B1-3	B1						B2				B3				B1,2,3
Possibly related	3	35	17	25	20	17	114	7	30	28	65	7	9	52	68	247
Definitely related	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1

Abbreviations: admin, administration; AE, adverse event; conn, connective; MSK, musculoskeletal; Pbo, placebo; resp, respiratory; SAE, severe adverse event; SOC, System Organ Classification; subcut, subcutaneous; subj, subjects; Surg/med, surgical/medical.

Note: Most common AEs for each SOC are:

[a]nausea, vomiting, diarrhoea, constipation: nausea and vomiting are separately reported as well; [b]injection site mass, erythema, pain; [c]seasonal allergy; [d](viral) upper respiratory tract infection, urinary tract infection and epididymitis; [e]confusion and limb injury; [f]decreased appetite; [g]joint swelling, muscle twitching and pain in extremity; [h]headache, dizziness and lethargy; [i]dry throat and cough; [j]tooth extraction; [k]hypoglycaemia.

For the SOC sub-table, number of subjects reporting (number of AEs reported) is shown unless it is zero.

Moderate between-participant variability in drug exposure parameters (C_{max} and $AUC_{0\text{-}t}$) was observed. Zinc-based formulations have been used successfully to prolong the pharmacokinetics of insulin and GLP-1 analogues, via formation of a subcutaneous depot, slow dissolution and release. The variation in drug exposure may be attributable to inconsistent dissolution of peptide/zinc aggregates in the depot. By changing zinc:peptide ratios, these properties may be adjusted: increasing the ratio was associated with protraction of release, reduced "burst release" and reduced frequency of nausea/vomiting TEAEs. Further studies will help to establish if a different dose schedule, refinement of the formulation, or the use of other strategies for prolonging Y14's half-life may reduce the variability in PKs, reduce the frequency of injection-site AEs and help to establish the exact relationship of drug exposure to AEs and efficacy.

Multiple-dose Y14 treatment was associated with clinically significant reductions in weight and food intake, even with short-term administration over 28 days. A clear PK/PD relationship between drug exposure and food intake reduction was established. The magnitude of weight loss over 4 weeks and its relationship to food intake reduction are consistent with previous studies on gut hormone analogues. For example, semaglutide, given at a maximal dose of 1.0 mg weekly, was associated with a reduction in total ad libitum food intake of 24% and a mean placebo-subtracted weight loss of approximately 1.5 kg at 4 weeks.[21] Cotadutide, a GLP-1/glucagon coagonist, led to a placebo-subtracted mean weight loss of 2.14 kg over 41 days, with 52% of participants reporting nausea and 32% vomiting.[22] Tirzepatide, a GLP-1/GIP coagonist, led to a dose-dependent 0.5-3.5 kg weight loss from baseline at 4 weeks, and up to 40% reported nausea and 26% vomiting at the highest doses tested.[23] Direct comparisons are difficult given the differences in dosing regimens and participant characteristics, but we note that Y14 achieved similar magnitudes of weight loss compared over similar study timespans, with only one of six participants (17%) reporting vomiting at the highest cumulative doses tested (Cohort B3). No significant change in glucose tolerance was seen, although any possible improvements are limited as no participant in Part B was diabetic and only two had impaired glucose tolerance. Intravenous infusion of $PYY_{3\text{-}36}$ did not have any significant acute effect on glucose tolerance in response to an intravenous glucose load in healthy volunteers,[24] consistent with the findings here. However, our findings do not rule out potential improvements in insulin sensitivity and glucose tolerance with weight loss induced by long-term treatment in people with diabetes.

In summary, this Phase 1 trial supports Y14's further development as a novel treatment for obesity. Future studies should establish its effects on weight and glucose tolerance in the context of diabetes and obesity when given for longer durations. The effect of Y14 on other phenomena, such as gastric emptying and changes in liver fat content, in the context of non-alcoholic fatty liver disease will be of interest. Finally, Y14's potential for enhanced effect when used in combination with other satiety hormones will be worth exploring.[10]

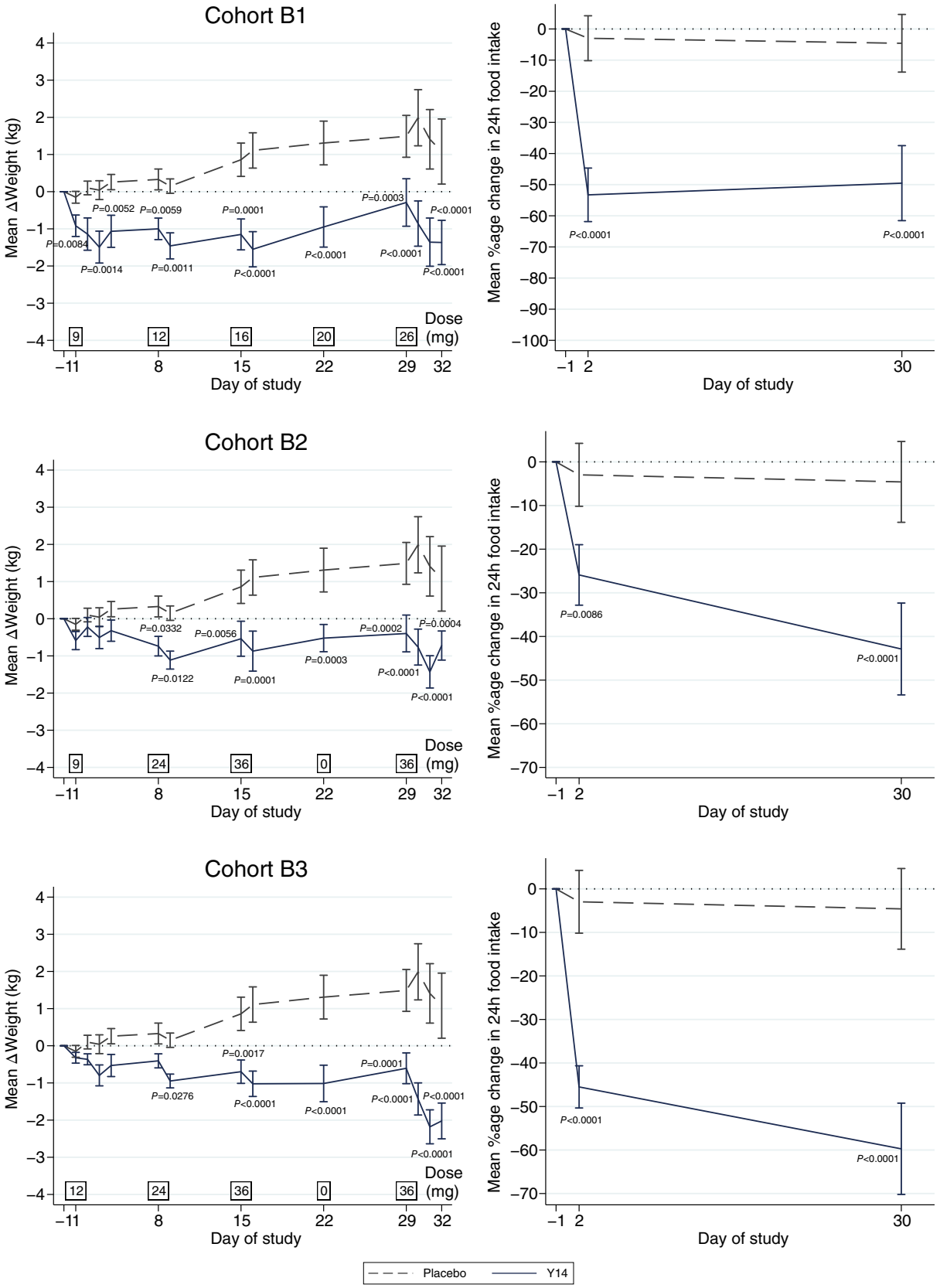

FIGURE 1 Changes in body weight and food intake from baseline in response to multiple doses of Y14 in Part B. Mean and SEM of change in weight from baseline plotted (left column) and percentage change in 24 hours food intake (right column) for aggregate placebo (dashed line) versus Y14 (solid line). Top row cohort B1, middle row cohort B2, bottom row cohort B3. Doses given at the timepoints indicated in boxes. Repeated measures mixed linear model analysis (with adjustment for baseline weight as covariate in body weight change analysis), *P* values calculated for contrast of placebo versus Y14 at the indicated day of study

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CONFLICT OF INTEREST

T.M.-M.T., J.M. and R.M. are consultants and share-holders in Zihipp, Ltd. S.R.B. is the chairman and founder of Zihipp, Ltd, and holds a patent (pending: PCT/GB2018/053513) related to the study. J.B. is an employee of Covance Clinical Research Unit, which was contracted to conduct the study. All other authors declare no conflict of interests relevant to this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of the report. T.M.-M.T., J.M. and S.R.B. designed the trial with input from J.B. J.M. supervised the preclinical evaluation of Y14. E.D., F.F. and B.K. prepared table listings and statistical analyses. R.M. and L.-J.B. coordinated the trial and checked table listings. C.B. prepared the PK analyses. S.R.B. was the Chief Investigator of the trial and J.B. the site Principal Investigator. S.R.B., T.M.-M.T., B.K., R.M., L.-J.B., E.D., F.F. certify that they have accessed and verified the underlying data. All authors have had full access to the full data in the study and take final responsibility for the decision to submit for publication.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14358.

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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REFERENCES

1. World Health Organisation. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:1-253.
2. Louie JK, Jean C, Acosta M, Samuel MC, Matyas BT, Schechter R. A review of adult mortality due to 2009 pandemic (H1N1) influenza a in California. *PLoS One*. 2011;6(4):e18221.
3. Hamer M, Gale CR, Kivimaki M, Batty GD. Overweight, obesity, and risk of hospitalization for COVID-19: a community-based cohort study of adults in the United Kingdom. *Proc Natl Acad Sci U S A*. 2020;117(35):21011-21013.
4. Ma C, Avenell A, Bolland M, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ*. 2017;359:j4849.
5. Bray GA, Heisel WE, Afshin A, et al. The science of obesity management: an Endocrine Society scientific statement. *Endocr Rev*. 2018;39(2):79-132.
6. Sjöström L. Review of the key results from the Swedish obese subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. *J Intern Med*. 2013;273(3):219-234.
7. Goldfine AB, Patti ME. How common is hypoglycemia after gastric bypass? *Obesity*. 2016;24(6):1210-1211.
8. Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity medicine Association, and American Society of Anesthesiologists - executive summary. *Endocr Pract*. 2019;25(12):1346-1359.
9. Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA*. 2016;315(22):2424-2434.
10. Khoo B, Tan TM. Combination gut hormones: prospects and questions for the future of obesity and diabetes therapy. *J Endocrinol*. 2020;246(3):R65-R74.
11. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392(10148):637-649.
12. Clement K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol*. 2020;8:960-970.
13. Batterham RL, Cowley MA, Small CJ, et al. Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature*. 2002;418(6898):650-654.
14. Batterham RL, Cohen MA, Ellis SM, et al. Inhibition of food intake in obese subjects by peptide YY3-36. *N Engl J Med*. 2003;349(10):941-948.
15. Sloth B, Davidsen L, Holst JJ, Flint A, Astrup A. Effect of subcutaneous injections of PYY1-36 and PYY3-36 on appetite, ad libitum energy intake, and plasma free fatty acid concentration in obese males. *Am J Physiol Endocrinol Metab*. 2007;293(2):E604-E609.
16. Gantz I, Erondu N, Mallick M, et al. Efficacy and safety of intranasal peptide YY3-36 for weight reduction in obese adults. *J Clin Endocrinol Metab*. 2007;92(5):1754-1757.
17. Behary P, Tharakan G, Alexiadou K, et al. Combined GLP-1, oxyntomodulin, and peptide YY improves body weight and glycemia in obesity and prediabetes/type 2 diabetes: a randomized, single-blinded, placebo-controlled study. *Diabetes Care*. 2019;42(8):1446-1453.
18. Rangwala SM, D'Aquino K, Zhang YM, et al. A long-acting PYY3-36 analog mediates robust anorectic efficacy with minimal emesis in nonhuman primates. *Cell Metab*. 2019;29(4):837-843 e835.
19. Novo Nordisk. R&D pipeline. 2021; https://www.novonordisk.com/science-and-technology/r-d-pipeline.html. Accessed 17 January 2021.
20. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372(9645):1240-1250.
21. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food

preference and body weight in subjects with obesity. *Diabetes Obes Metab*. 2017;19(9):1242-1251.
22. Ambery P, Parker VE, Stumvoll M, et al. MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study. *Lancet*. 2018;391(10140):2607-2618.
23. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392(10160):2180-2193.
24. Tan TM, Salem V, Troke RC, et al. Combination of peptide YY3-36 with GLP-1(7-36) amide causes an increase in first-phase insulin secretion after IV glucose. *J Clin Endocrinol Metab*. 2014;99(11):E2317-E2324.

SUPPORTING INFORMATION

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

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