Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA

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Summary

Background According to current consensus guidelines for type 2 diabetes management, bodyweight management is as important as attaining glycaemic targets. Retatrutide, a single peptide with agonist activity at the glucose-dependent insulinotropic polypeptide (GIP), GLP-1, and glucagon receptors, showed clinically meaningful glucose-lowering and bodyweight-lowering efficacy in a phase 1 study. We aimed to examine the efficacy and safety of retatrutide in people with type 2 diabetes across a range of doses.

Methods In this randomised, double-blind, double-dummy, placebo-controlled and active comparator-controlled, parallel-group, phase 2 trial, participants were recruited from 42 research and health-care centres in the USA. Adults aged 18–75 years with type 2 diabetes, glycated haemoglobin (HbA_{1c}) of 7·0–10·5% (53·0–91·3 mmol/mol), and BMI of 25–50 kg/m² were eligible for enrolment. Eligible participants were treated with diet and exercise alone or with a stable dose of metformin (≥1000 mg once daily) for at least 3 months before the screening visit. Participants were randomly assigned (2:2:2:1:1:1:1:2) using an interactive web-response system, with stratification for baseline HbA_{1c} and BMI, to receive once-weekly injections of placebo, 1·5 mg dulaglutide, or retatrutide maintenance doses of 0·5 mg, 4 mg (starting dose 2 mg), 4 mg (no escalation), 8 mg (starting dose 2 mg), 8 mg (starting dose 4 mg), or 12 mg (starting dose 2 mg). Participants, study site personnel, and investigators were masked to treatment allocation until after study end. The primary endpoint was change in HbA_{1c} from baseline to 24 weeks, and secondary endpoints included change in HbA_{1c} and bodyweight at 36 weeks. Efficacy was analysed in all randomly assigned, except inadvertently enrolled, participants, and safety was assessed in all participants who received at least one dose of study treatment. The study is registered at ClinicalTrials.gov, NCT04867785.

Findings Between May 13, 2021, and June 13, 2022, 281 participants (mean age 56·2 years [SD 9·7], mean duration of diabetes 8·1 years [7·0], 156 [56%] female, and 235 [84%] White) were randomly assigned and included in the safety analysis (45 in the placebo group, 46 in the 1·5 mg dulaglutide group, and 47 in the retatrutide 0·5 mg group, 23 in the 4 mg escalation group, 24 in the 4 mg group, 26 in the 8 mg slow escalation group, 24 in the 8 mg fast escalation group, and 46 in the 12 mg escalation group). 275 participants were included in the efficacy analyses (one each in the retatrutide 0·5 mg group, 4 mg escalation group, and 8 mg slow escalation group, and three in the 12 mg escalation group were inadvertently enrolled). 237 (84%) participants completed the study and 222 (79%) completed study treatment. At 24 weeks, least-squares mean changes from baseline in HbA_{1c} with retatrutide were –0·43% (SE 0·20; –4·68 mmol/mol [2·15]) for the 0·5 mg group, –1·39% (0·14; –15·24 mmol/mol [1·56]) for the 4 mg escalation group, –1·30% (0·22; –14·20 mmol/mol [2·44]) for the 4 mg group, –1·99% (0·15; –21·78 mmol/mol [1·60]) for the 8 mg slow escalation group, –1·88% (0·21; –20·52 mmol/mol [2·34]) for the 8 mg fast escalation group, and –2·02% (0·11; –22·07 mmol/mol [1·21]) for the 12 mg escalation group, versus –0·01% (0·21; –0·12 mmol/mol [2·27]) for the placebo group and –1·41% (0·12; –15·40 mmol/mol [1·29]) for the 1·5 mg dulaglutide group. HbA_{1c} reductions with retatrutide were significantly greater (p<0·0001) than placebo in all but the 0·5 mg group and greater than 1·5 mg dulaglutide in the 8 mg slow escalation group (p=0·0019) and 12 mg escalation group (p=0·0002). Findings were consistent at 36 weeks. Bodyweight decreased dose dependently with retatrutide at 36 weeks by 3·19% (SE 0·61) for the 0·5 mg group, 7·92% (1·28) for the 4 mg escalation group, 10·37% (1·56) for the 4 mg group, 16·81% (1·59) for the 8 mg slow escalation group, 16·34% (1·65) for the 8 mg fast escalation group, and 16·94% (1·30) for the 12 mg escalation group, versus 3·00% (0·86) with placebo and 2·02% (0·72) with 1·5 mg dulaglutide. For retatrutide doses of 4 mg and greater, decreases in weight were significantly greater than with placebo (p=0·0017 for the 4 mg escalation group and p<0·0001 for others) and 1·5 mg dulaglutide (all p<0·0001). Mild-to-moderate gastrointestinal adverse events, including nausea, diarrhoea, vomiting, and constipation, were reported in 67 (35%) of 190 participants in the retatrutide groups (from six [13%] of 47 in the 0·5 mg group to 12 [50%] of 24 in the 8 mg fast escalation group), six (13%) of 45 participants in the placebo group, and 16 (35%) of 46 participants in the 1·5 mg dulaglutide group. There were no reports of severe hypoglycaemia and no deaths during the study.

Published **Online** June 26, 2023 https://doi.org/10.1016/S0140-6736(23)01053-X

See **Online/Comment** https://doi.org/10.1016/S0140-6736(23)01182-0

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Interpretation **In people with type 2 diabetes, retatrutide showed clinically meaningful improvements in glycaemic control and robust reductions in bodyweight, with a safety profile consistent with GLP-1 receptor agonists and GIP and GLP-1 receptor agonists. These phase 2 data also informed dose selection for the phase 3 programme.**

Funding **Eli Lilly and Company.**

Introduction

Type 2 diabetes is a chronic multifactorial disease commonly associated with obesity.[1] Insulin resistance in peripheral tissues and the failure of the endocrine pancreas to secrete insulin are key contributors to the development and persistence of hyperglycaemia in type 2 diabetes.[2] Obesity is an important mediator of insulin resistance and increases the prevalence of other metabolic sequelae.[3] A comprehensive diabetes management regimen includes both glucose lowering and bodyweight lowering, ideally with treatments that can deliver both.[1,3] Current guidelines now recommend targeting 5–15% weight reduction as a primary goal because weight reduction of more than 10–15% can have disease-modifying effects, reduce cardiovascular risk, and potentially lead to remission of type 2 diabetes.[1,3]

The newer generation of glucose-lowering agents, such as GLP-1 receptor agonists, enable many patients to reach glycaemic treatment goals, with cardiovascular risk reduction, and the additional benefit of significant weight reduction.[1] Further improvements in glucose and weight management have been seen with the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist tirzepatide, which showed greater efficacy in lowering glycated haemoglobin (HbA_{1c}) and bodyweight than GLP-1 receptor agonists.[4,5] Despite these advances in type 2 diabetes management, some patients might need agents that provide greater efficacy than those that are

Research in context

Evidence before this study

We searched PubMed for research articles published in English up to April 15, 2023, using the terms "glucagon-like peptide-1 receptor agonist", "GLP-1", "glucose-dependent insulinotropic polypeptide", "GIP", "glucagon", "GIP and GLP-1 receptor agonist", "GLP-1 and glucagon receptor agonist", "GIP and GLP-1 and glucagon receptor agonist", "type 2 diabetes", "obesity", "acute body weight management", and "chronic body weight management". Reference lists of relevant studies were also searched. The search indicated that, although there is substantial research on GLP-1 receptor agonists, there is less evidence for the long-term human use of glucose-dependent insulinotropic polypeptide (GIP) or glucagon receptor agonists. This is probably because GIP receptor agonists are not currently available for clinical use, and glucagon receptor agonists are approved only for short-term use for hypoglycaemia. Evidence shows that the GIP and GLP-1 receptor agonist tirzepatide confers glycaemic control and bodyweight reductions that might result in additional efficacy when compared with GLP-1 receptor agonists. Studies in humans suggest that glucagon receptor agonist activity can increase energy expenditure. Several agonists that provide GLP-1 and glucagon receptor activity are in phase 1 and 2 development, including BI-456906, pemvidutide, cotadutide, SAR425899, and mazdutide. Cotadutide and SAR425899 showed meaningful glycaemic efficacy, but effects on bodyweight were similar to GLP-1 receptor agonists. Reports suggest that the ratio of glucagon versus GLP-1 activity is an important determinant of the efficacy and safety profile of GLP-1 and glucagon agonists. Preclinical evidence for the GIP, GLP-1, and glucagon receptor agonist retatrutide (LY3437943) suggests that such balance has been accomplished, as indicated by meaningful improvements in glucose control and lipid metabolism, as well as robust bodyweight reductions via decreased energy intake and increased energy expenditure. In single-dose and multiple-dose studies in people with type 2 diabetes, retatrutide was well tolerated and improved overall cardiometabolic risk measures. Other GIP, GLP-1, and glucagon receptor agonists, HM15211 and SAR441255, have also reached early clinical development.

Added value of this study

In the first phase 2 study in people with type 2 diabetes, we report efficacy and safety findings with multiple doses of the novel single peptide with triple receptor agonist activity, retatrutide, over a 36-week treatment period. Retatrutide treatment resulted in significant and clinically meaningful improvements in glycaemic control. Robust bodyweight reductions were also observed that did not appear to have plateaued by 36 weeks. Concurrently, retatrutide improved the lipid profile and reduced blood pressure, indicating overall improved cardiometabolic outcomes. The safety profile was consistent with the GLP-1 receptor agonist and GIP and GLP-1 receptor agonist classes, with mild-to-moderate and transient gastrointestinal adverse events being the most commonly reported.

Implications of all the available evidence

These phase 2 study findings support further investigation of the efficacy and safety of retatrutide in phase 3 clinical trials in people with obesity, including those with type 2 diabetes and other obesity-related complications.

currently available, especially with respect to reducing bodyweight by 15% or more.

Improving the bodyweight-lowering efficacy of GLP-1 receptor agonists or GIP and GLP-1 receptor agonists might be possible by adding glucagon to reduce energy intake, increase energy expenditure, or both.[6,7] GLP-1 and glucagon receptor agonists include cotadutide, efinopegdutide, mazdutide, pemvidutide, BI456906, NNC9204–1777, and SAR425899.[6] Their efficacy varies across type 2 diabetes, obesity, and non-alcoholic steatohepatitis, resulting in differences in respective pharmaceutical development strategies. These differences might be explained by varying ratios of GLP-1 to glucagon receptor activation. GLP-1, GIP, and glucagon receptor agonists include HM15211, which is currently in phase 1 and 2 development for the treatment of non-alcoholic fatty liver disease and obesity, and SAR441255.[6,8]

Retatrutide (LY3437943) is a once-weekly single peptide with agonist activity at the GIP, GLP-1, and glucagon receptors. Compared with the native hormones, retatrutide is more potent at human GIP receptors and less potent at human glucagon and GLP-1 receptors.[9] In preclinical models, retatrutide treatment reduced food intake and also increased energy expenditure, an effect attributable to glucagon receptor agonism.[9] In a phase 1, multiple-ascending dose study in people with type 2 diabetes, retatrutide showed robust reductions in glucose and bodyweight.[10]

We aimed to assess efficacy and safety of a wide dose range of retatrutide versus placebo and 1·5 mg dulaglutide in people with type 2 diabetes. The objectives were to characterise the effect of retatrutide on glucose and bodyweight control, as well as other important cardiometabolic risk factors.

Methods

Study design and participants

This randomised, double-blind, double-dummy, placebo-controlled and active comparator-controlled, parallel-group, phase 2 study was conducted at 42 research and health-care centres in the USA. Eligible participants were adults aged 18–75 years with type 2 diabetes and an HbA_{1c} of 7·0–10·5% (53·0–91·3 mmol/mol) who were treated with diet and exercise alone or with a stable dose of metformin (≥1000 mg once daily) for at least 3 months before the first of two screening visits. They had a stable bodyweight (±5 kg for 3 months before randomisation) and a BMI of 25–50 kg/m² at the first screening visit. Full inclusion and exclusion criteria are provided in the protocol (appendix pp 65–69). Ethical approval was obtained from local ethics committees at each site, and the study was conducted in accordance with the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines and Good Clinical Practice Guidelines. All participants provided written informed consent before entering the study.

Randomisation and masking

Participants were randomly assigned (2:2:2:1:1:1:1:2) to the placebo group, 1·5 mg dulaglutide group, or the retatrutide 0·5 mg group, 4 mg escalation group, 4 mg group, 8 mg slow escalation group, 8 mg fast escalation group, or 12 mg escalation group. This provided equal participant numbers in the six study treatment groups and four dose-escalation subgroups. Treatment groups were determined by a computer-generated random sequence using an interactive web-response system with stratification for baseline HbA_{1c} (≤8·5% or >8·5% [69·4 mmol/mol]) and BMI (<30 kg/m² or ≥30 kg/m²). Participants, study site personnel, and investigators were masked to treatment allocation until after study end. To maintain masking, a double-blind, double-dummy study design was used, in which participants administered a combination of two weekly injections: retatrutide active and dulaglutide placebo, dulaglutide active and retatrutide placebo, or retatrutide placebo and dulaglutide placebo.

Procedures

The study had a 3-week screening and 36-week treatment period, followed by a 4-week safety follow-up period (appendix p 31). During the treatment period, participants administered retatrutide (Eli Lilly and Company, Indianapolis, IN, USA) or matching placebo once weekly using a syringe and 1·5 mg dulaglutide (Eli Lilly and Company) or matching placebo once weekly using a single-dose pen. There were four maintenance doses of retatrutide: 0·5 mg, 4 mg, 8 mg, and 12 mg (appendix p 31). Participants in the 4 mg maintenance dose groups either started treatment at 2 mg with dose escalation (4 mg escalation group) or at 4 mg with no escalation (4 mg group). Participants assigned to the 8 mg maintenance dose underwent either a slow escalation (from 2 mg to 4 mg to 8 mg) or a fast dose escalation (from 4 mg to 8 mg). One dose-escalation scheme was used for the 12 mg group (from 2 mg to 4 mg to 8 mg to 12 mg). For dose escalation, the retatrutide dose was increased every 4 weeks until the maintenance dose was reached. Participants who discontinued treatment could remain in the trial until study end. Participants underwent training in use of the syringe and single-dose pen, and injected study treatments on site at randomisation. In addition, participants' injection techniques were reviewed at weeks 1, 2, 4, 8, and 12, with training repeated as needed. Study treatment compliance was assessed via participant diaries and the return of any unused study treatments at study visits.

See Online for appendix

Outcomes

The primary endpoint was HbA_{1c} change from baseline to 24 weeks as an early efficacy assessment. Secondary endpoints were HbA_{1c} change from baseline to 36 weeks, the percentage of participants reaching HbA_{1c} of less than 7·0% (53·0 mmol/mol) from baseline to 24 weeks

and 36 weeks, change in fasting blood glucose from baseline to 24 weeks and 36 weeks, and change in bodyweight from baseline to 24 weeks and 36 weeks. Additionally, prespecified exploratory efficacy endpoints included change in self-monitored blood glucose levels from baseline to 24 weeks and 36 weeks;

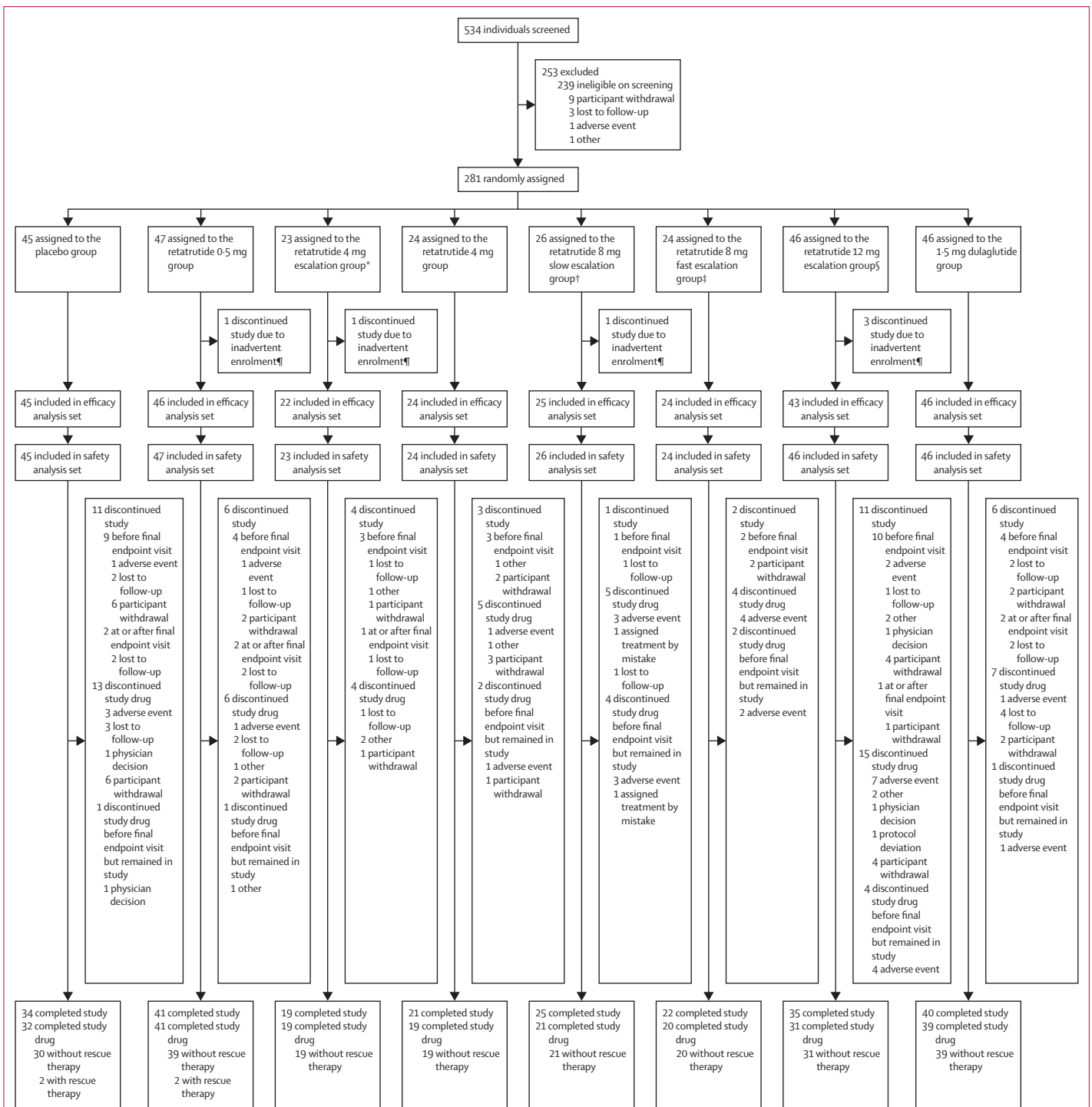

Figure 1: **Trial profile**

*Starting dose 2 mg. †Starting dose 2 mg, followed by escalation to 4 mg, and then to the maintenance dose of 8 mg. ‡Starting dose 4 mg. §Starting dose 2 mg, followed by escalation to 4 mg, then 8 mg, and then the maintenance dose of 12 mg. ¶These participants were included in the safety analysis set.

the proportion of participants reaching an HbA_{1c} of 6·5% (47·5 mmol/mol) or less and less than 5·7% (38·8 mmol/mol) from baseline to 24 weeks and 36 weeks; the proportion of participants with bodyweight reduction of at least 5%, 10%, and 15%, from baseline to 24 weeks and 36 weeks; and change from baseline to 36 weeks in lipid measures and mechanistic biomarkers related to target engagement (amino acid panel), insulin sensitivity, pancreatic α-cell and β-cell function, fatty acid oxidation, and lipolysis. Safety and tolerability endpoints were adverse events, laboratory parameters, electrocardiograms, and vital signs.

Statistical analysis

A sample size of 300 participants was estimated to provide at least 99% power to show the superiority of

	Placebo group (n=45)	Retatrutide 0·5 mg group (n=47)	Retatrutide 4 mg escalation group* (n=23)	Retatrutide 4 mg group (n=24)	Retatrutide 8 mg slow escalation group† (n=26)	Retatrutide 8 mg fast escalation group‡ (n=24)	Retatrutide 12 mg escalation group§ (n=46)	1·5 mg dulaglutide group (n=46)	Total (n=281)
Age, years	57·6 (10·8)	57·2 (9·7)	57·7 (8·1)	57·6 (10·0)	57·0 (7·4)	53·8 (9·0)	54·4 (9·7)	54·9 (10·4)	56·2 (9·7)
Sex									
Female	23 (51%)	23 (49%)	8 (35%)	12 (50%)	16 (62%)	15 (63%)	26 (57%)	33 (72%)	156 (56%)
Male	22 (49%)	24 (51%)	15 (65%)	12 (50%)	10 (38%)	9 (38%)	20 (43%)	13 (28%)	125 (44%)
Race¶									
American Indian or Alaska Native	0	0	0	0	0	0	2/45 (4%)	0	2/280 (1%)
Asian	3 (7%)	0	2 (9%)	0	0	0	2/45 (4%)	1 (2%)	8/280 (3%)
Black or African American	5 (11%)	6 (13%)	1 (4%)	2 (8%)	3 (12%)	4 (17%)	3/45 (7%)	9 (20%)	33/280 (12%)
White	36 (80%)	40 (85%)	20 (87%)	22 (92%)	23 (88%)	20 (83%)	38/45 (84%)	36 (78%)	235/280 (84%)
Multiple	1 (2%)	1 (2%)	0	0	0	0	0	0	2/280 (1%)
Hispanic or Latino	21 (47%)	27 (57%)	9 (39%)	13 (54%)	12 (46%)	9 (38%)	20 (43%)	20 (43%)	131 (47%)
HbA_{1c}, %	8·4% (1·1)	8·3% (1·2)	8·1% (0·9)	8·2% (1·2)	8·3% (1·1)	8·2% (1·3)	8·3% (1·1)	8·2% (0·9)	8·3% (1·1)
HbA_{1c}, mmol/mol	68·2 (12·5)	67·7 (12·8)	64·7 (9·5)	66·1 (13·2)	67·7 (12·2)	66·1 (13·8)	67·0 (11·7)	66·4 (10·0)	66·9 (11·9)
Fasting serum glucose, mg/dL	184·4 (61·4)	174·3 (65·8)	171·2 (49·0)	174·3 (52·3)	178·8 (50·2)	153·0 (36·9)	173·7 (56·6)	152·1 (39·6)	170·5 (54·3)
Fasting serum glucose, mmol/L	10·2 (3·4)	9·7 (3·7)	9·5 (2·7)	9·7 (2·9)	9·9 (2·8)	8·5 (2·1)	9·6 (3·1)	8·4 (2·2)	9·5 (3·0)
Duration of diabetes, years	8·7 (8·3)	8·8 (6·7)	8·1 (6·6)	10·5 (7·6)	7·2 (6·4)	6·0 (5·8)	7·9 (6·9)	7·2 (6·5)	8·1 (7·0)
Metformin use, yes	35 (78%)	35 (74%)	15 (65%)	14 (58%)	21 (81%)	18 (75%)	36 (78%)	28 (61%)	202 (72%)
Bodyweight, kg	94·6 (16·6)	96·7 (18·1)	108·3 (26·7)	93·1 (19·7)	98·4 (21·1)	95·9 (21·0)	99·9 (22·7)	100·3 (23·4)	98·2 (21·1)
BMI, kg/m²	33·8 (4·9)	34·7 (5·6)	36·3 (7·4)	34·0 (6·5)	35·0 (6·4)	34·1 (5·9)	35·5 (6·9)	36·3 (6·8)	35·0 (6·3)
Waist circumference, cm	108·6 (12·3)	110·5 (13·1)	114·3 (24·4)	110·5 (16·2)	111·1 (15·1)	109·3 (11·5)	113·8 (17·4)	115·7 (16·9)	111·8 (15·9)
Blood pressure, mm Hg									
Systolic	131·9 (15·0)	132·0 (11·6)	135·4 (9·8)	125·8 (12·8)	131·0 (11·9)	131·6 (11·6)	124·7 (13·7)	127·6 (12·1)	129·7 (12·9)
Diastolic	78·6 (9·8)	79·9 (8·0)	82·4 (7·3)	77·4 (9·9)	78·2 (9·6)	82·6 (7·2)	78·7 (8·4)	79·6 (8·1)	79·5 (8·6)
Pulse, beats per min	74·5 (12·7)	73·6 (8·9)	76·4 (11·5)	75·3 (9·1)	70·1 (7·7)	73·0 (8·3)	75·0 (10·0)	73·9 (10·1)	74·0 (10·1)
Lipid parameters, mg/dL									
Total cholesterol	164·1 (31·6)	172·5 (28·7)	182·3 (19·6)	184·5 (22·9)	180·4 (17·2)	168·7 (23·0)	182·0 (28·3)	178·5 (27·6)	175·7 (26·5)
HDL cholesterol	44·3 (28·7)	44·0 (28·3)	41·2 (22·0)	42·5 (24·7)	43·9 (26·5)	44·4 (17·1)	42·1 (36·0)	43·0 (23·9)	43·3 (27·1)
Non-HDL cholesterol	117·2 (40·3)	125·7 (37·1)	138·8 (27·0)	140·5 (27·1)	135·2 (18·6)	120·0 (28·0)	136·0 (36·7)	132·3 (37·2)	129·5 (34·2)
Triglycerides	143·7 (54·8)	154·4 (50·9)	168·2 (71·0)	175·4 (46·4)	163·8 (53·7)	145·3 (57·5)	191·3 (71·6)	137·6 (54·5)	157·6 (58·3)
eGFR‖, mL/min per 1·73 m²	90·7 (21·1)	95·1 (14·5)	90·6 (16·1)	91·6 (17·6)	86·0 (21·1)	90·4 (21·2)	91·1 (19·2)	91·1 (21·7)	91·2 (19·2)
Fasting insulin, mU/L	14·4 (101·4)	15·9 (58·6)	15·4 (47·5)	16·4 (79·8)	19·4 (94·8)	17·5 (60·9)	16·4 (75·8)	19·0 (69·2)	16·6 (75·0)
Fasting glucagon, pmol/L	9·7 (68·0)	8·2 (70·4)	9·7 (52·1)	8·8 (63·0)	10·5 (60·3)	9·1 (46·7)	9·4 (52·0)	7·6 (77·5)	8·9 (63·7)

Data are mean (SD) or n (%) and geometric mean (coefficient of variation [%]) for lipids, fasting insulin, and glucagon. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin. *Starting dose 2 mg. †Starting dose 2 mg, followed by escalation to 4 mg, and then to the maintenance dose of 8 mg. ‡Starting dose 4 mg. §Starting dose 2 mg, followed by escalation to 4 mg, then 8 mg, and then the maintenance dose of 12 mg. ¶Data were missing for one participant in the retatrutide 12 mg escalation group. ‖Calculated using the serum creatinine-based CKD-EPI equation.

Table 1: **Baseline clinical characteristics and demographics**

retatrutide (0·5 mg, 4 mg, 8 mg, or 12 mg) to placebo, relative to the primary endpoint, each at a two-sided significance level of 0·05 using two-sample *t* test. The sample size calculation assumed at least –2·1% difference of mean change from baseline in HbA_{1c} between the 12 mg retatrutide group and the placebo group, a common SD of 1·1%, and 20% dropout rate in respective retatrutide and placebo groups. No adjustment for multiplicity was performed.

The summary statistics for continuous measures include means with SDs and medians with IQRs, and those for categorical measures include frequencies with percentages. Fisher's exact test was used to examine the treatment difference in categorical outcomes.

The primary estimand of interest in comparing the efficacy of retatrutide doses with placebo was an efficacy estimand, representing the average treatment effect of retatrutide relative to placebo for all participants who had undergone randomisation, if the treatment was administered as intended (appendix p 3).

The primary analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time (in addition to the baseline and end-of-treatment measurements) was a mixed model for repeated measures with terms of treatment doses stratification strata defined by baseline HbA_{1c} stratum (<8·5% or ≥8·5%, 69·4 mmol/mol) and baseline BMI stratum (<30 kg/m² or ≥30 kg/m²), and continuous, fixed covariate of the baseline value, all nested within visits. We show the treatment group least-squares means with SEs and least-squares mean differences with 95% CIs, and p values for the treatment comparisons.

We used a logistic regression model to examine the treatment difference with 95% CI in the percentage of participants reaching HbA_{1c} of 6·5% (47·5 mmol/mol) or less, less than 5·7% (38·8 mmol/mol), and less than 7·0% (53·0 mmol/mol) at 24 and 36 weeks and the percentage of participants with at least 5%, at least 10%, at least 15%, and at least 20% (post-hoc) bodyweight loss from baseline to 24 and 36 weeks, with missing endpoints imputed. Details of the group mean approach are in the appendix (p 4). In a post-hoc analysis, we analysed change in BMI and waist circumference over time using a similar method to the primary analysis model.

The primary efficacy assessment, guided by the efficacy estimand, and secondary and prespecified and post-hoc exploratory efficacy assessments included all randomly assigned participants, excluding those discontinuing study drug due to inadvertent enrolment, and data after permanent discontinuation of study drug or initiation of rescue medication (efficacy analysis set). Safety analyses were done in all randomly assigned participants who took at least one dose of double-blind study treatment with all data from start of treatment to end of safety follow-up, unless otherwise specified. Details on estimands, handling of missing values, and other statistical analysis methods are provided in the appendix (pp 3–4).

Statistical analyses were done using R (version 4.0.3). This study is registered with ClinicalTrials.gov, NCT04867785.

Role of the funding source

Eli Lilly and Company as the funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between May 13, 2021, and June 13, 2022, we screened 534 participants for eligibility and randomly assigned 45 participants to the placebo group, 46 to the 1·5 mg dulaglutide group, and 47 to the retatrutide 0·5 mg group, 23 to the 4 mg escalation group, 24 to the 4 mg group, 26 to the 8 mg slow escalation group, 24 to the 8 mg fast escalation group, and 46 to the 12 mg escalation group. All 281 participants were included in the safety analyses and 275 participants were included in the efficacy analyses, excluding six (one each in the retatrutide 0·5 mg group, 4 mg escalation group, and 8 mg slow escalation group, and three in the 12 mg escalation group) who were inadvertently enrolled (figure 1). In the retatrutide groups, the lowest rate of discontinuation was in the 8 mg slow escalation group, with 25 (96%) participants completing the study, and the highest rate of discontinuation was in the 12 mg escalation group, with 11 (24%) of 46 participants not completing the study. 11 (24%) of 45 participants in the placebo group and six (13%) of 46 participants in the 1·5 mg dulaglutide group did not complete the study (figure 1). The most common reason for study discontinuation was participant withdrawal. Overall, 222 (79%) participants completed the study on treatment (figure 1). Baseline characteristics are shown in table 1. Mean age was 56·2 years (SD 9·7), mean duration of diabetes 8·1 years (7·0), 156 (56%) participants were female, and 235 (84%) were White. Mean HbA_{1c} was 8·3% (SD 1·1; 66·9 mmol/mol [11·9]), mean BMI was 35·0 kg/m² (6·3), and mean bodyweight was 98·2 kg (21·1).

At 24 weeks, in all retatrutide groups, HbA_{1c} decreased significantly from baseline, with the largest least-squares mean decrease in the 12 mg escalation group (2·02% [SE 0·11]; 22·07 mmol/mol [1·21]; table 2; figure 2A). Retatrutide HbA_{1c} reductions were significantly greater than placebo in all but the lowest 0·5 mg group (all p<0·0001) and greater than 1·5 mg dulaglutide in the 8 mg slow escalation group (p=0·0019) and 12 mg escalation group (p=0·0002). Similarly, at 36 weeks, the largest HbA_{1c} least-squares mean decrease occurred in the retatrutide 12 mg group (2·16% [SE 0·13; 23·59 mmol/mol [1·39]).

At 36 weeks, more participants in the retatrutide 4 mg groups, 8 mg groups, and 12 mg escalation group reached an HbA_{1c} of less than 7·0% (53·0 mmol/mol) than in the

	Placebo group (n=45)	Retatrutide 0·5 mg group (n=46)	Retatrutide 4 mg escalation group* (n=22)	Retatrutide 4 mg group (n=24)	Retatrutide 8 mg slow escalation group† (n=25)	Retatrutide 8 mg fast escalation group‡ (n=24)	Retatrutide 12 mg escalation group§ (n=43)	1·5 mg dulaglutide group (n=46)
HbA_{1c}, %								
Baseline	8·39 (0·17)	8·38 (0·17)	8·01 (0·18)	8·20 (0·24)	8·30 (0·22)	8·20 (0·25)	8·28 (0·16)	8·22 (0·13)
Change at 24 weeks	−0·01 (0·21); p=0·9580	−0·43 (0·20); p=0·0298	−1·39 (0·14); p<0·0001	−1·30 (0·22); p<0·0001	−1·99 (0·15); p<0·0001	−1·88 (0·21); p<0·0001	−2·02 (0·11); p<0·0001	−1·41 (0·12); p<0·0001
Versus placebo	..	−0·42 (−0·98 to 0·15); p=0·1470	−1·38 (−1·88 to −0·89); p<0·0001	−1·29 (−1·89 to −0·69); p<0·0001	−1·98 (−2·49 to −1·48); p<0·0001	−1·87 (−2·46 to −1·28); p<0·0001	−2·01 (−2·48 to −1·54); p<0·0001	..
Versus dulaglutide 1·5 mg		0·98 (0·53 to 1·43); p<0·0001	0·01 (−0·34 to 0·37); p=0·9370	0·11 (−0·39 to 0·60); p=0·6655	−0·58 (−0·95 to −0·22); p=0·0019	−0·47 (−0·95 to 0·01); p=0·0558	−0·61 (−0·93 to −0·29) p=0·0002	..
Change at 36 weeks	−0·30 (0·24); p=0·2091	−0·54 (0·20); p=0·0057	−1·30 (0·20); p<0·0001	−1·50 (0·19); p<0·0001	−2·13 (0·17); p<0·0001	−1·93 (0·22); p<0·0001	−2·16 (0·13); p<0·0001	−1·36 (0·13); p<0·0001
Versus placebo	..	−0·24 (−0·85 to 0·38); p=0·4481	−0·99 (−1·60 to −0·38); p=0·0014	−1·20 (−1·80 to −0·59); p=0·0001	−1·83 (−2·41 to −1·24); p<0·0001	−1·63 (−2·27 to −0·99); p<0·0001	−1·85 (−2·39 to −1·31); p<0·0001	..
Versus dulaglutide 1·5 mg	..	0·82 (0·35 to 1·29); p=0·0006	0·06 (−0·41 to 0·53); p=0·7964	−0·14 (−0·61 to 0·32); p=0·5483	−0·77 (−1·19 to −0·36); p=0·0003	−0·57 (−1·08 to −0·07); p=0·0250	−0·80 (−1·16 to −0·44); p<0·0001	..
HbA_{1c}, mmol/mol								
Baseline	68·24 (1·84)	68·05 (1·86)	64·09 (1·94)	66·13 (2·64)	67·26 (2·41)	66·13 (2·75)	66·99 (1·75)	66·36 (1·46)
Change at 24 weeks	−0·12 (2·27); p=0·9580	−4·68 (2·15); p=0·0298	−15·24 (1·56); p<0·0001	−14·20 (2·44); p<0·0001	−21·78 (1·60); p<0·0001	−20·52 (2·34); p<0·0001	−22·07 (1·21); p<0·0001	−15·40 (1·29); p<0·0001
Versus placebo	..	−4·56 (−10·72 to 1·60); p=0·1470	−15·12 (−20·52 to −9·72); p<0·0001	−14·08 (−20·62 to −7·55); p<0·0001	−21·66 (−27·18 to −16·14); p<0·0001	−20·40 (−26·84 to −13·96); p<0·0001	−21·95 (−27·06 to −16·84); p<0·0001	..
Versus dulaglutide 1·5 mg	..	10·72 (5·76 to 15·68); p<0·0001	0·16 (−3·75 to 4·06); p=0·9370	1·19 (−4·21 to 6·60); p=0·6655	−6·38 (−10·40 to −2·36); p=0·0019	−5·12 (−10·37 to 0·13); p=0·0558	−6·67 (−10·16 to −3·19); p=0·0002	..
Change at 36 weeks	−3·32 (2·65); p=0·2091	−5·92 (2·14); p=0·0057	−14·19 (2·18); p<0·0001	−16·42 (2·11); p<0·0001	−23·30 (1·84); p<0·0001	−21·15 (2·36); p<0·0001	−23·59 (1·39); p<0·0001	−14·86 (1·48); p<0·0001
Versus placebo	..	−2·60 (−9·32 to 4·12); p=0·4481	−10·87 (−17·53 to −4·20); p=0·0014	−13·09 (−19·72 to −6·47); p=0·0001	−19·98 (−26·35 to −13·61); p<0·0001	−17·82 (−24·79 to −10·86); p<0·0001	−20·26 (−26·17 to −14·36); p<0·0001	..
Versus dulaglutide 1·5 mg	..	8·94 (3·81 to 14·07); p=0·0006	0·68 (−4·46 to 5·81); p=0·7964	−1·55 (−6·61 to 3·51); p=0·5483	−8·44 (−13·00 to −3·88) p=0·0003	−6·28 (−11·77 to −0·79); p=0·0250	−8·72 (−12·66 to −4·78); p<0·0001	..
Fasting serum glucose, mg/dL								
Baseline	184·42 (9·05)	175·80 (9·59)	168·91 (10·19)	174·29 (10·44)	179·60 (10·00)	152·96 (7·38)	177·09 (8·34)	152·09 (5·78)
Change at 36 weeks	−17·26 (10·87); p=0·1126	−17·51 (5·59); p=0·0017	−21·46 (12·54); p=0·0869	−38·72 (10·81); p=0·0003	−69·10 (4·68); p<0·0001	−41·20 (14·43); p=0·0043	−67·84 (4·79); p<0·0001	−27·53 (9·07); p=0·0024
Versus placebo	..	−0·25 (−24·57 to 24·07); p=0·9839	−4·20 (−37·44 to 29·03); p=0·8042	−21·47 (−51·91 to 8·98); p=0·1670	−51·84 (−76·09 to −27·59); p<0·0001	−23·94 (−57·94 to 10·06); p=0·1676	−50·58 (−74·94 to −26·22); p<0·0001	..
Versus dulaglutide 1·5 mg	..	10·02 (−11·55 to 31·60); p=0·3624	6·07 (−24·34 to 36·48); p=0·6957	−11·19 (−39·38 to 16·99); p=0·4363	−41·57 (−62·89 to −20·25); p=0·0001	−13·67 (−46·75 to 19·42); p=0·4182	−40·31 (−60·77 to −19·85); p=0·0001	..
Fasting serum glucose, mmol/L								
Baseline	10·24 (0·50)	9·76 (0·53)	9·38 (0·57)	9·67 (0·58)	9·97 (0·56)	8·49 (0·41)	9·83 (0·46)	8·44 (0·32)
Change at 36 weeks	−0·96 (0·60); p=0·1126	−0·97 (0·31); p=0·0017	−1·19 (0·70); p=0·0869	−2·15 (0·60); p=0·0003	−3·84 (0·26); p<0·0001	−2·29 (0·80); p=0·0043	−3·77 (0·27); p<0·0001	−1·53 (0·50); p=0·0024
Versus placebo	..	−0·01 (−1·36 to 1·34); p=0·9840	−0·23 (−2·08 to 1·61); p=0·8042	−1·19 (−2·88 to 0·50); p=0·1670	−2·88 (−4·22 to −1·53); p<0·0001	−1·33 (−3·22 to 0·56); p=0·1676	−2·81 (−4·16 to −1·46); p<0·0001	..
Versus dulaglutide 1·5 mg	..	0·56 (−0·64 to 1·75); p=0·3624	0·34 (−1·35 to 2·02); p=0·6957	−0·62 (−2·19 to 0·94); p=0·4363	−2·31 (−3·49 to −1·12); p=0·0001	−0·76 (−2·60 to 1·08); p=0·4182	−2·24 (−3·37 to −1·10); p=0·0001	..

(Table 2 continues on next page)

	Placebo group (n=45)	Retatrutide 0·5 mg group (n=46)	Retatrutide 4 mg escalation group* (n=22)	Retatrutide 4 mg group (n=24)	Retatrutide 8 mg slow escalation group† (n=25)	Retatrutide 8 mg fast escalation group‡ (n=24)	Retatrutide 12 mg escalation group§ (n=43)	1·5 mg dulaglutide group (n=46)
(Continued from previous page)								
Self-monitored blood glucose daily mean, mg/dL								
Baseline	190·92 (7·61)	186·88 (6·63)	184·77 (10·14)	202·27 (13·06)	185·18 (7·64)	184·00 (10·96)	196·78 (8·41)	180·10 (6·79)
Change at 36 weeks	−16·45 (6·31); p=0·0092	−25·88 (6·38); p<0·0001	−50·89 (4·76); p<0·0001	−46·97 (7·48); p<0·0001	−64·58 (5·49); p<0·0001	−59·20 (7·25); p<0·0001	−67·45 (5·92); p<0·0001	−51·13 (2·94); p<0·0001
Versus placebo	..	−9·43 (−27·16 to 8·29); p=0·2969	−34·45 (−49·98 to −18·92); p<0·0001	−30·53 (−49·73 to −11·32); p=0·0018	−48·14 (−64·65 to −31·63); p<0·0001	−42·76 (−61·59 to −23·92); p<0·0001	−51·00 (−67·97 to −34·04); p<0·0001	..
Versus dulaglutide 1·5 mg	..	25·25 (11·76 to 38·75); p=0·0002	0·24 (−10·56 to 11·04); p=0·9653	4·16 (−11·61 to 19·94); p=0·6051	−13·45 (−25·54 to −1·36); p=0·0293	−8·07 (−23·39 to 7·25); p=0·3018	−16·31 (−29·04 to −3·59); p=0·0120	..
Self-monitored blood glucose daily mean, mmol/L								
Baseline	10·60 (0·42)	10·37 (0·37)	10·26 (0·56)	11·23 (0·72)	10·28 (0·42)	10·21 (0·61)	10·92 (0·47)	10·00 (0·38)
Change at 36 weeks	−0·91 (0·35); p=0·0092	−1·44 (0·35); p<0·0001	−2·83 (0·26); p<0·0001	−2·61 (0·42); p<0·0001	−3·58 (0·31); p<0·0001	−3·29 (0·40); p<0·0001	−3·74 (0·33); p<0·0001	−2·84 (0·16); p<0·0001
Versus placebo	..	−0·52 (−1·51 to 0·46); p=0·2969	−1·91 (−2·77 to −1·05); p<0·0001	−1·69 (−2·76 to −0·63); p=0·0018	−2·67 (−3·59 to −1·76); p<0·0001	−2·37 (−3·42 to −1·33); p<0·0001	−2·83 (−3·77 to −1·89); p<0·0001	..
Versus dulaglutide 1·5 mg	..	1·40 (0·65 to 2·15); p=0·0002	0·01 (−0·59 to 0·61); p=0·9653	0·23 (−0·64 to 1·11); p=0·6051	−0·75 (−1·42 to −0·08); p=0·0293	−0·45 (−1·30 to 0·40); p=0·3018	−0·91 (−1·61 to −0·20); p=0·0120	..
Fasting insulin, mU/L								
Baseline	14·35 (1·82)	15·91 (1·26)	15·44 (1·55)	16·41 (2·35)	19·36 (3·04)	17·46 (2·00)	16·35 (1·68)	18·95 (1·75)
Percentage change at 36 weeks	−22·17% (6·65); p=0·0033	5·01% (13·22); p=0·6975	−1·84% (14·16); p=0·8977	−20·42% (12·20); p=0·1363	−36·92% (11·00); p=0·0082	−41·65% (6·49); p<0·0001	−36·33% (5·20); p<0·0001	35·68% (12·02); p=0·0006
Versus placebo	..	34·93 (0·10 to 81·88); p=0·0493	26·13 (−9·01 to 74·83); p=0·1635	2·26 (−27·44 to 44·10); p=0·8986	−18·95 (−44·55 to 18·47); p=0·2780	−25·02 (−43·05 to −1·29); p=0·0401	−18·19 (−34·95 to 2·88); p=0·0859	..
Versus dulaglutide 1·5 mg	..	−22·60 (−42·49 to 4·16); p=0·0908	−27·65 (−48·21 to 1·06); p=0·0577	−41·35 (−58·54 to −17·03); p=0·0026	−53·51 (−68·28 to −31·85); p<0·0001	−56·99 (−67·44 to −43·19); p<0·0001	−53·07 (−63·08 to −40·36); p<0·0001	..
Fasting glucagon, pmol/L								
Baseline	9·70 (1·00)	8·18 (0·82)	9·68 (1·09)	8·80 (1·08)	10·53 (1·25)	9·12 (0·86)	9·38 (0·74)	7·57 (0·80)
Percentage change at 36 weeks	−27·36% (6·76); p=0·0006	−17·85% (10·51); p=0·1241	−71·95% (7·30); p<0·0001	−60·42% (7·65); p<0·0001	−86·22% (2·91); p<0·0001	−83·57% (3·99); p<0·0001	−83·92% (3·09); p<0·0001	−9·86% (7·48); p=0·2111
Versus placebo	..	13·09 (−16·60 to 53·34); p=0·4285	−61·39 (−77·52 to −33·68); p=0·0006	−45·51 (−64·20 to −17·07); p=0·0046	−81·02 (−87·93 to −70·17); p<0·0001	−77·38 (−86·40 to −62·40); p<0·0001	−77·87 (−85·46 to −66·30); p<0·0001	..
Versus dulaglutide 1·5 mg	..	−8·87 (−32·89 to 23·76); 0·5520	−68·89 (−81·85 to −46·66); p<0·0001	−56·09 (−70·98 to −33·56); p<0·0001	−84·71 (−90·19 to −76·16); p<0·0001	−81·78 (−88·99 to −69·83); p<0·0001	−82·17 (−88·13 to −73·21); p<0·0001	..
Bodyweight, kg								
Baseline	94·56 (2·44)	96·74 (2·67)	109·85 (5·46)	93·09 (3·94)	99·43 (4·09)	95·88 (4·20)	99·83 (3·53)	100·27 (3·42)
Change at 36 weeks	−3·28 (0·92); p=0·0004	−3·31 (0·62); p<0·0001	−7·28 (1·39); p<0·0001	−10·37 (1·49); p<0·0001	−16·48 (1·55); p<0·0001	−16·12 (1·63); p<0·0001	−17·18 (1·32); p<0·0001	−1·97 (0·87); p=0·0242
Versus placebo	..	−0·03 (−2·18 to 2·12); p=0·9789	−4·00 (−7·32 to −0·68); p=0·0181	−7·09 (−10·46 to −3·71); p<0·0001	−13·20 (−16·74 to −9·66); p<0·0001	−12·84 (−16·50 to −9·18); p<0·0001	−13·91 (−17·10 to −10·71); p<0·0001	..
Versus dulaglutide 1·5 mg	..	−1·34 (−3·45 to 0·77); p=0·2133	−5·31 (−8·66 to −1·97); p=0·0019	−8·40 (−11·76 to −5·04); p<0·0001	−14·51 (−18·00 to −11·01); p<0·0001	−14·15 (−17·77 to −10·54); p<0·0001	−15·22 (−18·36 to −12·07); p<0·0001	..

Data are least-squares mean (SE) and least-squares mean difference (95% CI) from mixed model repeated measures in the efficacy analysis set. Fasting insulin and glucagon data are estimate (SE) and estimate difference (95% CI) from mixed model repeated measures with log transformation in the efficacy analysis set. p values were calculated with the Wald test. HbA_{1c}=glycated haemoglobin. *Starting dose 2 mg. †Starting dose 2 mg, followed by escalation to 4 mg, and then to the maintenance dose of 8 mg. ‡Starting dose 4 mg. §Starting dose 2 mg, followed by escalation to 4 mg, then 8 mg, and then the maintenance dose of 12 mg.

Table 2: **Efficacy measures**

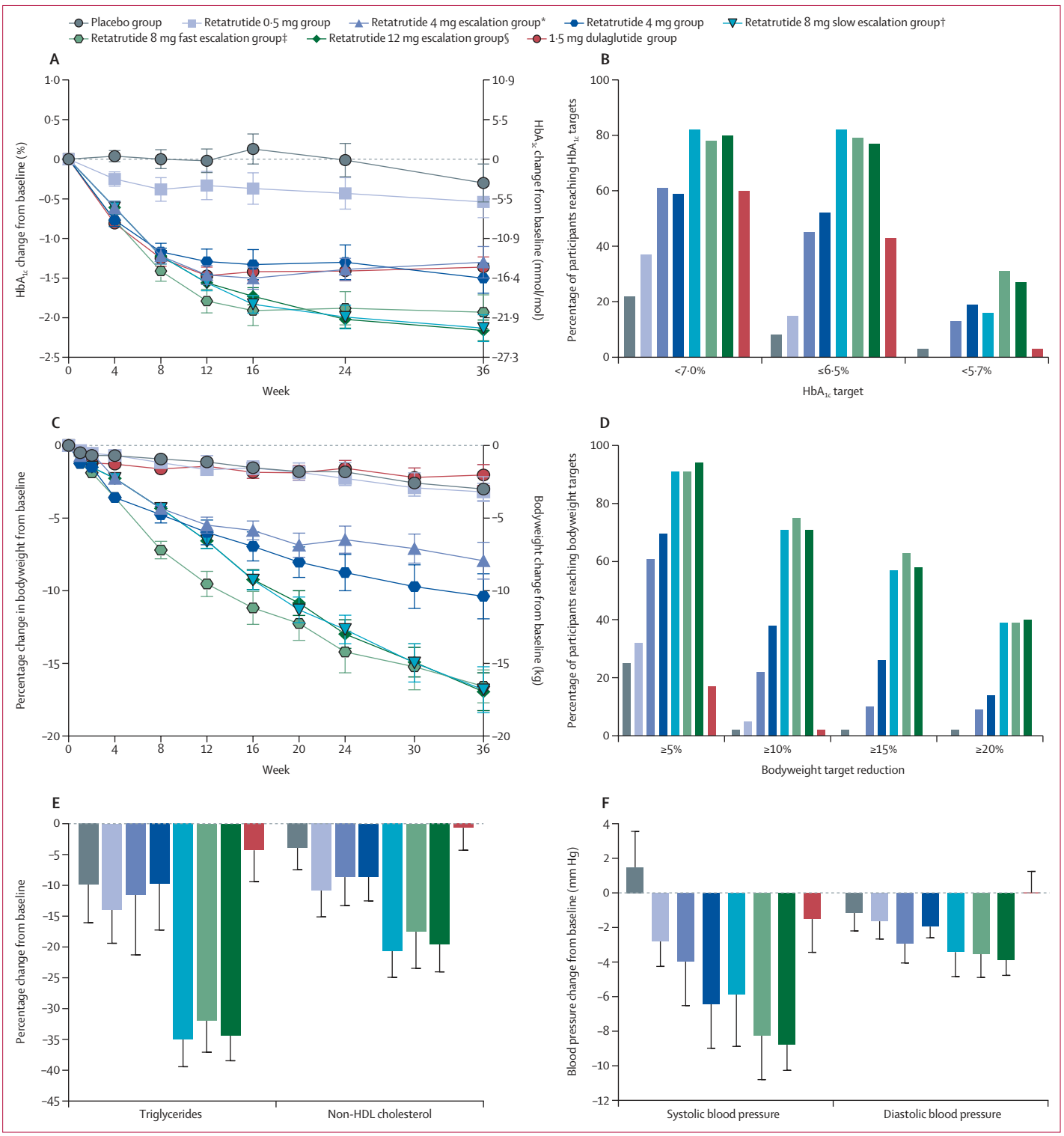

Figure 2: **HbA$_{1c}$, bodyweight, blood pressure, and lipids**

Data are least-squares means (with error bars showing SEs) from the efficacy analysis set, unless otherwise noted. (A) Change from baseline in HbA$_{1c}$ over time from the MMRM analysis. (B) Proportion of participants reaching HbA$_{1c}$ targets at week 36 from the logistic regression analysis with imputed missing values. (C) Percentage change from baseline in bodyweight over time from the MMRM analysis. (D) Proportion of participants reaching bodyweight reduction targets at week 36 from the logistic regression analysis with imputed missing values. (E) Percentage change from baseline in fasting triglycerides and non-HDL cholesterol at week 36 from the MMRM analysis with log transformation. (F) Change from baseline in systolic and diastolic blood pressure at week 36 from the MMRM analysis in the safety analysis set. HbA$_{1c}$=glycated haemoglobin. MMRM=mixed model repeated measures. *Starting dose 2 mg. †Starting dose 2 mg, followed by escalation to 4 mg, and then to the maintenance dose of 8 mg. ‡Starting dose 4 mg. §Starting dose 2 mg, followed by escalation to 4 mg, then 8 mg, and then the maintenance dose of 12 mg.

placebo group (group mean 61% [SE 10] in the 4 mg escalation group, 59% [9] in the 4 mg group, 82% [7] in the 8 mg slow escalation group, 78% [8] in the 8 mg fast escalation group, and 80% (7) in the 12 mg escalation group *vs* 22% [7] in the placebo group; p=0·0013 for the 4 mg escalation group, p=0·0019 for the 4 mg group, and p<0·0001 for others; figure 2B; appendix p 5). Significantly more participants in the 8 mg slow escalation group and the 12 mg escalation group also reached this HbA_{1c} target than participants in the 1·5 mg dulaglutide group (group mean 60% [SE 7]; p=0·0329 for the 8 mg slow escalation group and p=0·0437 for the 12 mg escalation group; figure 2B; appendix p 5). More participants in the retatrutide 4 mg groups, 8 mg groups, and 12 mg group reached an HbA_{1c} of 6·5% (47·5 mmol/mol) or less than in the placebo group (group mean 45% [SE 10] in the 4 mg escalation group, 52% [10] in the 4 mg group, 82% [7] in the 8 mg slow escalation group, 79% [8] in the 8 mg fast escalation group, and 77% [7] in the 12 mg escalation group *vs* 8% [5] in the placebo group; p=0·0011 for the 4 mg escalation group; p<0·0001 for the other retatrutide ≥4 mg groups). Differences in the proportion reaching HbA_{1c} 6·5% (47·5 mmol/mol) or less versus 1·5 mg dulaglutide (group mean 43% [SE 7]) were also significantly greater for the 8 mg groups (p=0·0001 for the 8 mg slow escalation group and p=0·0011 for the 8 mg fast escalation group) and 12 mg escalation group (p=0·0005). An HbA_{1c} of less than 5·7% (38·8 mmol/mol), an indication of normoglycaemia, was reached by more participants with retatrutide maintenance doses of 4 mg or higher (group mean 13% [SE 7] in the 4 mg escalation group, 19% [8] in the 4 mg group, 16% [8] in the 8 mg slow escalation group, 31% [11] in the 8 mg fast escalation group, and 27% [7] in the 12 mg escalation group) compared with placebo (3% [3]) and 1·5 mg dulaglutide (3% [3]), with these differences being significantly greater in the 8 mg fast escalation group (p=0·0110 *vs* placebo and p=0·0103 *vs* 1·5 mg dulaglutide) and 12 mg escalation group (p=0·0020 *vs* placebo and p=0·0018 *vs* 1·5 mg dulaglutide; appendix pp 5–6).

Fasting serum glucose decreased from baseline to 36 weeks, with decreases ranging from a least-squares mean of 21·46 mg/dL (SE 12·54) to 69·10 mg/dL (4·68; 1·19 mmol/L [0·70] to 3·84 mmol/L [0·26]) in the retatrutide 4 mg groups, 8 mg groups, and 12 mg escalation group, 17·26 mg/dL (10·87; 0·96 mmol/L [0·60]) with placebo, and 27·53 mg/dL (9·07; 1·53 mmol/L [0·50]) with 1·5 mg dulaglutide (table 2). In the 8 mg slow escalation group and 12 mg escalation group, differences were significantly greater than placebo (both p<0·0001) and 1·5 mg dulaglutide (both p=0·0001). At week 36, daily mean self-monitored blood glucose decreased from baseline in a dose-dependent manner with retatrutide (all p<0·0001), with the greatest decrease in the 12 mg escalation group (least-squares mean 67·45 mg/dL [SE 5·92]; 3·74 mmol/L [0·33]; table 2). Findings were consistent for self-monitored blood glucose pre-meal and post-meal daily means (appendix p 32). Glycaemia data at the earlier timepoint of 24 weeks were generally consistent with data at 36 weeks (appendix p 7).

Bodyweight decreased significantly from baseline to 36 weeks in the retatrutide groups (up to a least-squares mean of 16·94% [SE 1·30]), placebo group (3·00% [0·86]), and 1·5 mg dulaglutide group (2·02% [0·72]; all p<0·0001; table 2; figure 2C; appendix p 10). Except for the retatrutide 0·5 mg group, decreases with retatrutide were significant relative to placebo (p=0·0017 for the 4 mg escalation group, p<0·0001 for all other retatrutide groups) and 1·5 mg dulaglutide (p<0·0001 for all other retatrutide groups). Higher percentages of participants in the retatrutide groups reached the bodyweight reduction goals of at least 5%, at least 10%, and at least 15% (prespecified), and at least 20% (post-hoc) at week 36, with a dose-dependent effect, compared with placebo and 1·5 mg dulaglutide (figure 2D; appendix p 11). A group mean of 71% (SE 10) of participants in the retatrutide 8 mg slow escalation group, 75% (10) in the 8 mg fast escalation group, and 71% (7) in the 12 mg escalation group reached weight reduction of at least 10% versus 2% (2) in the placebo group and 2% (2) in the 1·5 mg dulaglutide group (all p<0·0001). Furthermore, a group mean of 57% (SE 11) of participants in the retatrutide 8 mg slow escalation group, 63% (11) in the 8 mg fast escalation group, and 58% (8) in the 12 mg escalation group reached the bodyweight reduction target of at least 15% and 39% (11), 39% (10), and 40% (8), respectively, reached the target of at least 20%. In a post-hoc analysis, a significant dose-dependent decrease in BMI relative to placebo and dulaglutide 1.5 mg was seen in all retatrutide groups except the 0·5 mg group and a significant decrease in waist circumference was seen in the retatrutide 8 mg groups and 12 mg escalation group relative to placebo and 1·5 mg dulaglutide at 36 weeks (appendix pp 13, 33). Bodyweight and BMI continued to decrease from the earlier timepoint of 24 weeks to the end of treatment at 36 weeks (appendix pp 7, 10, 33).

At 36 weeks, treatment with retatrutide increased insulin sensitivity, as indicated by decreases of up to 41·65% (SE 6·49; p<0·0001 in the 8 mg fast escalation group) in fasting insulin concentrations (table 2), 30·55% (6·34; p<0·0001 in the 8 mg fast escalation group) in fasting C-peptide concentrations, and 38·90% (10·52; p=0·0042 in the 8 mg slow escalation group) in homoeostasis model assessment of insulin resistance (HOMA2-IR, computed with insulin),[11] and by increases of up to 53·46% (12·27; p<0·0001 in the 8 mg fast escalation group) in adiponectin concentrations (appendix p 14). These changes were generally dose-dependent and significantly larger in the higher dose retatrutide groups than observed with dulaglutide.

Fasting endogenous glucagon concentrations decreased significantly from baseline in all but the retatrutide 0·5 mg group (table 2). These changes were significant relative to placebo and 1·5 mg dulaglutide in

the 4 mg or higher-dose retatrutide groups and consistent with glucagon receptor target engagement. Observed reductions in circulating amino acid concentrations, additional indicators of glucagon receptor activation, were generally larger in higher-dose groups of retatrutide at 36 weeks than in dulaglutide or placebo groups (appendix p 16).

At 36 weeks, treatment with retatrutide improved the fasting lipid profile in a dose-dependent manner (figure 2E; appendix pp 21–23). Total cholesterol decreased in the 8 mg and 12 mg escalation retatrutide groups by up to 16·67% (SE 3·17), compared with 2·23% (2·72) with placebo and 0·93% (2·60) with 1·5 mg dulaglutide (p=0·0007 for the 8 mg slow escalation group and p=0·0056 for the 12 mg escalation group *vs* placebo; p=0·0002 for the 8 mg slow escalation group and p=0·0025 for the 12 mg escalation group *vs* 1·5 mg dulaglutide). Triglyceride concentrations decreased in the retatrutide 8 mg groups and 12 mg escalation group by up to 35·02% (SE 4·41) versus 9·89% (6·15) with placebo (p=0·0006 for the 8 mg slow escalation group, p=0·0055 for the 8 mg fast escalation group, and p=0·0006 for the 12 mg escalation group) and 4·29% (5·09) with 1·5 mg dulaglutide (p=0·0002 for the 8 mg fast escalation group and p<0·0001 for the 8 mg slow escalation group and the 12 mg escalation group). Retatrutide treatment decreased non-HDL cholesterol by up to 20·71% (SE 4·21), with decreases of 3·90% (3·56) with placebo and 0·67% (3·62) with 1·5 mg dulaglutide. Differences were significantly greater than placebo with retatrutide 8 mg slow escalation (p=0·0028) and 12 mg escalation (p=0·0068) and greater than 1·5 mg dulaglutide with retatrutide 8 mg slow escalation (p=0·0005), 8 mg fast escalation (p=0·0221), and 12 mg escalation (p=0·0015). These changes in non-HDL cholesterol were driven by reductions in VLDL cholesterol concentrations of up to 33·76% (SE 4·06) with retatrutide treatment. Changes in LDL cholesterol, HDL cholesterol, and free fatty acids with retatrutide were generally not significantly different versus placebo or dulaglutide. β-hydroxybutyrate concentration increased by up to 66·17% (SE 25·12) in the retatrutide groups at 36 weeks. Differences were significantly greater than placebo with retatrutide 12 mg escalation (p=0·0048) and greater than 1·5 mg dulaglutide with retatrutide 8 mg slow escalation (p=0·0262), 8 mg fast escalation (p=0·0256), and 12 mg escalation (p=0·0006).

Systolic blood pressure decreased from baseline to 36 weeks with retatrutide treatment, with the largest least-squares mean decrease occurring in the 12 mg escalation group (8·79 mm Hg [SE 1·47]). Systolic blood pressure increased by 1·49 mm Hg (SE 2·08) with placebo (p=0·0153 for the 4 mg group, p=0·0438 for the 8 mg slow escalation group, p=0·0028 for the 8 mg fast escalation group, and p<0·0001 for the 12 mg escalation group for retatrutide *vs* placebo) and decreased by 1·53 mm Hg (1·90) with 1·5 mg dulaglutide (p=0·0335 for the 8 mg fast escalation group and p=0·0027 for the 12 mg escalation group for retatrutide *vs* dulaglutide; figure 2F; appendix pp 24, 34). Diastolic blood pressure also decreased from baseline during the study in the 4 mg escalation, 8 mg, and 12 mg retatrutide groups, with a change of up to –3·89 mm Hg (SE 0·88) in the 12 mg escalation group, –1·16 mm Hg (1·03) with placebo, and 0·02 mm Hg (1·22) with 1·5 mg dulaglutide (p=0·0418 for 12 mg escalation *vs* placebo, p=0·047 for 8 mg fast escalation *vs* 1·5 mg dulaglutide, and p=0·0097 for 12 mg escalation *vs* 1·5 mg dulaglutide) at 36 weeks. At this timepoint, pulse rate changes with retatrutide were 0·03 beats per min (bpm; SE 1·56) to 4·34 bpm (1·68), compared with –3·16 bpm (0·95) with placebo and 1·76 bpm (1·26) with 1·5 mg dulaglutide. In all retatrutide groups increases in pulse were not significantly different relative to 1·5 mg dulaglutide (all p>0·05), but differed significantly from placebo in all retatrutide groups except the 4 mg escalation group (p=0·0819; appendix pp 24, 34).

Overall, at least one treatment-emergent adverse event was reported in 129 (68%) of 190 participants in the retatrutide groups (from 26 [55%] of 47 in the 0·5 mg group to 19 [79%] of 24 in the 4 mg group) versus 28 (62%) of 45 in the placebo group and 31 (67%) of 46 in the 1·5 mg dulaglutide group. (table 3; appendix p 25). The most frequently reported treatment-emergent adverse events with retatrutide treatment were gastrointestinal, most commonly nausea, diarrhoea, vomiting, and constipation. These gastrointestinal treatment-emergent adverse events occurred in more participants in the retatrutide groups (from six [13%] of 47 in the 0·5 mg group to 12 [50%] of 24 in the 8 mg fast escalation group) than in those in the placebo group (six [13%] of 45) and 1·5 mg dulaglutide group (16 [35%] of 46). Gastrointestinal treatment-emergent adverse events were generally more common with higher retatrutide doses and occurred more frequently in the 4 mg rather than the 2 mg starting dose groups (appendix pp 35–36). Most gastrointestinal treatment-emergent adverse events were mild to moderate in severity. Overall, 16 (8%) of 190 participants in the retatrutide groups discontinued treatment due to an adverse event, most frequently gastrointestinal adverse events (six [3%] participants).

No participants died during the study. Overall, 20 serious adverse events occurred in 15 (5%) of 281 participants (13 events in 11 [6%] of 190 in the retatrutide groups, six events in three [7%] of 45 participants in the placebo group, and one event in one [2%] of 46 participants in the 1·5 mg dulaglutide 1·5 mg group; appendix p 26). In the retatrutide groups, three serious adverse events were attributed to study drug by the site investigator: one case of cholecystitis (in the 8 mg fast escalation group), one case of acute pancreatitis (in the 8 mg slow escalation group, 7 days after the initial and only dose), and one case of diabetic

	Placebo group (n=45)	Retatrutide 0·5 mg group (n=47)	Retatrutide 4 mg escalation group* (n=23)	Retatrutide 4 mg group (n=24)	Retatrutide 8 mg slow escalation group† (n=26)	Retatrutide 8 mg fast escalation group‡ (n=24)	Retatrutide 12 mg escalation group§ (n=46)	1·5 mg dulaglutide group (n=46)	Total (n=281)
Participants with ≥1 treatment-emergent adverse event	28 (62%)	26 (55%)	13 (57%)	19 (79%)	19 (73%)	17 (71%)	35 (76%)	31 (67%)	188 (67%)
Serious adverse events	3 (7%)	3 (6%)	1 (4%)	2 (8%)	2 (8%)	1 (4%)	2 (4%)	1 (2%)	15 (5%)
Death	0	0	0	0	0	0	0	0	0
Adverse events leading to discontinuation of study drug	2 (4%)	1 (2%)	0	1 (4%)	3 (12%)	4 (17%)	7 (15%)	1 (2%)	19 (7%)
Vomiting¶	0	0	0	0	1 (4%)	1 (4%)	1 (2%)	0	3 (1%)
Diarrhoea¶	0	0	0	1 (4%)	0	1 (4%)	0	0	2 (1%)
Acute pancreatitis¶	0	0	0	0	1 (4%)	0	0	0	1 (<1%)
Treatment-emergent adverse events occurring in ≥5% of total participants									
Nausea	2 (4%)	2 (4%)	2 (9%)	6 (25%)	7 (27%)	10 (42%)	9 (20%)	8 (17%)	46 (16%)
Diarrhoea	2 (4%)	1 (2%)	2 (9%)	6 (25%)	5 (19%)	7 (29%)	7 (15%)	4 (9%)	34 (12%)
Decreased appetite	0	2 (4%)	1 (4%)	5 (21%)	5 (19%)	4 (17%)	9 (20%)	6 (13%)	32 (11%)
Constipation	1 (2%)	3 (6%)	2 (9%)	4 (17%)	3 (12%)	2 (8%)	5 (11%)	3 (7%)	23 (8%)
COVID-19	3 (7%)	5 (11%)	3 (13%)	1 (4%)	1 (4%)	1 (4%)	2 (4%)	4 (9%)	20 (7%)
Vomiting	1 (2%)	1 (2%)	1 (4%)	0	2 (8%)	4 (17%)	5 (11%)	4 (9%)	18 (6%)
Headache	2 (4%)	2 (4%)	1 (4%)	1 (4%)	3 (12%)	1 (4%)	1 (2%)	3 (7%)	14 (5%)
Lipase increased	2 (4%)	1 (2%)	1 (4%)	2 (8%)	3 (12%)	1 (4%)	2 (4%)	1 (2%)	13 (5%)
Urinary tract infection	2 (4%)	0	0	1 (4%)	1 (4%)	3 (13%)	5 (11%)	1 (2%)	13 (5%)
Adverse events of special interest‖									
Hypersensitivity events**	1 (2%)	2 (4%)	3 (13%)	0	2 (8%)	2 (8%)	8 (17%)	3 (7%)	21 (8%)
Treatment-emergent antidrug antibodies	0	3 (7%)	1 (5%)	3 (13%)	5 (19%)	3 (13%)	4 (9%)	2 (5%)	21 (7%)
Supraventricular arrhythmias and cardiac conduction disorders	1 (2%)	2 (4%)	1 (4%)	1 (4%)	2 (8%)	2 (8%)	3 (7%)	2 (4%)	14 (5%)
Injection site reactions	2 (4%)	0	1 (4%)	1 (4%)	1 (4%)	0	1 (2%)	1 (2%)	7 (2%)
Hepatic or biliary disorders	1 (2%)	0	0	1 (4%)	1 (4%)	1 (4%)	0	0	4 (1%)
Hyperaesthesia and related adverse events	0	0	1 (4%)	0	0	1 (4%)	1 (2%)	0	3 (1%)
Hypoglycaemia (<54 mg/dL or severe)	0	0	0	1 (4%)	1 (4%)	0	1 (2%)	0	3 (1%)
Severe gastrointestinal adverse events	0	0	0	0	1 (4%)	0	1 (2%)	0	2 (<1%)
Pancreatitis††	0	1 (2%)	0	0	1 (4%)	0	0	0	2 (<1%)
Major adverse cardiovascular events††	0	1 (2%)	0	0	0	0	0	0	1 (<1%)
Acute renal events	1 (2%)	0	0	0	0	0	0	0	1 (<1%)

Data are n (%). MedDRA=Medical Dictionary for Regulatory Activities. *Starting dose 2 mg. †Starting dose 2 mg, followed by escalation to 4 mg, and then to the maintenance dose of 8 mg. ‡Starting dose 4 mg. §Starting dose 2 mg, followed by escalation to 4 mg, then 8 mg, and then the maintenance dose of 12 mg. ¶Adverse events in the gastrointestinal disorders system organ class leading to discontinuation of study drug. ‖With the exception of antidrug antibody incidence, adverse events of special interest were evaluated using predefined standardised MedDRA search queries or customised clusters of preferred terms. Adverse events of special interest with zero events are described in the main text. **Hypersensitivity was assessed using MedDRA search criteria including narrow and broad standardised MedDRA queries of anaphylactic reaction, hypersensitivity, and angio-oedema. There were no serious or generalised reactions and no association between treatment-emergent antidrug antibodies and hypersensitivity reactions. ††Adjudicated-confirmed.

Table 3: **Safety analysis in patients who received at least one dose of study treatment**

and starvation ketoacidosis (in the 12 mg escalation group). One other case of adjudication-confirmed pancreatitis was reported in the retatrutide 0·5 mg group and not attributed to study drug by the site investigator. Moderate hypoglycaemia (glucose <54 mg/dL [3·0 mmol/L]) was reported in one participant in each of the retatrutide 4 mg, 8 mg slow escalation, and 12 mg escalation groups. In terms of adverse events of special interest, no severe or serious events of hypoglycaemia occurred, and no events of severe persistent hyperglycaemia, thyroid malignancies, or C-cell hyperplasia were reported. Mean alanine aminotransferase and aspartate aminotransferase generally decreased from baseline with retatrutide treatment, with little change in bilirubin (appendix p 28). Additional safety measures are in table 3 and the appendix (p 30).

Discussion

In this phase 2 trial, retatrutide reduced HbA_{1c} and bodyweight in participants with type 2 diabetes compared with placebo and 1·5 mg dulaglutide. We also observed meaningful reductions in blood pressure, triglycerides, and non-HDL cholesterol. These results confirm our observations from an earlier 12-week phase 1 study in a similar population and support phase 3 development of retatrutide.[10] Glucagon receptor activation, with either GLP-1 or GIP plus GLP-1 receptor activation, might complement the bodyweight-lowering efficacy of these injectable treatments, potentially due to the effect of glucagon on substrate use in the liver and effects on energy expenditure.[7,12,13] One concern with glucagon receptor activation is the potential for hyperglycaemia by increasing hepatic glucose production, as occurs with the counter-regulatory response to hypoglycaemia. However, the actions of glucagon under normoglycaemic and hyperglycaemic conditions are less well characterised, given historically focused investigation on hypoglycaemia.[14] Findings from development programmes of incretin agents with glucagon receptor activity are variable.[6] Differences in efficacy and safety between these agents are potentially related to relatively greater or lower glucagon receptor activity or a differential degree of activation of GLP-1 and GIP receptors. For example, cotadutide and SAR425899 showed meaningful glycaemic efficacy, but effects on bodyweight were similar to GLP-1 receptor agonists, potentially relating to relatively lower glucagon activity.[15,16] By contrast, pemvidutide had meaningful bodyweight reductions but no apparent effect on HbA_{1c}.[17] Retatrutide has similar glucagon and GLP-1 receptor activity, with more GIP receptor activity.[9] Data so far suggest that the ratios of receptor activities provided by retatrutide might strike a favourable balance between safety, glucose-lowering efficacy, and bodyweight-lowering efficacy.[9,10]

In this trial, HbA_{1c} reductions of up to 2·16% (23·59 mmol/mol) were observed with retatrutide (12 mg escalation group) after 36 weeks of treatment. Decreases were robust with doses of 4 mg and higher and showed dose dependency up to 8 mg, with smaller differences between the 8 mg and 12 mg groups, suggesting a maximal effect or perhaps requiring more time on treatment to further differentiate at higher doses. A similar effect was also observed with fasting serum glucose. Notably, although the proportion of participants reaching HbA_{1c} of less than 7·0% (53·0 mmol/mol; 82% *vs* 78%) and 6·5% (47·5 mmol/mol) or less (82% *vs* 79%) were similar in the 8 mg slow and fast escalation groups, there was a larger difference in the proportions reaching less than 5·7% (38·8 mmol/mol) between these groups (16% *vs* 31%). Initiating retatrutide at 4 mg might cause a numerically higher responder rate at this relatively early timepoint than 12 mg, with treatment initiated at 2 mg. Glycaemic efficacy with retatrutide 4 mg was similar to 1·5 mg dulaglutide and was significantly greater with the 8 mg and 12 mg retatrutide doses. However, retatrutide has not been tested in head-to-head studies against higher doses of dulaglutide or other selective GLP-1 receptor agonists or GIP and GLP-1 receptor agonists, because the higher doses of dulaglutide (3·0 mg or 4·5 mg) and tirzepatide were not available when this study was being planned. In phase 3 studies in people with type 2 diabetes after treatment periods of 40–52 weeks, HbA_{1c} reductions of 1·8% (20·0 mmol/mol) were reported with 4·5 mg dulaglutide,[18] 2·2% (24·1 mmol/mol) with semaglutide 2·0 mg (SUSTAIN FORTE),[19] and 2·5% (26·9 mmol/mol) with tirzepatide 15 mg (SURPASS-2),[4] indicating that retatrutide is likely to be an effective treatment for type 2 diabetes, with glycaemic control efficacy on par with currently approved incretin-based therapies. Retatrutide improves glycaemic efficacy through multiple mechanisms, including enhancing glucose-dependent insulin secretion and improving insulin sensitivity, as shown by decreasing fasting insulin and C-peptide concentrations and HOMA2-IR indices, while increasing adiponectin concentrations all in the setting of substantial weight reduction, with a pattern distinct from results with dulaglutide.[10]

Robust bodyweight reduction is increasingly recognised as a crucial component of type 2 diabetes treatment.[1,3] We observed dose-dependent bodyweight reductions of up to 16·94% with retatrutide (12 mg escalation group) at 36 weeks, which did not appear to have reached nadir, as participants were still losing weight. This magnitude of bodyweight reduction has not been reported so far in any other phase 2 or 3 trials testing weekly GLP-1 or GIP and GLP-1 receptor agonists in people with type 2 diabetes.[4,5,18–22] For context, although not directly comparable due to study design and population differences, weight reduction of up to approximately 5% was observed with 4·5 mg dulaglutide,[18] 7·2% with 2 mg semaglutide,[19] 10·6% with 2·4 mg semaglutide (STEP 2),[21] and 12% with 15 mg tirzepatide,[4] after treatment periods of 40–68 weeks. Additionally, up to 63% of retatrutide-treated participants lost at least 15% of bodyweight at 36 weeks, whereas 40% reached this target at 40 weeks with 15 mg tirzepatide in SURPASS-2.[4] A bodyweight reduction of 15% or more can have disease-modifying effects and potentially lead to type 2 diabetes remission.[3] In a preclinical study, we showed that the glucagon activity of retatrutide provided additional weight reduction that was attributable to increased energy expenditure.[9] Although our study did not assess energy expenditure, we hypothesise that the potentially greater weight reduction effect observed with retatrutide relative to GLP-1 receptor agonists and GIP and GLP-1 receptor agonists might in part be due to the effects of glucagon pharmacology to increase energy expenditure and fatty acid oxidation, and provide additive effects to the GLP-1 and GIP receptor activation in reducing food intake.[7,14,23,24] Observed increases in

β-hydroxybutyrate concentration with higher retatrutide doses were consistent with increased fatty acid oxidation.

Concurrently with reductions in glycaemia and bodyweight, retatrutide dose-dependently reduced systolic and diastolic blood pressure and improved lipid measures, notably reducing non-HDL cholesterol concentrations, while decreasing triglycerides by up to 35%. In a separate study in people with type 2 diabetes, 40 weeks of tirzepatide treatment reduced triglycerides by up to 25%.[4] Retatrutide and other molecules containing glucagon activity might reduce liver fat and improve lipid profiles through multiple potential mechanisms, including glucagon receptor-mediated increases in hepatic fatty acid oxidation and reductions in hepatic lipogenesis.[6,25] Furthermore, retatrutide might increase lipolysis in adipose tissue through GIP receptor activation.[24] The potential for glucagon and GIP receptor agonism to reduce circulating lipid concentrations and increase fatty acid oxidation might also contribute to reductions in ectopic fat and improved cellular health in multiple tissues.[7,14,24,26] GLP-1 receptor agonists reduce cardiovascular risk in people with type 2 diabetes[27] and tirzepatide has shown cardiovascular safety with no evidence of increased cardiovascular risk.[28] Potential for benefit, as indicated by reductions in cardiovascular risk-related measures[4] is being assessed in a large scale cardiovascular outcomes trial (SURPASS-CVOT, NCT04255433). Additional clinical trials will be needed to assess the effect of retatrutide treatment on long-term clinical outcomes.

We assessed glucagon receptor target engagement by measuring fasting endogenous glucagon and circulating amino acid concentrations. Reductions in endogenous glucagon concentrations in response to higher doses of retatrutide were much larger (up to 86%) than expected from previously observed reductions in clinical trials with GLP-1 receptor agonists or tirzepatide.[4,5,18,20] This pattern probably represents compensatory regulation of endogenous glucagon secretion in the setting of chronic glucagon receptor agonism. Retatrutide treatment also decreased concentrations of circulating amino acids, indicative of adaptive regulation of hepatic amino acid metabolism in response to glucagon receptor activation. We observed significant dose-related decreases in concentrations of gluconeogenic amino acids, including alanine and arginine, and smaller reductions in concentrations of some essential amino acids, such as phenylalanine and histidine. Retatrutide, similar to tirzepatide, significantly reduced concentrations of the branched-chain amino acids leucine, isoleucine, and valine, which have been associated with insulin resistance and metabolic dysfunction in many cohorts.[29] To better interpret potential clinical implications of these patterns of amino acid reductions in the context of substantial weight reduction, additional studies evaluating corresponding changes in relative fat and lean body mass in conjunction with functional assessments of muscle strength and physical performance might be of interest. Changes in amino acid concentrations have also been observed in many cohorts with weight reduction from bariatric surgery or dietary restriction.[30] Reductions in lean mass and grip strength observed after gastric bypass surgery have been accompanied by improvements in relative muscle strength and physical function.[31]

The safety profile of retatrutide in this study is consistent with that of tirzepatide and GLP-1 receptor agonists in people with type 2 diabetes.[4,5,18–22] Transient and mostly mild-to-moderate gastrointestinal events were the most frequently reported adverse events and occurred more frequently with the 4 mg starting dose groups rather than the 2 mg starting dose groups. Glucagon and GLP-1 can exert positive chronotropic and inotropic effects on the heart.[32,33] In the retatrutide phase 1 multiple-ascending dose study, an increase in pulse rate was observed, with the peak occurring at 12 weeks in the higher-dose groups.[10] In this phase 2 study, an increase in pulse rate, up to approximately 7 bpm, was observed early in treatment, but this decreased by 36 weeks, at which time the changes with retatrutide were not significantly different to those with dulaglutide 1·5 mg. The increases in heart rate are also consistent with those observed for other GLP-1 receptor agonists and GIP and GLP-1 receptor agonists in people with type 2 diabetes.[4,5,18–22]

Strengths of this study include the detailed study design testing multiple titration regimens and different starting doses to assess safety and tolerability to help inform dose selection for the phase 3 clinical programme. The extended 36-week design was unique for a phase 2 study in people with type 2 diabetes, allowing accumulation of sufficient data to assess the initial robustness of the glucose-lowering and weight-lowering properties and other cardiometabolic risk measures, and the safety profile.

Study limitations include a relatively smaller sample size and homogeneous population conducted only in the USA as compared with larger phase 3 studies, which limits generalisability to a broader population of people with type 2 diabetes. Although the decrease in HbA_{1c} appeared to have plateaued at 36 weeks, the trial duration might not have captured the full effect of retatrutide on bodyweight, which did not appear to have plateaued by study completion. The study was not designed to measure contributions of energy intake or expenditure to overall bodyweight reduction. Although glycaemic time in range is of increasing interest, it was not feasible to include assessment of continuous glucose monitoring in this study. As this is a relatively small phase 2 study, adjustment for multiple comparisons was not possible and data should be viewed as exploratory in nature, with phase 3 studies required to confirm our findings.

These data, the first phase 2 data for retatrutide in

people with type 2 diabetes, show clinically meaningful improvements in glycaemic control. Robust bodyweight reductions were also observed, which exceeded what has previously been achieved by incretin-based therapies in type 2 diabetes in studies of similar duration in this population. The safety profile was similar to that observed with GLP-1 receptor agonists and GIP and GLP-1 receptor agonists. These results suggest that retatrutide is a promising therapeutic agent for the management of hyperglycaemia and obesity in the setting of type 2 diabetes, and support phase 3 clinical development.

Contributions

TC, AH, MLH, MKT, and ZM contributed to the study design. TC and SG provided medical oversight during the trial. JF and JR were study investigators. JL and YD were responsible for the statistical analyses. TC and JR wrote the first draft with medical writing support. All authors 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 had responsibility for the decision to submit for publication.

Declaration of interests

JR has received grants and research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Hanmi, Merck, Oramed, Novartis, Novo Nordisk, Pfizer, and Sanofi; served on scientific advisory boards and received honorarium or consulting fees from Applied Therapeutics, Boehringer Ingelheim, Eli Lilly and Company, Hanmi, Novo Nordisk, Oramed, Sanofi, Structure Therapeutics, Terns Pharma, and Zealand; received honorarium for lectures or educational events from Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, and Sanofi; and received support for attending meetings or travel from Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, and Sanofi. AMJ has received grants and contracts (paid to their institution) from Novo Nordisk, Eli Lilly and Company, Rhythm Pharmaceutical, and the US National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases; consults for Amgen and Scholar Rock; has received honoraria or travel expenses from Eli Lilly and Company, Novo Nordisk, and WeightWatchers; has stock options from Intellihealth; and serves on advisory boards for AstraZeneca, Boehringer Ingelheim, Biohaven, Eli Lilly and Company, Intellihealth, Novo Nordisk, Rhythm Pharmaceuticals, Structure Therapeutics, Terns Pharmaceuticals, and WeightWatchers. JF reports research funding from Akero, AstraZeneca, Boehringer Ingelheim, 89bio, Eli Lilly and Company, Intercept, IONIS, Janssen, Madrigal, Metacrine, Merck, NorthSea Therapeutics, Novartis, Novo Nordisk, Oramed, Pfizer, Poxel, and Sanofi; consulting fees from Akero, Altimmune, Boehringer Ingelheim, Carmot Therapeutics, Echosens, 89bio, Eli Lilly and Company, Merck, Novo Nordisk, Pfizer, and Sanofi; speaker bureau fees from Eli Lilly and Company; support for attending meetings or travel from Eli Lilly and Company, Novo Nordisk, Pfizer, and Sanofi; participation on advisory boards and consulting for Altimmune, Becton Dickenson, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly and Company, Gilead, Intercept, Merck, Novo Nordisk, Pfizer, and Sanofi; and is on the Board of Directors of T1D Exchange. YD, JL, SG, MKT, MLH, AH, ZM, and TC are employees and shareholders of Eli Lilly and Company. MKT also reports roles as Industry Chair, Steering Committee for Accelerating Medicines Partnership-Type 2 Diabetes and Steering Committee Member for Accelerating Medicines Partnership-Common Metabolic Diseases.

Data sharing

Eli Lilly and Company 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 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 online.

For more on **submitting a request** see http://www.vivli.org

Acknowledgments

The study was funded by Eli Lilly and Company. Eli Lilly and Company thanks the clinical trial participants and their caregivers, without whom this work would not be possible. We thank Eli Lilly and Company employees Andrea Hemmingway for medical writing and editorial support, Christopher Knight for medical monitoring and safety support, Charlie Harris for medical monitoring and safety support and critical review of the manuscript, and Kieren Mather for study oversight and critical review of the manuscript.

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