LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial

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Summary

Background Treating hyperglycaemia and obesity in individuals with type 2 diabetes using multi-receptor agonists can improve short-term and long-term outcomes. LY3437943 is a single peptide with agonist activity for glucagon, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) receptors that is currently in development for the treatment of type 2 diabetes and for the treatment of obesity and associated comorbidities. We investigated the safety, pharmacokinetics, and pharmacodynamics of multiple weekly doses of LY3437943 in people with type 2 diabetes in a 12-week study.

Methods In this phase 1b, proof-of-concept, double-blind, placebo-controlled, randomised, multiple-ascending dose trial, adults (aged 20–70 years) with type 2 diabetes for at least 3 months, a glycated haemoglobin A_{1c} (HbA_{1c}) value of 7·0–10·5%, body-mass index of 23–50 kg/m², and stable bodyweight (<5% change in previous 3 months) were recruited at four centres in the USA. Using an interactive web-response system, participants were randomly assigned to receive once-weekly subcutaneous injections of LY3437943, placebo, or dulaglutide 1·5 mg over a 12-week period. Five ascending dose cohorts were studied, with randomisation in each cohort such that a minimum of nine participants received LY3437943, three received placebo, and one received dulaglutide 1·5 mg within each cohort. The top doses in the two highest dose cohorts were attained via stepwise dose escalations. The primary outcome was to investigate the safety and tolerability of LY3437943, and characterising the pharmacodynamics and pharmacokinetics were secondary outcomes. Safety was analysed in all participants who received at least one dose of study drug, and pharmacodynamics and pharmacokinetics in all participants who received at least one dose of study drug and had evaluable data. This trial is registered at ClinicalTrials.gov, NCT04143802.

Findings Between Dec 18, 2019, and Dec 28, 2020, 210 people were screened, of whom 72 were enrolled, received at least one dose of study drug, and were included in safety analyses. 15 participants had placebo, five had dulaglutide 1·5 mg and, for LY3437943, nine had 0·5 mg, nine had 1·5 mg, 11 had 3 mg, 11 had 3/6 mg, and 12 had 3/6/9/12 mg. 29 participants discontinued the study prematurely. Treatment-emergent adverse events were reported by 33 (63%), three (60%), and eight (54%) participants who received LY3437943, dulaglutide 1·5 mg, and placebo, respectively, with gastrointestinal disorders being the most frequently reported treatment-emergent adverse events. The pharmacokinetics of LY3437943 were dose proportional and its half-life was approximately 6 days. At week 12, placebo-adjusted mean daily plasma glucose significantly decreased from baseline at the three highest dose LY3437943 groups (least-squares mean difference –2·8 mmol/L [90% CI –4·63 to –0·94] for 3 mg; –3·1 mmol/L [–4·91 to –1·22] for 3/6 mg; and –2·9 mmol/L [–4·70 to –1·01] for 3/6/9/12 mg). Placebo-adjusted HbA_{1c} also decreased significantly in the three highest dose groups (–1·4% [90% CI –2·17 to –0·56] for 3 mg; –1·6% [–2·37 to –0·75] for 3/6 mg; and –1·2% [–2·05 to –0·45] for 3/6/9/12 mg). Placebo-adjusted bodyweight reduction with LY3437943 appeared to be dose dependent (up to –8·96 kg [90% CI –11·16 to –6·75] in the 3/6/9/12 mg group).

Interpretation In this early phase study, LY3437943 showed an acceptable safety profile, and its pharmacokinetics suggest suitability for once-weekly dosing. This finding, together with the pharmacodynamic findings of robust reductions in glucose and bodyweight, provides support for phase 2 development.

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Introduction

Weight management in treatment of type 2 diabetes is an accepted component of any treatment regimen in individuals with overweight and obesity. Bodyweight reduction can improve insulin sensitivity and metabolic abnormalities associated with this disease, as well as

Research in context

Evidence before this study

We searched PubMed on Jun 17, 2022, using the terms "glucagon-like peptide-1 receptor agonist", "GLP-1", "glucose-dependent insulinotropic polypeptide", "GIP", "glucagon" "type 2 diabetes", "obesity", "acute bodyweight management", and "chronic bodyweight management". English language was the only search restriction. Reference lists of relevant studies were also searched. Our search highlighted that, although there is a rich database for glucagon-like peptide 1 (GLP-1) receptor agonists, there is no evidence for the chronic human use of glucose-dependent insulinotropic polypeptide (GIP) or glucagon receptor agonists as a monotherapy, due to the unavailability of those agonists in clinical practice. In recent years, more clinical data have become available for dual GIP and GLP-1 and GLP-1 and glucagon receptor agonists, indicating that such agonists enable superior management of type 2 diabetes or bodyweight compared with single agents, such as GLP-1 receptor agonists. Previously, we and others reported through preclinical and single-dose clinical evidence that a triple GIP, GLP-1, and glucagon receptor agonist was safe and improved overall metabolic health. The preclinical evidence suggests that a triple GIP, GLP-1, and glucagon receptor agonist can improve lipid metabolism control and provide bodyweight management via increased energy expenditure.

Added value of this study

We report for the first time safety and pharmacodynamic findings with multiple doses of the triple GIP, GLP-1, and glucagon receptor agonist LY3437943 during a 12-week treatment period in people with type 2 diabetes. In this phase 1b, multiple-ascending dose clinical study, safety data indicated that LY3437943 was well tolerated, with the most common adverse events being mild and transient gastrointestinal adverse events. The pharmacokinetics of LY3437943 were dose proportional and its half-life supports once-weekly dosing. Glycated haemoglobin A_{1c} and daily plasma glucose data showed significant improvements in glycaemic control. LY3437943 also showed strong bodyweight-lowering effects that might surpass the efficacy of currently available pharmacological agents approved for treatment of obesity.

Implications of all the available evidence

These multiple-ascending dose study findings motivated us to explore the efficacy of LY3437943 in people with type 2 diabetes (NCT04867785) and with obesity (NCT04881760) in phase 2 clinical trials. The outcomes of these studies will help to determine further clinical explorations in phase 3 trials.

non-metabolic cardiovascular risk factors.[1] When weight loss is a desired treatment goal, select treatments for type 2 diabetes, such as incretins or sodium-glucose cotransporter-2 inhibitors, promote bodyweight reduction and are preferred therapeutic options.[2] However, the magnitude of weight loss with these agents is generally modest and pharmacological agents with greater efficacy are needed. Metabolic surgery has well established benefits for people with type 2 diabetes and a high body-mass index (BMI; ≥35 kg/m²), often leading to remission of diabetes and amelioration of many comorbidities associated with obesity.[3] Although studies of people after bariatric surgery provide robust evidence for the benefits of substantial weight loss on metabolic disorders, high short-term costs, low patient acceptance, and scalability limit the widespread application of bariatric surgery as a means to reduce the public health impact of obesity.[1]

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones essential for typical control of nutrient metabolism. GLP-1 receptor agonists reduce food intake, delay gastric emptying, increase meal-stimulated insulin secretion, and inhibit glucagon secretion in hyperglycaemic or euglycaemic states.[4] Short-acting and long-acting GLP-1 receptor agonists can improve glycaemic control and reduce bodyweight in people with type 2 diabetes.[1,2] GIP also enhances meal-stimulated insulin secretion[4] and facilitates lipid clearance.[5] GIP differs from GLP-1 by stimulating glucagon secretion during fasting and hypoglycaemia.[4,6] The unimolecular GIP and GLP-1 receptor agonist tirzepatide (Mounjaro; Eli Lilly and Company, Indianapolis, IN, USA), which was approved by the US Food and Drug Administration on May 13, 2022, causes significant and clinically meaningful reductions in glycated haemoglobin A_{1c} (HbA_{1c}) and bodyweight, as well as improvements in cardiovascular risk factors, such as blood pressure and lipid profile.[7,8] These improvements were of a significantly greater magnitude with tirzepatide than with the selective GLP-1 receptor agonist semaglutide 1 mg, indicating potential benefit of targeting more than one incretin receptor.[8]

Glucagon, a peptide hormone produced by pancreatic α cells, has a well established role in glucose metabolism by increasing hepatic glucose output between meals.[9] Glucagon can also reduce appetite and increase energy expenditure to reduce bodyweight, reduce gastrointestinal motility, enhance hepatic fatty acid oxidation and lipolysis, and stimulate insulin secretion in hyperglycaemic states.[9–12] Postprandially, glucagon modulates amino acid metabolism and, together with GLP-1 and GIP, mediates proper disposal of nutrient substrates in response to meals.[9,13] Thus, the actions of glucagon, in combination with those of GIP and GLP-1, might have novel metabolic benefits, such as increased energy expenditure and metabolic flexibility, offering a potential new therapeutic approach for people with type 2 diabetes and overweight or obesity. Early preclinical data suggest the potential efficacy of glucagon and GLP-1 co-agonists

in bodyweight lowering in rodents.[14] Given their distinct effects, an agonist targeting GLP-1, GIP, and glucagon might provide enhanced glycaemic control and weight loss relative to agonists targeting one or two receptors.[15–17] Additionally, the effects of glucagon in the liver and kidney are of interest in individuals with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis and chronic kidney disease, respectively.[18,19]

LY3437943 is a 39 amino acid single peptide conjugated to a C20 fatty diacid moiety that possesses agonist activity at the glucagon, GIP, and GLP-1 receptors. LY3437943 is less potent at the human glucagon and GLP-1 receptors compared with native glucagon and GLP-1, and more potent at human GIP compared with native GIP and exhibits an extended pharmacokinetic half-life while providing desired pharmacological properties.[17] In mice, LY3437943 promotes bodyweight loss, with glucagon receptor agonism contributing to an increase in energy expenditure while GIP and GLP-1 contribute to reduced food intake.[17] In a single-ascending dose study in healthy participants, LY3437943 was well tolerated and showed pronounced effects on weight loss and appetite regulation, albeit within the typical confines of a first-in-human study.[17]

In this multiple-ascending dose study, we aimed to assess the safety, pharmacokinetics, and pharmacodynamics of LY3437943 in people with type 2 diabetes.

Methods

Study design and participants

This phase 1b, double-blind, placebo-controlled, randomised, multiple-ascending dose study was conducted at four centres in the USA. Ethical approval was obtained from Midlands Independent Review Board (KS, USA) and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol is available in the appendix (p 9).

Adults aged 20–70 years with type 2 diabetes for at least 3 months before screening, HbA_{1c} level of 7·0–10·5% at lead-in and screening, BMI of 23–50 kg/m², stable bodyweight (<5% change during the previous 3 months), and without advanced known possible complications of diabetes were eligible. Participants could not have used any glucose-lowering medication other than metformin within 3 months before screening. If taking a stable dose of metformin at study entry, participants must have been willing to maintain this dose during the trial. All participants provided written informed consent before study entry.

Randomisation and masking

Participants were randomly assigned (9:3:1) to receive LY3437943, placebo, or dulaglutide 1·5 mg treatment via a computer-generated random sequence using an interactive web-response system. Five ascending dose cohorts were studied, with randomisation in each cohort such that a minimum of nine participants received LY3437943, three received placebo, and one received dulaglutide 1·5 mg within each cohort (appendix p 5). Treatment allocation was concealed from participants, investigators, and all site study personnel except those who prepared, dispensed, and administered study medication.

Procedures

All treatments were given as once-weekly subcutaneous injections for 12 weeks, after screening and lead-in periods. For LY3437943, cohort one received 0·5 mg, cohort two received 1·5 mg, and cohort three received 3·0 mg for 12 weeks. In cohorts four and five, a stepwise dose escalation was used. In cohort four, participants received 3 mg for their first 4 weeks, followed by 6 mg for the remaining 8 weeks (represented as 3/6 mg dose group). In cohort five, participants received 3 mg for their first 2 weeks, followed by 6 mg for the next 2 weeks, then 9 mg for the following 4 weeks and 12 mg for the last 4 weeks (represented as 3/6/9/12 mg dose group). During the treatment period, participants attended in-patient stays and outpatient visits at the clinical research units. The study ended with a follow-up period of 4 weeks after treatment, in which patients attended two outpatient visits, with the second visit being at least 28 (±3) days after the last dose of treatment was received.

Outcomes

The primary objective was to investigate the safety and tolerability of LY3437943. Safety endpoints included treatment-emergent adverse events (TEAEs), serious adverse events, and adverse events of special interest, which were recorded by the investigator at each centre. The investigator at each of the four study centres determined if an adverse event had a reasonable possibility of being related to study treatment. During study visits, blood pressure and pulse rate were measured twice after the participant was sitting for at least 5 min and then averaged. Laboratory blood and urine chemistry, including fasting lipase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl-transferase, and calcitonin, were also monitored to assess safety.

See Online for appendix

Secondary pharmacodynamic outcomes were changes from baseline in mean daily plasma glucose from a 6-point plasma glucose profile, HbA_{1c}, and bodyweight, with exploratory pharmacodynamic measures, including changes from baseline in waist circumference and oral glucose tolerance test measures (C-peptide, glucagon, glucose, and insulin) Fasting lipid parameters were also measured. Additionally, appetite was assessed using a validated visual analog scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption.[20] These individual scores were used to calculate an overall appetite score, with a higher score indicative of a lower appetite.

Pharmacokinetic measurements for LY3437943 included area under the concentration–time curve (AUC) during one dosing interval $AUC_{(0-\tau)}$, maximum observed

drug concentration (C_{max}), time at which C_{max} was observed (t_{max}), and half-life associated with the terminal rate constant in non-compartmental analysis.

Statistical analysis

We planned to enrol approximately 80 people so that approximately 13 participants per cohort would complete the study. This sample size is typical for phase 1 studies evaluating safety, pharmacokinetic, or pharmacodynamic parameters and was considered sufficient to evaluate the primary outcome of this study, which was safety and tolerability. Regarding pharmacodynamics, the sample size of nine in each treatment group of LY3437943 and 15 in the pooled placebo group provided more than 80% power to detect a placebo-adjusted difference in means of 1·4% for HbA_{1c} change from baseline at week 12, assuming a common standard deviation of 1·1 using a two group *t*-test with a 10% two-sided significance level. This approach also had more than 90% power to detect a placebo-adjusted difference in mean bodyweight change from baseline of 7 kg at week 12, assuming a common standard deviation of 3 kg using a two group *t*-test with a 10% two-sided significance level. The safety population consisted of all participants who received at least one dose of study drug, whether or not they completed all protocol requirements. Pharmacodynamics and pharmacokinetics were assessed in all patients who received at least one dose of study drug and had evaluable data (pharmacokinetic and pharmacodynamic population). We applied an intention-to-treat principle to the statistical analysis, so the analyses were completed using the planned treatment groups for the participants, instead of the actual treatment assignments.

An efficacy estimand was used for pharmacodynamic measures, defined as the average treatment effect of LY3437943 relative to placebo or dulaglutide 1·5 mg at 12 weeks in the participants who were randomly assigned had they remained on their randomised treatment for the entire planned 12 weeks' treatment duration.[21] Regarding participant drop-outs, we assumed hypothetically that all the participants would remain on their randomised treatment for the entire planned treatment duration. By making this assumption, we exclude all the data points after the treatment discontinuation before doing the mixed-model repeated-measure analyses, a likelihood-based estimation method. Absolute values, as well as change from baseline in each parameter, were analysed using a mixed-model repeated-measure model to evaluate treatment effects, and to perform treatment comparisons. The model included treatment, timepoint (of measurement), and treatment-by-timepoint interaction as fixed effects and patient as a random effect. Baseline values were used as a covariate in the change from baseline analysis. Differences between each LY3437943-treated group and the placebo group were estimated. Patients who received placebo and dulaglutide 1·5 mg were pooled across all cohorts. Least-squares means (LSMs) and 90% CIs are reported. An unstructured covariance structure was used primarily; a compound symmetric structure was used if the model failed to converge.

Pharmacokinetic dose proportionality was explored by use of log-transformed C_{max} and AUC of LY3437943 within a power model (with the log-dose acting as an explanatory variable) to estimate ratios of dose-normalised geometric means and corresponding 90% CIs. The estimated ratio of dose-normalised geometric means of pharmacokinetic parameters between the highest and lowest doses was used to assess dose proportionality.

Analyses were completed using SAS version 9.4. The study is registered at ClinicalTrials.gov, NCT04143802.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report through the assistance of a medical writer employed by Eli Lilly and Company.

Results

Between Dec 18, 2019 (first patient, first visit), and Dec 28, 2020 (last patient, last visit), 210 people were screened, of whom 72 were enrolled and received at least one dose of study drug (figure 1). Of these enrolled participants, 43 (60%) completed the study. The most common reason for study discontinuation (21 participants) was a medical decision related to COVID-19 by a participant's physician. Discontinuation due to COVID-19 pandemic restrictions largely affected cohorts one and two: in the LY3437943 0·5 mg group no participants completed the study, and only one participant in the 1·5 mg group completed the study. In these groups, participants received treatment for a mean of 10 weeks and 5 weeks, respectively. Of the 72 participants, 37 (51%) were female, mean age was 58·4 (SD 7·4) years, and mean BMI was 32·1 (5·1) kg/m². There was variability between the groups for some baseline parameters, including age, sex, and BMI (table 1). All participants used metformin throughout the study.

TEAEs were reported by 33 (63%) of the 52 participants who received LY3437943, three (60%) of the five participants who received dulaglutide 1·5 mg, and eight (54%) of the 15 participants who received placebo (table 2). 23 (44%) of the 52 participants who received LY3437943 reported TEAEs that were considered related to study treatment, as determined by the investigator. The proportion of participants with TEAEs that were considered related to study treatment increased with increasing dose of LY3437943. However, with the exception of the LY3437943 3/6/9/12 mg group and the 3/6 mg group, the proportion of participants with TEAEs in the LY3437943-treated groups was similar to or less than that observed in the placebo and dulaglutide 1·5 mg groups.

Gastrointestinal TEAEs were reported in nine (33%) participants who received placebo, 12 (60%) participants who received dulaglutide 1·5 mg, and 24 (46%)

participants who received LY3437943 (table 2). Diarrhoea and nausea were the most frequently reported gastrointestinal TEAEs. Within the LY3437943-treated groups, higher proportions of participants in the 3/6/9/12 mg group reported gastrointestinal-related TEAEs (including diarrhoea, nausea, abdominal distention, eructation, dyspepsia, vomiting, and soft faeces) compared with the lower LY3437943 dose groups (table 2). Most gastrointestinal-related TEAEs were mild or moderate and resolved within approximately 10 days of onset, despite continuing study treatment exposure. Overall, 15 (18%) participants reported decreased

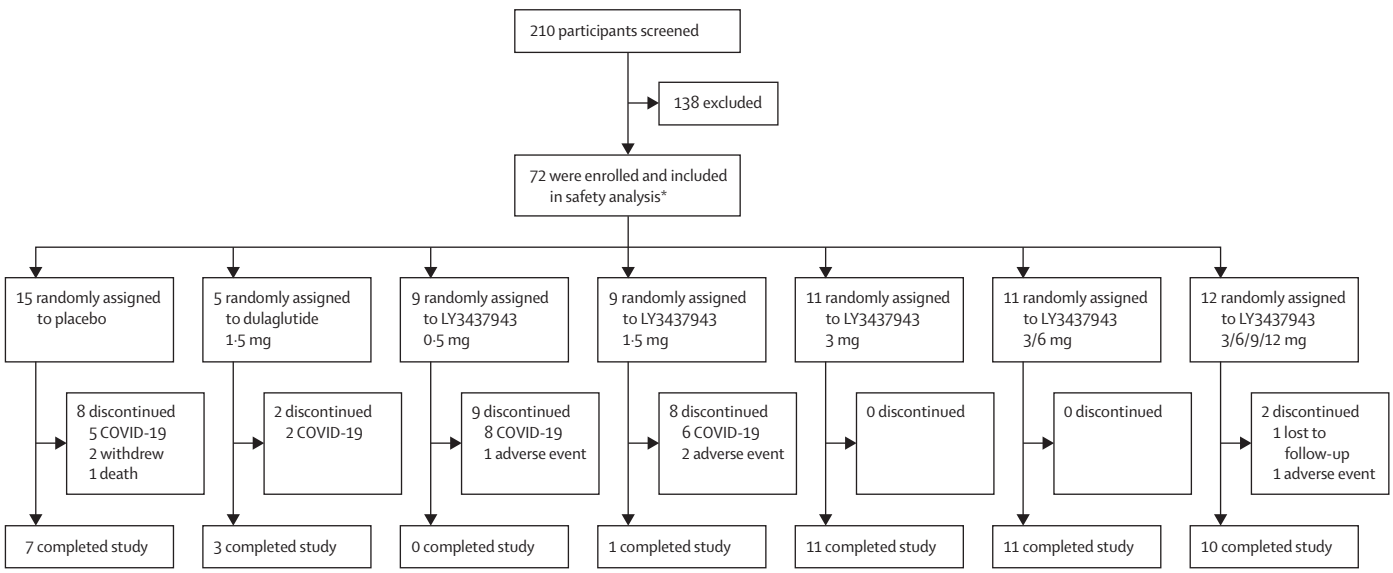

Figure 1: **Trial profile**
One death occurred in a placebo-treated participant and was not related to study treatment. *All participants who received at least one dose of study drug.

	Placebo (n=15)	Dulaglutide 1·5 mg (n=5)	LY3437943 0·5 mg (n=9)	LY3437943 1·5 mg (n=9)	LY3437943 3 mg (n=11)	LY3437943 3/6 mg (n=11)	LY3437943 3/6/9/12 mg (n=12)	Total (n=72)
Age, years	58·8 (6·4)	59·8 (7·5)	59·2 (6·6)	56·8 (5·7)	56·8 (8·0)	55·8 (10·7)	61·5 (6·3)	58·4 (7.4)
Sex								
Male	3 (20%)	4 (80%)	4 (44%)	3 (33%)	6 (55%)	7 (64%)	8 (67%)	35 (49%)
Female	12 (80%)	1 (20%)	5 (56%)	6 (67%)	5 (46%)	4 (36%)	4 (33%)	37 (51%)
Ethnicity								
Not Hispanic or Latino	4 (27%)	0	2 (22%)	1 (11%)	4 (36%)	2 (18%)	1 (8%)	14 (19%)
Hispanic or Latino	11 (73%)	5 (100%)	7 (78%)	8 (89%)	7 (64%)	9 (82%)	11 (92%)	58 (81%)
Race								
Asian	0	0	0	0	0	1 (9%)	0	1 (1%)
Black or African American	2 (13%)	0	3 (33%)	1 (11%)	3 (27%)	1 (9%)	1 (8%)	11 (15%)
White	12 (80%)	5 (100%)	6 (67%)	8 (89%)	8 (73%)	9 (82%)	11 (92%)	59 (82%)
Weight, kg	84·1 (19·9)	84·9 (14·1)	86·6 (24·1)	82·5 (17·3)	84·5 (14·4)	92·4 (15·2)	84·7 (14·7)	85·7 (17·1)
BMI, kg/m^2	32·3 (6·2)	30·1 (2·0)	33·3 (6·3)	32·4 (6·1)	31·7 (5·1)	33·7 (3·9)	30·5 (3·6)	32·1 (5·1)
Waist circumference, cm	105·8 (17·6)	103·9 (6·5)	108·1 (13·4)	104·1 (12·3)	106·4 (8·9)	109·2 (10·4)	103·7 (10·7)	106·0 (12·2)
Duration of diabetes, years	9·2 (6·0)	14·2 (4·5)	10·7 (5·2)	9·0 (5·8)	10·2 (4·6)	12·9 (7·7)	10·0 (5·4)	10·6 (5·8)
HbA_{1c}, %	8·83 (1·06)	8·50 (0·86)	8·07 (0·74)	8·87 (0·79)	8·65 (0·98)	9·05 (0·81)	8·45 (0·92)	8·66 (0·92)

Data are mean (SD) or n (%). BMI=body-mass index; HbA_{1c}=glycated haemoglobin. n=number of patients who were enrolled and received at least one dose of study drug (intention-to-treat population).

Table 1: **Demographics and baseline characteristics**

	Placebo (n=15)	Dulaglutide 1·5 mg (n=5)	LY3437943 0·5 mg (n=9)	LY3437943 1·5 mg (n=9)	LY3437943 3 mg (n=11)	LY3437943 3/6 mg (n=11)	LY3437943 3/6/9/12 mg (n=12)
All TEAEs	8 (53%)	3 (60%)	3 (33%)	5 (56%)	5 (46%)	9 (82%)	11 (92%)
Treatment-related TEAEs	5 (33%)	3 (60%)	1 (11%)	3 (33%)	4 (36%)	4 (36%)	11 (92%)
Serious adverse events	1 (7%)	1 (20%)	1 (11%)	1 (11%)	0	0	0
Deaths	1 (7%)*	0	0	0	0	0	0
TEAEs leading to study treatment discontinuation	0	0	1 (11%)	2 (22%)	0	0	1 (9%)
Gastrointestinal TEAEs	5 (33%)	3 (60%)	1 (11%)	4 (44%)	4 (36%)	5 (46%)	10 (83%)
Diarrhoea	2 (13%)	3 (60%)	1 (11%)	3 (33%)	1 (9%)	2 (18%)	6 (50%)
Nausea	2 (13%)	2 (20%)	0	0	1 (9%)	4 (36%)	6 (50%)
Abdominal distension	1 (7%)	1 (20%)	0	3 (33%)	0	0	3 (25%)
Dyspepsia	1 (7%)	1 (20%)	0	1 (11%)	1 (9%)	0	2 (17%)
Constipation	1 (7%)	0	0	1 (11%)	1 (9%)	1 (9 %)	1 (8%)
Eructation	0	0	0	0	0	0	5 (42%)
Vomiting	0	1 (20%)	0	1 (11%)	0	0	3 (25%)
Abdominal pain	0	1 (20%)	0	1 (11%)	0	0	0
Soft faeces	0	0	0	0	0	0	2 (17%)
Dry mouth	0	0	0	0	0	0	1 (8%)
Flatulence	1 (7%)	0	0	0	0	0	0
Gastro-oesophageal reflux disease	0	0	0	0	0	1 (9%)	0

Data are number of patients with event (%). n=number of patients who were enrolled and received at least one dose of study drug (intention-to-treat population). TEAE=treatment-emergent adverse event. *One death occurred in a placebo-treated participant and was not related to study treatment.

Table 2: **Summary of safety and TEAEs**

appetite, with the highest incidence observed in the 3/6/9/12 mg group.

Four (6%) participants discontinued because of a TEAE. Of these TEAEs, two were considered related to study drug: one treatment-related adverse event of diarrhoea in the LY3437943 1·5 mg group and one treatment-related adverse event of nausea after the 6 mg LY3437943 dose at week 4 in the 3/6/9/12 mg group. Six serious adverse events were reported in four participants, none of which were related to study drug. One death occurred in a placebo-treated participant due to a motor vehicle accident. Regarding adverse events of special interest with incretin agents, there were no reported TEAEs relating to pancreatitis, major adverse cardiovascular events, severe persistent hypoglycaemia, thyroid malignancies, C-cell hyperplasia, cardiovascular events, hypersensitivity reactions, injection-site reactions, hepatobiliary disorders, severe gastrointestinal events, or acute renal events during the study. Mean alanine aminotransferase and aspartate aminotransferase concentrations decreased from baseline to end of treatment in all groups except for the dulaglutide 1·5 mg group (appendix p 2).

Changes in HbA_{1c}, bodyweight, lipids, and vital signs are shown in figure 2A–F. Mean systolic blood pressure generally decreased from baseline in the LY3437943 groups, with reductions of up to 12 mm Hg (figure 2D, appendix p 3), and a similar trend was observed for diastolic blood pressure, with reductions of up to 2 mm Hg (figure 2E, appendix p 3). Pulse rate increased from baseline in the higher LY3437943 dose groups (figure 2F, appendix p 3). The magnitude of this increase in the three highest dose LY3437943 groups was between 2 beats per min (bpm) and 13 bpm at 24 h after the last treatment dose and between –1 bpm and 10 bpm when averaged over the final 4 weeks of treatment. The changes with dulaglutide 1·5 mg were 2 bpm (24 h after last treatment dose) and –4 bpm (over final 4 weeks).

Pharmacokinetic data indicated that the plasma concentrations of LY3437943, $AUC_{(0\text{-}\tau)}$, and C_{max} were approximately proportional across the dose range studied (appendix pp 4, 6). Median time to t_{max} was 12–48 h post-dose, and the half-life was approximately 6 days.

At week 12, mean daily plasma glucose decreased in all groups (table 3, appendix p 7). Decreases were significantly greater with LY3437943 in the 3 mg (LSM difference –2·8 mmol/L [90% CI –4·63 to –0·94]), 3/6 mg (–3·1 mmol/L [–4·91 to –1·22]), and 3/6/9/12 mg (–2·9 mmol/L [–4·70 to –1·01]) groups compared with the placebo group. The effect on plasma glucose increased with increasing LY3437943 doses up to 6 mg, with no further reductions in participants who received the 9 mg and 12 mg doses of LY3437943 within the 3/6/9/12 mg group. The LSM placebo-adjusted change in plasma glucose in participants who received dulaglutide 1·5 mg was –2·4 mmol/L (90% CI –4·90 to 0·01). HbA_{1c} values also decreased in all the active treatment groups compared with those at baseline. The 90% CI for the placebo-adjusted changes in HbA_{1c} excluded zero in the three highest dose LY3437943 groups, with a similar magnitude of decrease in the 3 mg (LSM difference –1·4% [90% CI

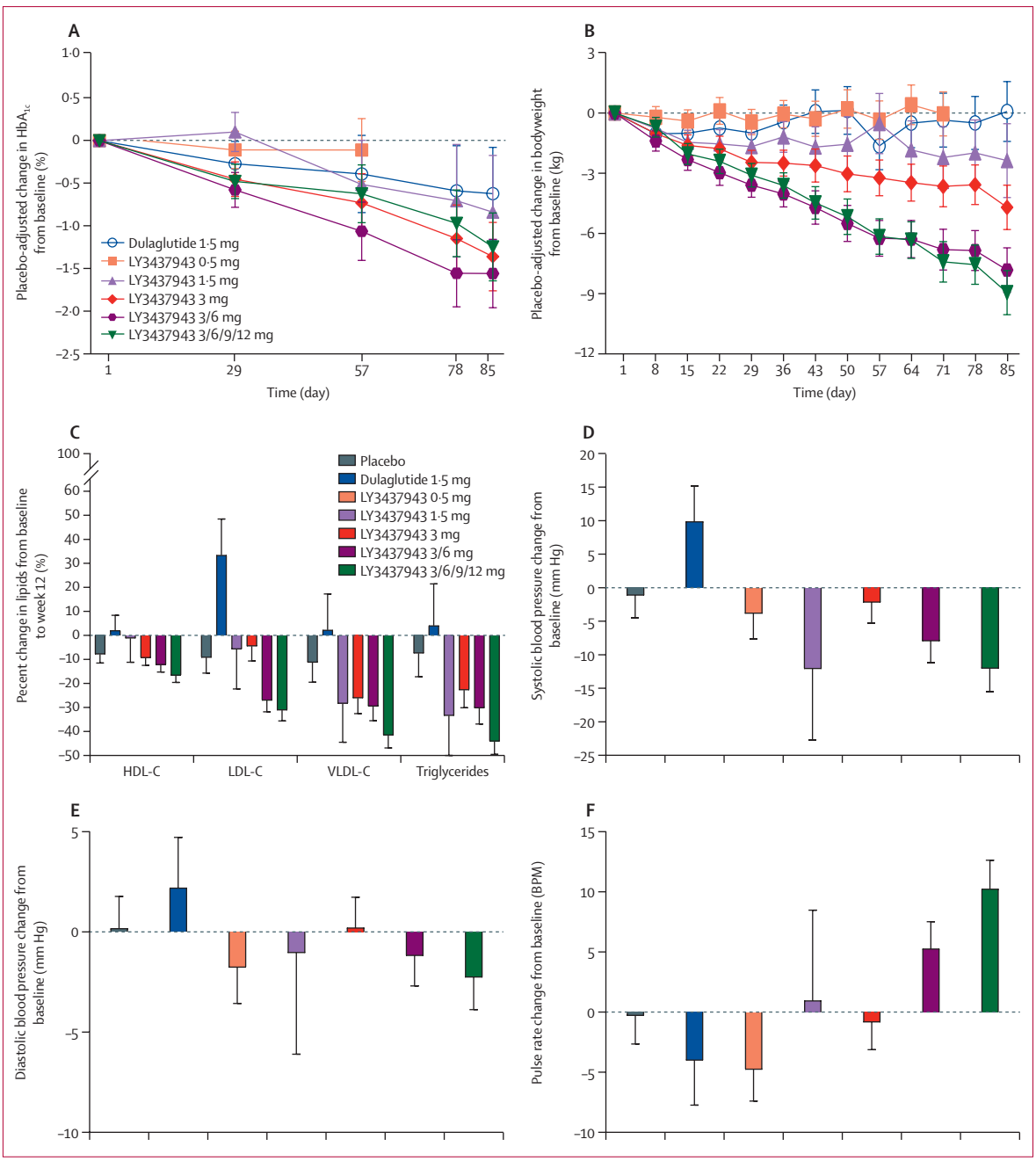

Figure 2: **HbA_{1c}, bodyweight, lipids, and vital signs**
LSM (SE) placebo-adjusted change from baseline in HbA_{1c} (A) and bodyweight (B) over time. (C) LSM (SE) percent change from baseline to week 12 (day 80) for lipids. LS mean (SE) change from baseline to end of study (values averaged over the final 4 weeks) for systolic blood pressure (D), diastolic blood pressure (E), and pulse rate (F). Due largely to COVID-19-related pandemic restrictions, no participants in the LY3437943 0·5 mg group and only one participant in the LY3437943 1·5 mg group completed the study. In these groups, participants received treatment for an average of 10 weeks and 5 weeks, respectively. BPM=beats per minute. C=cholesterol. HbA_{1c}=glycated haemoglobin A_{1c}. LSM=least-squares mean.

–2·17 to –0·56]), 3/6 mg (–1·6% [–2·37 to –0·75]), and 3/6/9/12 mg (–1·2% [–2·05 to –0·45]) groups (table 3, figure 2A). The LSM placebo-adjusted change in HbA_{1c} with dulaglutide 1·5 mg was –0·6% (90% CI –1·71 to 0·47).

At week 12, fasting glucose across LY3437943 doses of 1·5 mg and higher decreased to a greater extent than placebo (LSM difference –3·2 mmol/L [90% CI –5·91 to –0·57) for the 1·5 mg group, –1·6 mmol/L [–2·95 to –0·32] for the 3 mg group, –1·8 mmol/L [–3·09 to –0·47] for the 3/6 mg group, and –2·0 mmol/L [–3·29 to –0·64] for the 3/6/9/12 mg group; table 3). The LSM placebo-adjusted change with

	Placebo (n=15)	Dulaglutide 1·5 mg (n=5)	LY3437943 0·5 mg (n=9)*	LY3437943 1·5 mg (n=9)*	LY3437943 3 mg (n=11)	LY3437943 3/6 mg (n=11)	LY3437943 3/6/9/12 mg (n=12)
Mean daily plasma glucose, mmol/L							
Baseline	10·7 (0·65)	11·8 (1·13)	10·0 (0·63)	12·5 (0·77)	12·5 (0·71)	12·5 (1·05)	11·5 (0·92)
Change from baseline†	−1·3 (0·65)	−3·7 (1·03)	..	−3·2 (1·38)	−4·1 (0·64)	−4·4 (0·64)	−4·1 (0·65)
Placebo-adjusted change†	..	−2·4 (−4·90 to 0·01)	..	−1·9 (−4·94 to 1·20)	−2·8 (−4·63 to −0·94)	−3·1 (−4·91 to −1·22)	−2·9 (−4·70 to −1·01)
HbA_{1c}, %							
Baseline	8·82 (0·27)	8·42 (0·44)	8·10 (0·25)	8·71 (0·28)	8·63 (0·28)	8·96 (0·26)	8·45 (0·27)
Change from baseline‡	−0·34 (0·28)	−0·96 (0·47)	..	−1·18 (0·61)	−1·70 (0·29)	−1·90 (0·29)	−1·59 (0·29)
Placebo-adjusted change‡	..	−0·6 (−1·71 to 0·47)	..	−0·84 (−2·18 to 0·50)	−1·4 (−2·17 to −0·56)	−1·6 (−2·37 to −0·75)	−1·2 (−2·05 to −0·45)
HbA_{1c}, mmol/mol							
Baseline	73·0 (2·99)	68·6 (4·81)	65·1 (2·74)	71·8 (3·09)	70·9 (3·09)	74·6 (2·78)	69·0 (2·97)
Change from baseline‡	−3·7 (3·05)	−10·5 (5·10)	..	−12·9 (6·63)	−18·6 (3·16)	−20·7 (3·17)	−17·3 (3·11)
Placebo-adjusted change‡	..	−6·8 (−18·72 to 5·11)	..	−9·2 (−23·80 to 5·41)	−14·9 (−23·71 to −6·08)	−17·1 (−25·89 to −8·24)	−13·6 (−22·39 to −4·90)
Bodyweight, kg							
Baseline	84·1 (5·13)	84·9 (6·31)	86·6 (8·02)	82·5 (5·76)	84·5 (4·35)	92·4 (4·58)	84·7 (4·25)
Change from baseline‡	0·3 (0·77)	0·4 (1·28)	..	−2·1 (1·67)	−4·4 (0·79)	−7·5 (0·80)	−8·6 (0·79)
Placebo-adjusted change‡	..	0·08 (−2·92 to 3·07)	..	−2·37 (−6·03 to 1·29)	−4·71 (−6·93 to −2·48)	−7·83 (−10·06 to −5·61)	−8·96 (−11·16 to −6·75)
Waist circumference, cm							
Baseline	105·8 (4·53)	103·9 (2·88)	108·1 (4·46)	104·1 (4·11)	106·4 (2·69)	109·2 (3·12)	103·7 (3·10)
Change from baseline‡	−0·7 (1·90)	−3·3 (3·01)	..	−6·6 (4·60)	−5·8 (1·73)	−1·9 (1·73)	−7·1 (1·75)
Placebo-adjusted change‡	..	−2·6 (−9·72 to 4·56)	..	−5·9 (−15·91 to 4·09)	−5·1 (−10·31 to 0·02);	−1·2 (−6·39 to 3·95)	−6·4 (−11·59 to −1·21)
Fasting glucose, mmol/L							
Baseline	10·1 (0·69)	9·3 (0·64)	9·7 (0·74)	10·5 (1·03)	11·5 (0·59)	10·7 (0·96)	10·0 (0·66)
Change from baseline†	−1·8 (0·49)	−2·7 (0·76)	..	−5·0 (1·23)	−3·4 (0·43)	−3·6 (0·43)	−3·8 (0·44)
Placebo-adjusted change†	..	−0·9 (−2·73 to 0·90)	..	−3·2 (−5·91 to −0·57)	−1·6 (−2·95 to −0·32)	−1·8 (−3·09 to −0·47)	−2·0 (−3·29 to −0·64)
Fasting insulin, pmol/L							
Baseline	94·5 (15·61)	72·7 (22·94)	141·6 (28·11)	93·0 (17·30)	104·1 (30·89)	70·6 (11·6)	75·4 (14·13)
Change from baseline†	−10·0 (12·49)	−5·6 (19·18)	..	−9·1 (33·03)	−9·8 (10·08)	4·9 (10·09)	−13·7 (10·51)
Placebo-adjusted change†	..	4·4 (−41·58 to 50·44)	..	0·9 (−70·50 to 72·34)	0·2 (−32·24 to 32·74)	14·9 (−17·32 to 47·20)	−3·7 (−36·54 to 29·16)
Fasting C-peptide, pmol/L							
Baseline	734·5 (75·65)	704·2 (119·01)	915·7 (106·88)	753·2 (83·30)	665·3 (67·37)	673·0 (80·50)	660·8 (78·80)
Change from baseline†	39·0 (76·37)	12·9 (117·65)	..	−23·4 (204·25)	−37·8 (62·62)	19·0 (62·61)	19·3 (65·44)
Placebo-adjusted change†	..	−26·0 (−308·98 to 256·89)	..	−62·4 (−503·15 to 378·32)	−76·8 (−276·04 to 122·39)	−19·9 (−219·16 to 179·28)	−19·7 (−222·50 to 183·18)
OGTT $AUC_{(0\text{-}2\ h)}$							
Glucose, mmol·h/L							
Baseline	32·5 (1·63)	34·2 (1·86)	30·3 (1·66)	32·3 (1·69)	37·3 (1·95)	35·2 (1·40)	32·0 (0·90)
Change from baseline§	−4·2 (1·61)	−9·9 (2·49)	..	−5·4 (3·77)	−11·3 (1·47)	−13·5 (1·44)	−10·7 (1·48)
Placebo-adjusted change§	..	−5·7 (−11·63 to 0·29)	..	−12 (−9·41 to 7·11)	−7·1 (−11·47 to −2·65)	−9·2 (−13·58 to −4·88)	−6·5 (−10·86 to −2·11)
Insulin, pmol·h/L							
Baseline	485·5 (90·58)	386·6 (159·52)	671·9 (111·55)	430·9 (76·80)	395·5 (105·39)	354·6 (60·37)	395·1 (98·26)
Change from baseline§	46·7 (166·64)	541·2 (250·08)	..	410·2 (353·89)	296·3 (148·03)	372·7 (148·13)	446·6 (148·36)
Placebo-adjusted change§	..	494·5 (−112·22 to 1101·14)	..	363·5 (−422·40 to 1149·37)	249·6 (−201·60 to 700·72)	326·0 (−125·68 to 777·71)	399·8 (−51·32 to 851·02)

(Table 3 continues on next page)

	Placebo (n=15)	Dulaglutide 1·5 mg (n=5)	LY3437943 0·5 mg (n=9)*	LY3437943 1·5 mg (n=9)*	LY3437943 3 mg (n=11)	LY3437943 3/6 mg (n=11)	LY3437943 3/6/9/12 mg (n=12)
(Continued from previous page)							
C-peptide, pmol·h/L							
Baseline	2341·3 (245·64)	2292·3 (510·47)	3085·8 (299·93)	2079·5 (244·18)	2138·9 (253·90)	2310·9 (279·51)	2382·4 (451·96)
Change from baseline§	344·5 (357·58)	1493·7 (567·85)	..	1091·5 (818·89)	645·5 (332·80)	946·5 (348·73)	949·6 (335·12)
Placebo-adjusted change§	..	1149·2 (–200·49 to 2498·99)	..	747·1 (–1048·96 to 2543·09)	301·1 (–682·80 to 1284·93)	602·0 (–403·88 to 1607·93)	605·2 (–380·42 to 1590·75)
Glucagon, pmol·h/L							
Baseline	20·2 (2·13)	25·6 (4·59)	25·2 (2·39)	21·4 (2·57)	28·2 (3·30)	23·7 (1·79)	27·7 (3·09)
Change from baseline§	0·6 (2·15)	–2·2 (3·32)	..	–12·0 (4·41)	–19·5 (2·04)	–19·4 (2·02)	–23·9 (2·06)
Placebo-adjusted change§	..	–2·8 (–10·79 to 5·17)	..	–12·6 (–22·44 to –2·82)	–20·1 (–26·17 to –14·11)	–20·0 (–25·99 to –14·10)	–24·5 (–30·57 to –18·48)

Data are least-squares mean (SE) at baseline or change from baseline and least-squares mean difference (90% CI) placebo-adjusted change from baseline. AUC=area under the concentration–time curve. HbA_{1c}=glycated haemoglobin A1c. n=number of patients who were enrolled and received at least one dose of study drug (intention-to-treat population). OGTT=oral glucose tolerance test. *Due largely to COVID-19 related pandemic restrictions, no participants in the LY3437943 0·5 mg group and only one participant in the LY3437943 1·5 mg group completed the study. †At day 80. ‡At day 85. §At day 79. Mean daily glucose is calculated from 6-point plasma glucose.

Table 3: **Summary of pharmacodynamics**

dulaglutide 1·5 mg was –0·9 mmol/L (90% CI –2·73 to 0·90). There were no statistically significant changes in fasting insulin and C-peptide from baseline to week 12 in any of the treatment groups compared with placebo (table 3).

An oral glucose tolerance test was conducted to assess the effects of LY3437943 on key pancreatic regulatory hormones. Glucose $AUC_{(0–2\ h)}$ during the test decreased from baseline in all groups (table 3). The 90% CI for the placebo-adjusted decreases in the three highest dose LY3437943 groups excluded zero (LSM difference –7·1 mmol·h/L [90% CI –11·47 to –2·65] for the 3 mg group, –9·2 mmol·h/L [–13·58 to –4·88] for the 3/6 mg group, and –6·5 mmol·h/L [–10·86 to –2·11] for the 3/6/9/12 mg group), and the greatest differences occurred at the end of study treatment. There was no apparent dose-dependent effect. The LSM placebo-adjusted change in glucose $AUC_{(0–2\ h)}$ observed with dulaglutide 1·5 mg was –5·7 mmol·h/L (90% CI –11·63 to 0·29). At week 12, mean insulin and C-peptide $AUC_{(0–2\ h)}$ were changed in all groups and were not significantly different between LY3437943 and placebo (table 3). The LY3437943 3 mg, 3/6 mg, and 3/6/9/12 mg groups showed a similar pattern in these measures. The increases in insulin and C-peptide $AUC_{(0–2\ h)}$ also did not differ significantly between dulaglutide 1·5 mg and placebo. Glucagon $AUC_{(0–2\ h)}$ decreased from baseline in the LY3437943 groups to a significantly greater extent than that in the placebo group (LSM difference –12·6 pmol·h/L [90% CI –22·44 to –2·82) for 1·5 mg, –20·1 pmol·h/L (–26·17 to –14·11) for 3 mg, –20·0 pmol·h/L (–25·99 to –14·10) for 3/6 mg, and –24·5 pmol·h/L (–30·57 to –18·48) for 3/6/9/12 mg). These decreases were greatest at week 12, at the end of the treatment period. The decreases were also the largest in the three highest LY3437943 dose groups. The LSM change in glucagon $AUC_{(0–2\ h)}$ relative to placebo at week 12 in the dulaglutide 1·5 mg group was –2·8 pmol·h/L (90% CI –10·79 to 5·17).

Bodyweight decreased with LY3437943 treatment (table 3, figure 2B). These decreases were significantly greater than with placebo in the three highest dose LY3437943 groups (LSM difference –4·71 kg [90% CI –6·93 to –2·48] for the 3 mg group, –7·83 kg [–10·06 to –5·61] for the 3/6 mg group, and –8·96 kg [–11·16 to –6·75] for the 3/6/9/12 mg group). Bodyweight reductions did not appear to plateau over the 12-week treatment period and were dose dependent, with the greatest weight loss in the 3/6/9/12 mg group. The LSM placebo-adjusted change from baseline in bodyweight in the dulaglutide 1·5 mg group at week 12 was 0·08 kg (90% CI –2·92 to 3·07). Waist circumference decreased over time in the LY3437943 dose groups, with a significant decrease relative to placebo in the highest dose LY3437943 group at 12 weeks (LSM difference –6·4 cm [90% CI –11·59 to –1·21]; table 3). Waist circumference also decreased with dulaglutide 1·5 mg but the 90% CI did not exclude zero (LSM difference –2·6 [90% CI –9·72 to 4·56]).

Appetite VAS scores generally increased from baseline in the LY3437943 dose groups, indicating a reduction in overall appetite (appendix p 8). At week 12, this effect was significant relative to placebo in the LY3437943 3/6 mg group (LSM difference 23·3 [90% CI 6·72 to 39·86]), but not in the LY3437943 3/6/9/12 mg group (11·4 [–5·34 to 28·21]). With respect to individual components of the overall score, prospective food consumption (appetite) and hunger scores generally decreased from baseline in the LY3437943 groups, with no significant placebo-adjusted decreases from baseline in any group. Fullness and satiety scores generally increased from baseline with LY3437943 treatment, with

statistically significant placebo-adjusted increases at week 12 in the 3/6 mg LY3437943 group (LSM difference 27·7 [90% CI 5·29 to 50·20] for fullness and 30·7 [9·25 to 52·13] for satiety). Changes and magnitude in VAS with dulaglutide 1·5 mg showed generally similar trends to LY3437943 (appendix p 8).

LY3437943 showed several effects on serum lipid parameters (figure 2C). At week 12, LDL cholesterol decreased in the LY3437943 groups. LSM decreases in LDL cholesterol were greater in the LY3437943 3/6 mg and 3/6/9/12 mg groups than that in the LY3437943 3 mg group, achieving reductions as large as 31%. Placebo-adjusted changes from baseline were significant in the two higher dose LY3437943 groups (LSM difference –19·6% [90% CI –33·54 to –2·83] and –24·1% [–37·26 to –8·20]). In contrast to the LY3437943 groups, placebo-adjusted LDL cholesterol increased in the dulaglutide 1·5 mg group at week 12 (LSM difference 47·0% [90% CI 12·99 to 91·19]). VLDL cholesterol decreased in a dose-dependent manner with LY3437943 at week 12; the decrease was significant versus placebo in the 3/6/9/12 mg group (LSM difference –34·2% [90% CI –49·00 to –14·98]). Triglycerides also decreased in a dose-dependent manner in the LY3437943 groups, resulting in reductions of up to 44% from baseline, and with significant changes relative to placebo in the 3/6 mg (LSM difference –24·6% [90% CI –43·05 to –0·27]) and 3/6/9/12 mg (–39·6% [–54·45 to –19·93]) groups. A decrease in HDL cholesterol was observed in the LY3437943 and placebo groups at week 12, with non-statistically significant differences between LY3437943 and placebo. There were no statistically significant placebo-adjusted changes in VLDL cholesterol (LSM difference 15·3% [90% CI –18·13 to 62·26]), triglycerides (12·5% [–23·75 to 65·89]), or HDL cholesterol (7·2% [–13·42 to 32·80]) after 12 weeks of treatment with dulaglutide 1·5 mg.

Discussion

The findings from this multiple-ascending dose, phase 1 clinical trial provide initial evidence of the safety and efficacy of the triple GLP-1, GIP, and glucagon receptor agonist LY3437943 in participants with type 2 diabetes. LY3437943 showed a safety profile that is consistent with the safety profile reported with other incretin-based therapeutic agents in early phases of development. The findings suggest that simultaneous agonism on these three receptors is a therapeutic approach that has acceptable safety and tolerability across a range of doses administered over 12 weeks. The pharmacokinetics of LY3437943 were dose proportional, with a half-life of approximately 6 days enabling attainment and maintenance of meaningful steady-state exposures after once-weekly dosing. LY3437943 showed glycaemic efficacy with significant and clinically meaningful decreases in fasting and postprandial plasma glucose, and HbA_{1c} compared with placebo. Bodyweight loss was also significant relative to placebo and appeared to be dose dependent across the entire dose range studied in the trial. These results suggest that triple-receptor agonism on GIP, GLP-1, and glucagon receptors enabled by LY3437943 is a promising option for treatment of common metabolic abnormalities, such as type 2 diabetes or obesity and its comorbidities, and support phase 2 development.

In the assessment of the potential of LY3437943 treatment for common metabolic conditions, key efficacy data for other incretin agents that have received regulatory approval or are currently in clinical development are of interest. After initial approval of shorter acting GLP-1 receptor agonists, such as exenatide and liraglutide, more potent once-weekly GLP-1 receptor agonists, such as semaglutide or dulaglutide, became available. For the treatment of type 2 diabetes, semaglutide has been approved in doses up to 2 mg that provide reductions of up to 2·2% in HbA_{1c} and 6·9 kg in bodyweight loss after 40 weeks.[22] Semaglutide 2·4 mg provided reductions of up to 16·9% in bodyweight in individuals with obesity and without type 2 diabetes in the STEP-1 trial.[23]

The next generation incretins incorporate additional incretin receptor activity by combining GIP receptor agonism with GLP-1 receptor agonism. Tirzepatide is the only agent with dual GIP and GLP-1 receptor agonism that has received regulatory approval to date. In the phase 3 SURPASS trials, tirzepatide reduced HbA_{1c} by up to 2·6% and bodyweight by up to 12·9 kg in individuals with type 2 diabetes.[8] In people with overweight or obesity without type 2 diabetes, the mean percentage weight reduction was up to 22·5% after 72 weeks of tirzepatide treatment (SURMOUNT-1).[24] These findings show that the addition of GIP receptor activity enhances the efficacy of GLP-1 receptor agonism.

Agonists with combined glucagon and GLP-1 receptor agonist activity have also been in development for treatment of type 2 diabetes or obesity. Clinical efficacy and safety data for these agents are currently scarce. Cotadutide (MEDI-0382) is the only agent in late-stage development. In a phase 2b, 54-week trial,[25] the highest dose of cotadutide (300 µg) yielded reductions of 1·2% in HbA_{1c} and 5·0% in bodyweight. In a phase 2, 12-week study with JNJ-64565111,[26] decreases of up to 7·9% in bodyweight were reported; however there was no effect on HbA_{1c} and worsening of fasting glycaemia was observed. The difference in ratio potency on glucagon and GLP-1 receptors between cotadutide and JNJ-64565111 might explain the discrepant effect on glycaemic control, suggesting the importance of the activity ratio for clinical outcomes.[17] There are no long-term data in individuals with obesity for these agents. Other dual glucagon and GLP-1 receptor agonists, including BI-456906 (NCT04667377, NCT04153929, NCT04771273),[27] mazdutide (LY3305677),[28] and pemvidutide (ALT-801; NCT05295875, NCT05134662)[29] are in early stage development for various indications, and long-term glycaemia-lowering or bodyweight-lowering efficacy data are currently not available.

Another approach is targeting all three receptors of interest—namely, GIP, GLP-1, and glucagon—with a single molecule, as with LY3437943. One such agent (SAR441255) had a single-ascending dose study in healthy individuals, but further development has been halted.[15] Another triple agonist, HM-15211, is in development for non-alcoholic steatohepatitis only (NCT04505436). As with dual glucagon and GLP-1 receptor agonists, the molecular structure and ratio of activities on each receptor with triple GLP-1, GIP, and glucagon receptor agonists might have differentiated effects on clinical outcomes.

Incretin agonists have been associated with gastrointestinal adverse events, including nausea, vomiting, and diarrhoea, which are generally more frequent during dose escalation.[30–32] Similarly, the most common adverse events for dual GLP-1 and glucagon receptor agonists are gastrointestinal related.[25,26,33] In this study, more LY3437943-treated participants reported gastrointestinal TEAEs than did those treated with placebo, but at a frequency similar to those treated with dulaglutide 1·5 mg. Notably, we did not escalate dulaglutide by using a lower 0·75 mg dose as the starting dose due to the short duration of the study and the primary focus on comparisons with placebo, which might have affected the incidence of these adverse events in this group. A higher occurrence of gastrointestinal adverse events in the highest dose LY3437943 group (ie, 3/6/9/12 mg) could potentially be mitigated by optimisation of a stepwise dose escalation scheme for patients.

We observed decreases in systolic and diastolic blood pressure and increases in heart rate with LY3437943 treatment. These effects were consistent with data from other incretin development programmes but potentially of greater magnitude.[25,26,30–34] Although most incretin agents reduce systolic blood pressure in low single digits, we observed a greater effect with LY3437943 during the 12-week treatment period. Increases in heart rate were shown with the highest investigated doses of LY3437943, without any meaningful differences in other cardiovascular safety parameters between the treatment groups, including major cardiovascular events or supraventricular tachyarrhythmias. Because of the short duration of the trial, we could not assess long-term changes in heart rate, especially whether early increases diminish over time, as shown with other incretins.[8,25] In addition to the known factors that contribute to the heart rate effect, such as blood pressure lowering and the direct effect of GLP-1 on the sinoatrial node, glucagon receptor signalling with LY3437943 might also be involved. More long-term data are required to determine if this mechanism might result in differential effects with triple GIP, GLP-1, and glucagon receptor agonists versus single GLP-1 receptor agonists and dual GIP and GLP-1 receptor agonists. A long-term cardiovascular outcome trial will be needed for complete assessment of the effect of LY3437943 on cardiovascular risk factors and relevant outcomes, including major cardiovascular events and tachyarrhythmias.

LY3437943 showed glycaemic control efficacy, as shown by reductions in mean daily plasma glucose and HbA_{1c}, which were significant relative to placebo and clinically meaningful. Although increased gluconeogenesis in the fasting state is a well defined physiological role of glucagon, our results showed that combining glucagon, GIP, and GLP-1 receptor activity did not substantially reduce glucose-lowering efficacy. Importantly, during the oral glucose tolerance test, LY3437943 reduced glucose excursions and endogenous glucagon concentrations, without significantly increasing placebo-adjusted insulin concentrations. This finding suggests that the combined effects on target receptors provided by LY3437943 might reduce the burden on pancreatic β cells. Whether this effect is mediated by a lowering of insulin resistance or by an increasing energy expenditure needs to be investigated in appropriately designed studies in the future.

A strong reduction in bodyweight in LY3437943-treated participants appeared to be dose dependent across the entire dose range, with a placebo-adjusted decrease of approximately 9 kg (10%) in the highest dose group. By contrast, bodyweight did not significantly change in the dulaglutide 1·5 mg group. The changes with LY3437943 treatment appear of a similar or greater magnitude relative to other agents in the incretin class within the short 12-week duration of this study.[25,26,30–33] Although there was some improvement in the overall appetite VAS scores that was also similar to the effects of dulaglutide in this trial, this does not fully explain the effect of LY3437943 on bodyweight. One more mechanism that might be involved in bodyweight-lowering efficacy in LY3437943-treated participants is an increase in energy expenditure resulting from glucagon receptor signalling. Multiple studies have shown that glucagon increases energy expenditure.[10,35] Use of higher doses of LY3437943 resulted in large reductions of LDL cholesterol, VLDL cholesterol, and triglycerides, illustrative of the potential to provide clinically meaningful improvements in dyslipidaemia. HDL cholesterol decreased in the LY3437943 groups, but not the dulaglutide 1·5 mg group. The pattern of these findings appears to be consistent with dual GLP-1 and glucagon receptor agonists.[25,26]

The strong effect of LY3437943 on bodyweight and potential beneficial metabolic actions of glucagon signalling in the liver, including increased lipid oxidation, raises a question of possible use of this agent for treatment of non-alcoholic fatty liver disease or non-alcoholic steatohepatitis. We did not include direct measures of liver fat in this trial, but we did observe a reduction in serum aminotransferase concentrations, which are commonly used biomarkers for these conditions. This important question is currently being explored in the phase 2 development programme for LY3437943 (NCT04867785 and NCT04881760).

An inherent limitation of this phase 1 study is its small sample size. Additionally, the within-cohort dose escalation scheme used might have not been fully

optimised. With relatively short steady-state exposure, the 12-week treatment period might not have allowed elucidation of the full glycaemic and weight loss potential of LY3437943. Given that participants in the trial represent a relatively restricted population of people with type 2 diabetes, the findings we report here might not be extrapolated to other groups of patients with type 2 diabetes. The inclusionary BMI range was wide, which might have affected pharmacodynamic outcomes. There were between-group differences in some of the baseline demographics and characteristics (eg, age, sex, and BMI) and, although the statistical models adjusted for the baseline response in an effort to address the covariate imbalance, these between-group differences could have influenced pharmacodynamic findings. Although key outcomes were measured, other measures of interest, such as energy expenditure and body composition, could not be explored. These measures can only be assessed in specialised centres and should be evaluated in dedicated studies. Comparison of LY3437943 with tirzepatide is also of interest, and would perhaps be a more suitable active comparator than a GLP-1 receptor agonist, but this evaluation was not possible in this study because tirzepatide was approved for treatment of type 2 diabetes only after study completion. Approximately 60% of participants completed our study. Discontinuations were primarily related to the COVID-19 pandemic, which meant that some participants were discontinued early from the study, which particularly limited the data availability in the LY3437943 0·5 mg and 1·5 mg groups, and the dulaglutide group. Notwithstanding these limitations, our findings support continued development, and phase 2 studies of LY3437943 are in progress in people living with type 2 diabetes (NCT04867785) and obesity or overweight (NCT04881760).

In summary, safety and tolerability data from this study suggest LY3437943 has a comparable safety profile to other incretin agonists. LY3437943 showed robust improvements in glycaemic control and bodyweight over the 12-week treatment period, indicating potential to improve metabolic health. In totality, these findings support further study of LY3437943 as a therapeutic agent for people living with type 2 diabetes and obesity.

Contributors

SU, CTB, and ZM contributed to the study design, SU and ZM provided medical oversight during the trial, and MH-I was the coordinating investigator. YD was responsible for the statistical analyses. SU, TC, MTL, YD, MKT, SG, AH, CTB, and ZM are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in interpretation of the data and critical review of the manuscript, had full access to the data, and approved this manuscript to be submitted for publication.

Declaration of interests

SU, TC, MTL, YD, SG, AH, CTB, and ZM are employees and shareholders of Eli Lilly and Company. MKT is an employee and shareholder of Eli Lilly and Company, and reports being industry chair of a steering committee on Accelerating Medicines Partnership-Type 2 Diabetes, and a steering committee member on Accelerating Medicines Partnership-Common Metabolic Diseases. DAD reports research grants and advisory fees from Eli Lilly and Company; research grants from Merck; consulting fees from Intarcia and Sun Pharmaceuticals; and editorial fees from American Diabetes Association journals. MH-I is an employee of QPS and was the principal investigator of this study. We declare no other competing interests.

Data sharing

Eli Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and in the EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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