Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

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Summary

Background LY3298176 is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed for the treatment of type 2 diabetes. We aimed to examine the efficacy and safety of co-stimulation of the GLP-1 and GIP receptors with LY3298176 compared with placebo or selective stimulation of GLP-1 receptors with dulaglutide in patients with poorly controlled type 2 diabetes.

Methods In this double-blind, randomised, phase 2 study, patients with type 2 diabetes were randomly assigned (1:1:1:1:1:1) to receive either once-weekly subcutaneous LY3298176 (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1·5 mg), or placebo for 26 weeks. Assignment was stratified by baseline glycated haemoglobin A_{1c} (HbA_{1c}), metformin use, and body-mass index (BMI). Eligible participants (aged 18–75) had type 2 diabetes for at least 6 months (HbA_{1c} 7·0–10·5%, inclusive), that was inadequately controlled with diet and exercise alone or with stable metformin therapy, and a BMI of 23–50 kg/m². The primary efficacy outcome was change in HbA_{1c} from baseline to 26 weeks in the modified intention-to-treat (mITT) population (all patients who received at least one dose of study drug and had at least one postbaseline measurement of any outcome). Secondary endpoints, measured in the mITT on treatment dataset, were change in HbA_{1c} from baseline to 12 weeks; change in mean bodyweight, fasting plasma glucose, waist circumference, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and proportion of patients reaching the HbA_{1c} target (≤6·5% and <7·0%) from baseline to weeks 12 and 26; and proportion of patients with at least 5% and 10% bodyweight loss from baseline to 26 weeks. This study is registered with ClinicalTrials.gov, number NCT03131687.

Findings Between May 24, 2017, and March 28, 2018, 555 participants were assessed for eligibility, of whom 318 were randomly assigned to one of the six treatment groups. Because two participants did not receive treatment, the modified intention-to-treat and safety populations included 316 participants. 258 (81·7%) participants completed 26 weeks of treatment, and 283 (89·6%) completed the study. At baseline, mean age was 57 years (SD 9), BMI was 32·6 kg/m² (5·9), duration from diagnosis of diabetes was 9 years (6), HbA_{1c} was 8·1% (1·0), 53% of patients were men, and 47% were women. At 26 weeks, the effect of LY3298176 on change in HbA_{1c} was dose-dependent and did not plateau. Mean changes from baseline in HbA_{1c} with LY3298176 were –1·06% for 1 mg, –1·73% for 5 mg, –1·89% for 10 mg, and –1·94% for 15 mg, compared with –0·06% for placebo (posterior mean differences [80% credible set] *vs* placebo: –1·00% [–1·22 to –0·79] for 1 mg, –1·67% [–1·88 to –1·46] for 5 mg, –1·83% [–2·04 to –1·61] for 10 mg, and –1·89% [–2·11 to –1·67] for 15 mg). Compared with dulaglutide (–1·21%) the posterior mean differences (80% credible set) for change in HbA_{1c} from baseline to 26 weeks with the LY3298176 doses were 0·15% (–0·08 to 0·38) for 1 mg, –0·52% (–0·72 to –0·31) for 5 mg, –0·67% (–0·89 to –0·46) for 10 mg, and –0·73% (–0·95 to –0·52) for 15 mg. At 26 weeks, 33–90% of patients treated with LY3298176 achieved the HbA_{1c} target of less than 7·0% (*vs* 52% with dulaglutide, 12% with placebo) and 15–82% achieved the HbA_{1c} target of at least 6·5% (*vs* 39% with dulaglutide, 2% with placebo). Changes in fasting plasma glucose ranged from –0·4 mmol/L to –3·4 mmol/L for LY3298176 (*vs* 0·9 mmol/L for placebo, –1·2 mmol/L for dulaglutide). Changes in mean bodyweight ranged from –0·9 kg to –11·3 kg for LY3298176 (*vs* –0·4 kg for placebo, –2·7 kg for dulaglutide). At 26 weeks, 14–71% of those treated with LY3298176 achieved the weight loss target of at least 5% (*vs* 22% with dulaglutide, 0% with placebo) and 6–39% achieved the weight loss target of at least 10% (*vs* 9% with dulaglutide, 0% with placebo). Changes in waist circumference ranged from –2·1 cm to –10·2 cm for LY3298176 (*vs* –1·3 cm for placebo, –2·5 cm for dulaglutide). Changes in total cholesterol ranged from 0·2 mmol/L to –0·3 mmol/L for LY3298176 (*vs* 0·3 mmol/L for placebo, –0·2 mmol/L for dulaglutide). Changes in HDL or LDL cholesterol did not differ between the LY3298176 and placebo groups. Changes in triglyceride concentration ranged from 0 mmol/L to –0·8 mmol/L for LY3298176 (*vs* 0·3 mmol/L for placebo, –0·3 mmol/L for dulaglutide). The 12-week outcomes were similar to those at 26 weeks for all secondary outcomes. 13 (4%) of 316 participants across the six treatment groups had 23 serious adverse events in total. Gastrointestinal events (nausea, diarrhoea, and vomiting) were the most common treatment-emergent adverse

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events. The incidence of gastrointestinal events was dose-related (23·1% for 1 mg LY3298176, 32·7% for 5 mg LY3298176, 51·0% for 10 mg LY3298176, and 66·0% for 15 mg LY3298176, 42·6% for dulaglutide, 9·8% for placebo); most events were mild to moderate in intensity and transient. Decreased appetite was the second most common adverse event (3·8% for 1 mg LY3298176, 20·0% for 5 mg LY3298176, 25·5% for 10 mg LY3298176, 18·9% for 15 mg LY3298176, 5·6% for dulaglutide, 2·0% for placebo). There were no reports of severe hypoglycaemia. One patient in the placebo group died from lung adenocarcinoma stage IV, which was unrelated to study treatment.

Interpretation **The dual GIP and GLP-1 receptor agonist, LY3298176, showed significantly better efficacy with regard to glucose control and weight loss than did dulaglutide, with an acceptable safety and tolerability profile. Combined GIP and GLP-1 receptor stimulation might offer a new therapeutic option in the treatment of type 2 diabetes.**

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Introduction

Native glucagon-like peptide-1 (GLP-1) is released into the circulation from intestinal enteroendocrine L cells in response to glucose and other nutrients.[1,2] GLP-1 potentiates the release of insulin from β-cells in a glucose-dependent manner.[1–3] At pharmacological concentrations, GLP-1 delays gastric emptying, reduces appetite, and thus decreases food intake.[1–3] These effects contribute to improved glucose homeostasis and reductions in bodyweight.[2] Pharmacological treatment of type 2 diabetes with GLP-1 receptor agonists is widely recommended because incretins address the key pathophysiological problems of type 2 diabetes and positively alter the course of chronic macrovascular and microvascular complications with long-term use.[4,5] Despite these benefits, some patients treated with GLP-1 receptor agonists do not achieve their individualised glycaemic and bodyweight targets with currently approved incretins, making

Research in context

Evidence before this study

We searched PubMed on July 17, 2018, using the terms "liraglutide", "exenatide", "lixisenatide", "dulaglutide", "albiglutide", "semaglutide", "glucagon-like peptide-1 receptor agonist", and "type 2 diabetes" with no date or study duration restrictions. Non-English references were excluded. The published literature describes glycated haemoglobin A_{1c} (HbA_{1c}) reductions (depending upon baseline HbA_{1c}) of up to 1·5 %, and bodyweight reduction up to 5 kg (on average, large interindividual differences) with the most effective glucagon-like peptide-1 (GLP-1) receptor agonists being liraglutide, dulaglutide, and semaglutide. Four small studies have reported on dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists. A 6-week study with a pegylated dual agonist showed clinically relevant glucose reduction and weight loss with a relatively low incidence of gastrointestinal side-effects. A 12-week study with a dual agonist, and balanced activity at the two receptors, showed similar glycaemic efficacy and modest weight loss compared with liraglutide. In a single ascending dose study and a 14-day multiple ascending dose study, another dual GIP and GLP-1 receptor agonist, RG7697, showed glycaemic improvement and weight loss.

Added value of this study

LY3298176 is a novel dual GIP and GLP-1 receptor agonist balanced towards GIP. In this study, we compared LY3298176 with dulaglutide, a selective GLP-1 receptor agonist, and placebo. We show that simultaneous stimulation of both receptors by LY3298176 caused a statistically significant and clinically meaningful improvement in glucose lowering and bodyweight reduction, compared with selective agonism at the GLP-1 receptor with dulaglutide. Notably, these results are consistent with observations reported in preclinical studies of GIP and GLP-1 costimulation, suggesting its potential for greater metabolic effects versus selective GLP-1 receptor stimulation, especially for weight reduction. To confirm the superior clinical profile of LY3298176, additional clinical studies versus the most potent GLP-1 receptor agonists are warranted. When compared with dulaglutide, LY3298176 had a greater effect on both homeostatic model assessment of pancreatic β-cell function and insulin resistance and caused a greater reduction in glucagon concentration. Although we did not assess the effect of LY3298176 on appetite and food intake, the multifold increase in the reporting of reduced appetite as an adverse event with LY3298176, compared with dulaglutide, suggests that the effect on appetite might contribute to the metabolic effects of LY3298176.

Implications of all the available evidence

Our findings show that treatment with LY3298176, a novel dual GIP and GLP-1 receptor dual agonist, resulted in statistically significant and clinically meaningful control of HbA_{1c} with greater weight loss and an acceptable tolerability profile, as compared with dulaglutide, a GLP-1 receptor agonist. Larger confirmatory studies are needed to assess whether LY3298176 has advantageous therapeutic effects with regard to glycaemic control and bodyweight reduction when compared with the selective GLP-1 receptor agonist class of agents in patients with type 2 diabetes.

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continued optimisation of these agents a clinically important goal.

One way to enhance the metabolic effects of GLP-1 receptor agonists is to combine them with complementary or synergistic actions of other enteropancreatic hormones, such as glucose-dependent insulinotropic polypeptide (GIP). GIP is secreted from enteroendocrine K cells and, like GLP-1, is a potent stimulator of glucose-dependent insulin secretion.[6,7] In type 2 diabetes, however, the insulinotropic effects of GIP are severely impaired, which explains the absence of a relevant effect of GIP on insulin secretion or glucose concentrations in these patients, as seen in acute infusion studies.[8,9] It is hypothesised that hyperglycaemia is responsible for this scarcity of insulinotropic effectiveness.[10] Evidence suggests that the insulinotropic effects might be partially restored after several weeks of near-normal glycaemic control.[9,11,12] However, chronic treatment with selective GIP receptor agonists alone has not been tested in humans. There might also be other GIP-related actions, beyond its role as an incretin, that could enhance therapeutic efficacy in combination with GLP-1 receptor agonists. The GIP receptor is highly expressed in adipose tissue, and acute infusion of GIP under conditions of high insulin and modest hyperglycaemia increases adipose tissue glucose uptake, blood flow, and triglyceride hydrolysis in humans.[11,13,14] Although the mechanisms are not yet understood, rodent and human studies show that GIP plays a role in the regulation of lipolysis and lipogenesis in adipose tissue, which could contribute to improved lipid homeostasis and whole-body energy metabolism.[15,16] Therefore, GIP might increase metabolic flexibility by enabling increased fat utilisation in the fasting state and reducing fat availability in the postprandial state.[11,16] In addition, GIP receptors in the brain can, when stimulated, reduce food intake and bodyweight under specific circumstances in animals.[17–19] Similar studies in humans have not yet been done.

Combined treatment with GLP-1 and GIP receptor agonists could result in additive effects on glucose and bodyweight regulation. In rodent models of obesity and type 2 diabetes, treatment with a dual agonist improves insulin responses and glycaemic control compared with a GLP-1 receptor agonist alone.[20] Rodents chronically treated with a dual agonist had greater weight loss than with a GLP-1 receptor agonist alone, not only by reducing appetite but also by increasing energy expenditure.[19] In humans, a 6-week proof-of-concept study with a pegylated dual GIP and GLP-1 receptor agonist showed clinically relevant glucose and bodyweight reduction, with low incidence of gastrointestinal side-effects, indicating that the therapeutic window might be broader than that of a selective GLP-1 receptor agonist.[21]

LY3298176 is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. Its structure is primarily based on the GIP amino acid sequence and includes a C20 fatty di-acid moiety that prolongs the duration of action, allowing once-weekly subcutaneous administration.[22] Preclinical data showed that LY3298176 has a greater affinity to GIP relative to GLP-1 receptors expressed on cells.[19] This phase 2 study aimed to explore the dose-response relationship of LY3298176 (1, 5, 10, and 15 mg) in patients with type 2 diabetes and collect initial efficacy and safety data in comparison with placebo and dulaglutide 1·5 mg.

Methods

Study design and participants

This 26-week, phase 2b, randomised, double-blind study was done at 47 sites (medical and clinical research centres) in Poland, Puerto Rico, Slovakia, and USA. Eligible participants (aged 18–75) had type 2 diabetes for at least 6 months (glycated haemoglobin A_{1c} [HbA_{1c}] 7·0–10·5%, inclusive) that was inadequately controlled with diet and exercise alone or with stable metformin therapy for at least 3 months before screening, and a body-mass index (BMI) of 23–50 kg/m². The full list of inclusion and exclusion criteria is given in the appendix. An independent adjudication committee (Duke Clinical Research Institute, Durham, NC, USA) adjudicated certain outcomes to ensure consistency in the assessment of clinical cases that were of special interest in this trial. The study protocol was approved by local ethics committees and was done in accordance with the principles of Declaration of Helsinki, Council of International Organizations of Medical Sciences International Ethical Guidelines, and Good Clinical Practice guidelines. All patients gave written informed consent before participation in the study. The protocol is given in the appendix.

See Online for appendix

Randomisation and masking

Participants who met the enrolment criteria were randomly allocated (1:1:1:1:1:1) to one of the six parallel treatment groups by use of an interactive web response system with three stratification variables: baseline HbA_{1c} (<8·5% or ≥8·5%), metformin use (yes or no), and BMI (<30 kg/m² or ≥30 kg/m²). The principal investigators at each site enrolled the participants. To ensure masking of patients and investigators from treatment identification due to the differences in volumes and titration regimes across the treatment groups, the patients in the placebo and dulaglutide groups were further randomised to the four LY3298176 dosing groups (1, 5, 10, and 15 mg).

Procedures

After a 1-week screening and 2-week lead-in period, participants were treated for 26 weeks and then followed-up for safety outcomes for 4 weeks (appendix). Participants treated with metformin or other pre-study medications continued to take these medications throughout the study.

All the treatments were subcutaneously administered once a week. The 1 mg LY3298176, 5 mg LY3298176, and 1·5 mg dulaglutide groups were given the respective doses of the treatment without dose titration.

To improve gastrointestinal tolerability, patients assigned to the 10 mg LY3298176 group received 5 mg for the first 2 weeks and then 10 mg for the rest of the study. Patients assigned to 15 mg LY3298176 received 5 mg for the first 2 weeks, 10 mg for the next 4 weeks, and 15 mg for the rest of the study.

Outcomes

The primary efficacy outcome was change in HbA_{1c} from baseline to 26 weeks in the modified intention-to-treat (mITT) population, defined as all participants who took at least one dose of study drug and had at least one postbaseline measurement of any outcome. Secondary endpoints were change in HbA_{1c} from baseline to 12 weeks, change in mean bodyweight, fasting plasma glucose, and waist circumference from baseline to weeks 12 and 26, proportion of patients with at least 5% and 10% bodyweight loss from baseline to 26 weeks, proportion of patients reaching the HbA_{1c} target (≤6·5% and <7·0%), and change in lipid laboratory data from baseline to 26 weeks. We did additional post-hoc analyses to measure the proportion of patients reaching normoglycaemia (indicated by a HbA_{1c} target of <5·7%) and the proportion of patients reaching the weight loss target of 15% or more. Safety and tolerability outcomes were overall adverse events; adverse events related to gastrointestinal tolerability, hypersensitivity, injection site reactions, cardiovascular events, thyroid-related events, and pancreatitis; vital signs; ECG; anti-drug antibodies to LY3298176; laboratory analytes; and incidence and rate of hypoglycaemia in the safety population, consisting of all participants who received at least once dose of study drug (appendix).

Tertiary exploratory outcomes were change from baseline in the 7-point self-monitoring of blood glucose profiles at weeks 4, 12, 26, and 30, and change from baseline in homeostatic model assessment of β-cell function (HOMA2-B) and of insulin resistance (HOMA2-IR), fasting insulin, and glucagon at weeks 12 and 26 (appendix).

All cases of the following events were adjudicated by an independent adjudication committee: suspected acute or chronic pancreatitis, confirmed lipase or amylase concentrations 3 times the upper limit of normal, adverse events of severe or serious abdominal pain of unknown aetiology, death (cardiovascular and non-cardiovascular), non-fatal myocardial infarction, supraventricular arrhythmia, non-fatal stroke, transient ischaemic attack, or admission to hospital for unstable angina, heart failure, and coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention). Further details of the adjudication process are provided in the appendix.

Statistical analysis

The sample size calculations assumed a change from baseline in HbA_{1c} profile of 0% for placebo, –0·74% for 1 mg LY3298176, –1·17% for for 5 mg LY3298176, –1·29% for 10 mg LY3298176, –1·44% for 15 mg LY3298176, and –1·28% for dulaglutide, and a standard deviation of 1·0%. With an estimated discontinuation rate of 10%, a sample size of 300 participants provided about 98% probability, with 90% confidence, that at least one of the doses of LY3298176 would result in superior glycaemic control versus placebo for change in HbA_{1c} from baseline to 26 weeks, with a superiority margin of –0·8%. This sample size also provided about 95% probability, with 90% confidence, that at least one of the doses of LY3298176 would have non-inferior glycaemic control compared with dulaglutide (non-inferiority margin 0·3%).

To address the confounding effect of adherence to study treatment and glucose-lowering rescue interventions after randomisation, we present results of the analyses done on two different mITT datasets. The primary objective dataset (referred to as the mITT without postrescue dataset) included all data, irrespective of adherence, except efficacy data collected after rescue therapy was started. The second dataset (referred to as the mITT on treatment dataset) included all data, except efficacy data collected after discontinuation of study treatment and data collected after rescue therapy was started.

We used a Bayesian hierarchical logistic dose-response model and a longitudinal integrated two-component prediction model to estimate missing values for change from baseline in HbA_{1c}. We applied this to the mITT without postrescue dataset and, as a sensitivity analysis, to the mITT on treatment dataset. Superiority to placebo with a margin of –0·8% would be met if at least one of the LY3298176 treatment groups' 90% (one-sided) upper credible interval excluded –0·8%. We did additional sensitivity analyses using a mixed-effect model for repeated measures in the mITT on treatment dataset to compare LY3298176 doses to placebo and dulaglutide for the primary efficacy outcome of change in HbA_{1c} from baseline to 26 weeks. The mixed-effect model for repeated measures included metformin use (yes/no), baseline BMI category, treatment, visit, and treatment-by-visit interaction as fixed effects, baseline HbA_{1c} as a covariate, and patient as a random effect. We did not adjust the significance level for multiplicity.

We also used a similar mixed-effect model for repeated measures to analyse other continuous secondary efficacy variables. For changes from baseline in bodyweight, we also did Bayesian dose-response analyses. For assessment of fasting insulin, fasting glucagon, HOMA2-B, and HOMA2-IR, we did log transformation before the analyses. We did categorical analyses of participants achieving prespecified HbA_{1c} and bodyweight targets at 26 weeks using logistic regression with fixed effects of

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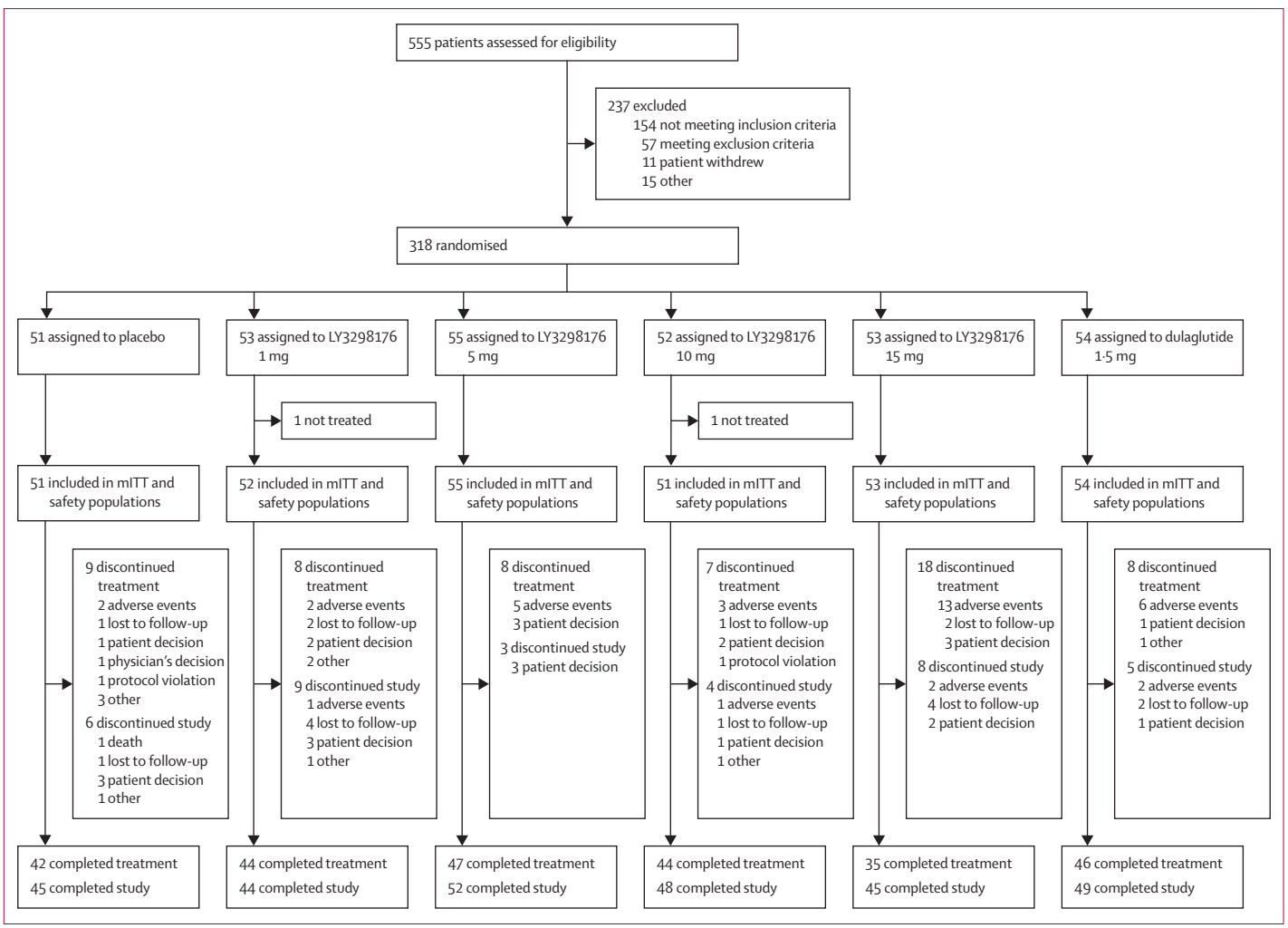

Figure 1: **Study profile**
mITT=modified intention-to-treat.

treatment and strata, and baseline as a covariate in the mITT on treatment dataset. For participants who discontinued the study early or with missing measurement at week 26, the last observation was carried forward to week 26.

All safety data are reported in the safety population, consisting of all randomised participants who received at least one dose of study drug. Key continuous safety measures, including vital signs and ECG variables, were analysed using a similar mixed-effect model for repeated measures as described for the primary outcome.

Summaries for both efficacy and safety parameters included descriptive statistics for continuous measures (sample size, mean, standard deviation, median, minimum, and maximum) and for categorical measures (sample size, frequency, and percentages). All statistical analyses were performed using SAS version 9.4.

This study is registered with ClinicalTrials.gov, number NCT03131687.

Role of the funding source

The study sponsor provided the study drugs and was involved in the study design, data collection, data review, data analysis, and drafting of this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 24, 2017, and March 28, 2018, we assessed 555 individuals for eligibility; 318 were randomly assigned to one of the six treatment groups (figure 1). One participant each in the 1 mg and 10 mg LY3298176 groups was not treated; thus the mITT and safety population included 316 participants. 258 (82%) participants completed 26 weeks of treatment and 283 (90%) completed the study. The proportion of participants completing treatment was similar across the groups (range 82–86%), except for the 15 mg LY3298176

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	Placebo (n=51)	1 mg LY3298176 (n=52)	5 mg LY3298176 (n=55)	10 mg LY3298176 (n=51)	15 mg LY3298176 (n=53)	1·5 mg dulaglutide (n=54)
Demographic variables						
Mean age (years)	56·6 (8·9)	57·4 (8·9)	57·9 (8·2)	56·5 (9·9)	56·0 (7·6)	58·7 (7·8)
Sex						
Female	22 (43%)	23 (44%)	21 (38%)	21 (41%)	31 (59%)	30 (56%)
Male	29 (57%)	29 (56%)	34 (62%)	30 (59%)	22 (42%)	24 (44%)
Race						
White	41 (80%)	42 (81%)	46 (84%)	37 (74%)	43 (81%)	44 (83%)
Asian	1 (2%)	0	0 (0%)	1 (2%)	1 (2%)	2 (4%)
Black or African American	2 (4%)	5 (10%)	6 (11%)	7 (14%)	6 (11%)	4 (8%)
Ethnic origin						
Hispanic or Latino	27 (59%)	25 (52%)	22 (49%)	26 (57%)	23 (46%)	19 (41%)
Not Hispanic or Latino	19 (41%)	23 (48%)	23 (51%)	20 (44%)	27 (54%)	27 (59%)
Clinical characteristics						
HbA_{1c} concentration						
Values in %	8·0 (0·9)	8·2 (0·9)	8·2 (1·0)	8·2 (1·1)	8·1 (1·1)	8·1 (1·0)
Values in mmol/mol	63·93 (9·84)	66·11 (9·84)	66·11 (10·93)	66·11 (12·02)	65·02 (12·02)	65·02 (10·93)
Fasting plasma glucose concentration						
Values in mmol/L	9·1 (2·3)	8·9 (2·3)	9·4 (2·5)	9·5 (2·8)	9·2 (2·7)	9·9 (3·6)
Values in mg/dL*	163·1 (41·4)	161·1 (40·7)	168·6 (44·3)	170·6 (50·3)	164·8 (48·6)	178·1 (64·5)
eGFR (BSA CKD-EPI calculation; ml/min per 1·73 m^2)*	95·3 (15·3)	95·6 (16·8)	92·2 (17·2)	93·7 (18·6)	91·8 (17·9)	90·7 (17·6)
Bodyweight (kg)	91·5 (23·1)	93·2 (24·4)	92·8 (19·0)	92·7 (19·5)	89·1 (22·7)	89·8 (16·9)
Body-mass index (kg/m^2)	32·4 (6·0)	32·9 (6·1)	32·9 (5·7)	32·6 (5·8)	32·2 (6·2)	32·4 (5·4)
Diabetes duration (years)	8·6 (7·0)	7·8 (5·4)	8·9 (5·7)	7·9 (5·8)	8·5 (6·1)	9·3 (7·1)
Diabetes medication at randomisation						
Metformin	47 (92·2%)	46 (88·5%)	49 (89·1%)	44 (86·3%)	51 (96·2%)	48 (88·9%)

Data are mean (SD) or n (%), unless otherwise specified. CKD-EPI=chronic kidney disease epidemiology collaboration. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin A_{1c}. *All postbaseline data, safety population. The modified intention-to-treat population was used for the rest of the variables.

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

group, which had the lowest number of patients (66%) completing therapy (figure 1). Baseline demographics and clinical characteristics were similar across all the six groups (table 1). Overall duration of drug exposure to LY3298176, dulaglutide, and placebo was similar across the groups, except for shorter mean exposure in the 15 mg LY3298176 group versus all other groups. Six patients took rescue medication during the treatment period, of whom two patients were on placebo, two on dulaglutide, and one each on LY3298176 1 mg and 15 mg.

Relative to placebo, the reduction in HbA_{1c} from baseline to 26 weeks was greater with LY3298176, across all doses, in a dose-dependent manner. Mean changes with LY3298176 were –1·06% for 1 mg, –1·73% for 5 mg, –1·89% for 10 mg, and –1·94% for 15 mg, compared with –0·06% for placebo (posterior mean differences [80% credible set] *vs* placebo: –1·00% [–1·22 to –0·79] for 1 mg, –1·67% [–1·88 to –1·46] for 5 mg, –1·83% [–2·04 to –1·61] for 10 mg, and –1·89% [–2·11 to –1·67] for 15 mg). Compared with dulaglutide (–1·21%) the posterior mean differences (80% credible set) for change in HbA_{1c} from baseline to 26 weeks with the LY3298176 doses were 0·15% (–0·08 to 0·38) for 1 mg, –0·52% (–0·72 to –0·31) for 5 mg, –0·67% (–0·89 to –0·46) for 10 mg, and –0·73% (–0·95 to –0·52) for 15 mg. Non-inferiority of LY3298176 versus dulaglutide was established. We also excluded –0·3% upper limit of the interval for 5 mg, 10 mg, and 15 mg LY3298176, indicating a greater magnitude of lowering of HbA_{1c} for these doses compared with dulaglutide (figure 2A). The results were consistent across the mITT without postrescue and the mITT on treatment datasets (figure 2A, appendix). The results of the mixed-effect model for repeated measures in the mITT on treatment datasets were consistent with those of the analyses with the Bayesian model, and demonstrated greater reductions in HbA_{1c} with 5 mg, 10 mg, and 15 mg LY3298176 compared with dulaglutide (p=0·0152 for 5 mg, p=0·0001 for 10 mg, p<0·0001 for 15 mg; figure 2B, appendix). 10 mg and 15 mg LY3298176 had the greatest glycaemic effect in all analyses, with greatest difference in HbA_{1c} of 0·4% seen between these two doses of LY3298176 in the mixed-effect model for repeated measures mITT on treatment dataset.

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At 26 weeks, 33–90% of patients treated with LY3298176 achieved the HbA_{1c} target of less than 7·0% (*vs* 52% with dulaglutide, 12% with placebo) and 15–82% achieved the HbA_{1c} target of at least 6·5% (*vs* 39% with dulaglutide, 2% with placebo; figure 2C, appendix). More participants who received LY3298176 (all doses) or dulaglutide achieved the HbA_{1c} targets of less than 7·0% and 6·5% or less, compared with placebo (for HbA_{1c} <7·0%: p=0·0075 for 1 mg LY3298176, p<0·0001 for all other groups; for HbA_{1c} ≤6·5%: p=0·0297 for 1 mg LY3298176, p=0·0003 for dulaglutide, p<0·0001 for all other groups; figure 2C, appendix). A greater proportion of participants treated with 5 mg, 10 mg, or 15 mg LY3298176 achieved these two HbA_{1c} targets than did those treated with dulaglutide (for HbA_{1c} <7·0%: p=0·0449 for 5 mg LY3298176, p<0·0001 for 10 mg LY3298176, p=0·0038 for 15 LY3298176; for HbA_{1c} ≤6·5%: p=0·0121 for 1 mg LY3298176, p=0·0077 for 5 mg LY3298176, p<0·0001 for 10 mg LY3298176, p=0·0412 for 15 mg LY3298176; figure 2C, appendix). Nine (18%) of 51 participants treated with 10 mg LY3298176 and 16 (30%) of 53 treated with 15 mg LY3298176 reached normoglycaemia (HbA_{1c} target <5·7%), compared with one (2%) of 54 participants treated with dulaglutide (figure 2C, appendix).

Changes in fasting plasma glucose from baseline to week 26 ranged from –0·4 mmol/L (–6·8 mg/dL) to –3·4 mmol/L (–60·7 mg/dL) for the LY3298176 groups (*vs* 0·9 mmol/L [15·5 mg/dL] for placebo, –1·2 mmol/L [–21·2 mg/dL]) for dulaglutide; appendix). All doses of LY3298176 reduced the concentration of fasting plasma glucose from baseline to week 26 relative to placebo, in a dose-dependent manner (p=0·0102 for 1 mg LY3298176, p<0·0001 for all other LY3298176 groups; table 2, appendix). Treatment with the 5 mg, 10 mg, and 15 mg LY3298176 reduced fasting plasma glucose more than did dulaglutide (p=0·0197 for 5 mg, p<0·0001 for all other LY3298176 groups; table 2, appendix). At week 26, the mean values of all self-monitored blood glucose concentrations, including pre-meal and 2-h postprandial concentrations, were reduced from baseline for all LY3298176 doses and for dulaglutide relative to placebo (p<0·0001; table 2, appendix). Compared with dulaglutide, treatment with 10 mg and 15 mg LY3298176 resulted in greater reductions in these self-monitored blood glucose variables (p=0·0113 for 10 mg, p=0·0002 for 15 mg; table 2, appendix).

HOMA2-B increased with 5 mg, 10 mg, and 15 mg LY3298176 and with dulaglutide compared with placebo (p<0·0001; table 2). 10 mg and 15 mg LY3298176 increased HOMA2-B versus dulaglutide (p=0·0267 for 10 mg, p=0·0315 for 15 mg; table 2, appendix). HOMA2-IR decreased with 10 mg and 15 mg LY3298176 versus dulaglutide (p=0·0027 for 10 mg, p=0·0107 for 15 mg; table 2, appendix). At week 26, concentrations of fasting serum insulin decreased from baseline with 10 mg and 15 mg LY3298176 versus dulaglutide (p=0·0006 for

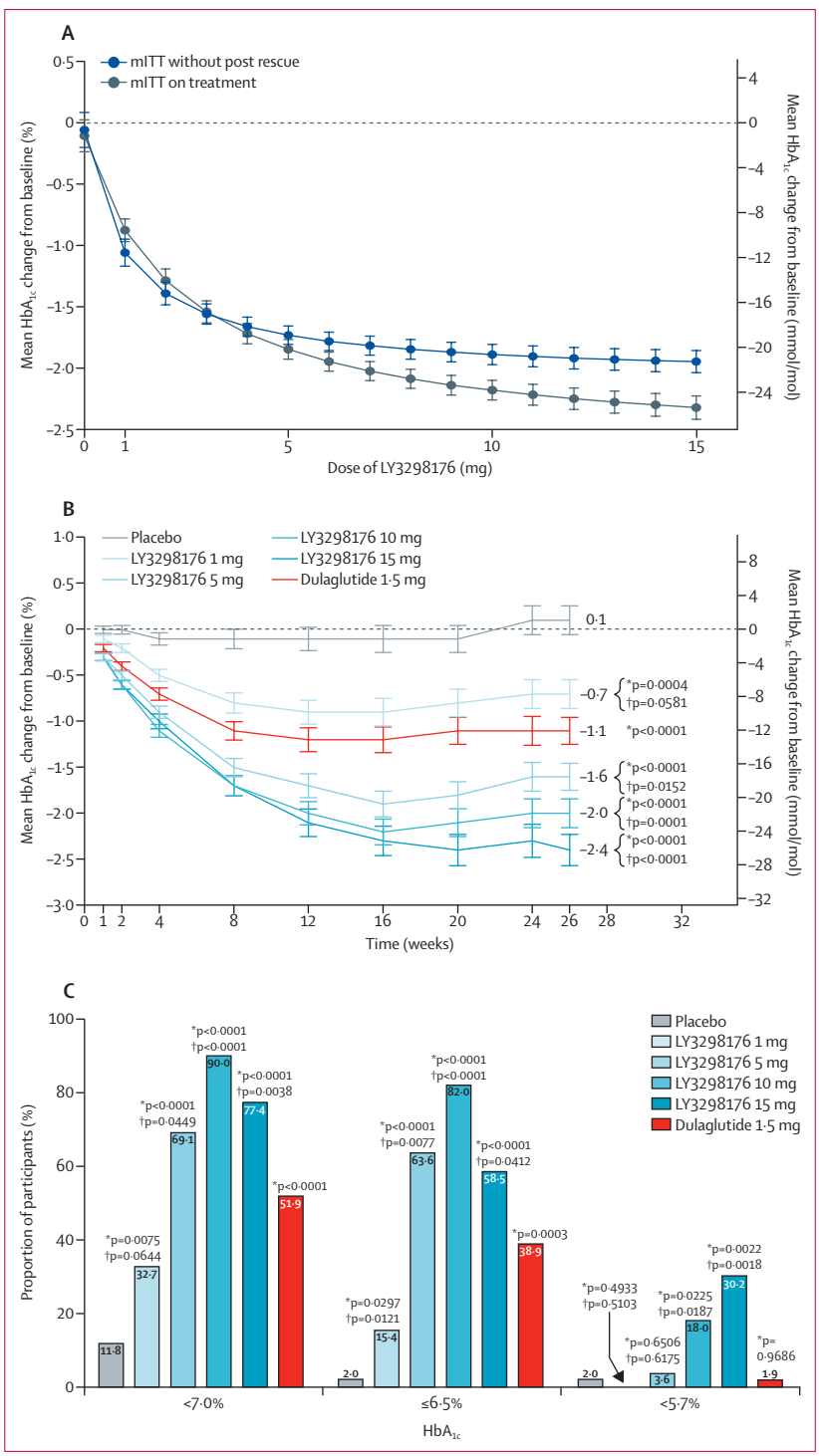

Figure 2: **Efficacy outcomes of treatment with LY3298176 at week 26 after once-weekly subcutaneous administration**

(A) Bayesian dose response efficacy curve of LY3298176 by dataset. Data are posterior mean, with SD error bars. (B) Mixed model repeated measures analysis of the mITT on treatment dataset. Data are least squares mean, with SE error bars. (C) Last observation carried forward endpoint data of the mITT on treatment dataset. HbA_{1c}=glycated haemoglobin A_{1c}. mITT=modified intention-to-treat. *p values versus placebo. †p values versus dulaglutide 1·5 mg.

Ex. 2014-007

	Placebo (n=51)		1 mg LY3298176 (n=52)		5 mg LY3298176 (n=55)		10 mg LY3298176 (n=51)		15 mg LY3298176 (n=53)		1·5 mg dulaglutide (n=54)	
	Baseline	CFB	Baseline	CFB	Baseline	CFB	Baseline	CFB	Baseline	CFB	Baseline	CFB
Glycaemic variables												
Mean fasting plasma glucose												
Values in mmol/L	9·1 (0·38)	0·9 (0·37)	8·9 (0·38)	–0·4 (0·36)*	9·4 (0·37)	–2·3 (0·35)†‡	9·5 (0·39)	–3·4 (0·35)†§	9·2 (0·38)	–3·2 (0·39)†§	9·9 (0·37)	–1·2 (0·36)†
Values in mg/dL	163·1 (6·87)	15·5 (6·66)	161·1 (6·80)	–6·8 (6·43)*	170·0 (6·67)	–40·7 (6·23)†‡	170·6 (6·94)	–60·7 (6·36)†§	165·2 (6·87)	–57·5 (7·10)†§	178·6 (6·74)	–21·2 (6·40)†
7-point self-measured plasma glucose (mg/dL)	178·5 (7·05)	–9·7 (5·33)	191·1 (7·05)	–38·7 (5·14)†	195·5 (6·70)	–57·5 (4·94)†	195·3 (7·05)	–63·3 (5·10)†‡	195·1 (7·21)	–72·3 (5·76)†§	187·8 (6·83)	–46·7 (5·07)†
Mean pre-meal	166·8 (6·77)	–8·7 (4·68)	178·4 (6·92)	–34·6 (4·60)†	178·7 (6·44)	–51·3 (4·38)†	180·4 (6·70)	–56·0 (4·50)†‡	181·1 (7·07)	–60·8 (5·19)†‡	171·8 (6·51)	–42·5 (4·54)†
Mean 2-h postprandial	190·4 (7·61)	–9·8 (6·12)	202·5 (7·69)	–40·1 (5·92)†	209·3 (7·16)	–60·3 (5·67)†	208·7 (7·53)	–70·3 (5·82)†‡	208·2 (7·86)	–79·5 (6·67)†§	205·2 (7·37)	–51·2 (5·97)†
Fasting serum insulin (pmol/L)	75·1 (11·45)	13·0 (11·32)	81·5 (11·33)	10·3 (10·93)	80·9 (11·00)	–7·4 (10·36)	93·7 (11·33)	–27·9 (10·53)*‡‖	96·3 (12·26)	–28·0 (12·79)*‡¶	79·0 (11·00)	5·7 (10·38)
Fasting plasma glucagon (pmol/L) <on treatment>	13·7 (0·98)	1·4 (0·96)	12·5 (0·99)	–0·4 (0·94)	11·9 (0·97)	–1·7 (0·91)*¶	12·7 (1·00)	–1·8 (0·93)*‖	12·1 (1·06)	–3·4 (1·11)†‡‖	13·2 (0·97)	–0·2 (0·91)
C-peptide (pmol/L)	884·9 (58·19)	33·2 (63·60)	913·2 (58·78)	69·1 (60·59)	971·6 (57·62)	–4·1 (59·33)	1030·5 (59·39)	–172·3 (59·88)*§	882·9 (62·03)	26·3 (71·38)	957·5 (57·62)	118·7 (59·49)
HOMA2-B	45·6 (4·44)	–4·9 (6·08)	49·1 (4·64)	9·0 (5·95)‡¶	45·6 (4·59)	25·9 (5·82)†	46·6 (4·69)	36·2 (5·82)†¶	42·5 (5·14)	33·4 (6·88)†¶	41·4 (4·30)	23·8 (5·63)†
HOMA2-IR	1·6 (0·16)	0·2 (0·18)	1·7 (0·16)	0·3 (0·18)	1·8 (0·16)	–0·1 (0·17)	1·8 (0·17)	–0·5 (0·18)*‡‖	1·7 (0·18)	–0·3 (0·21)¶	1·7 (0·15)	0·1 (0·17)
Other weight outcomes												
Mean BMI (kg/m²)	32·4 (0·82)	–0·1 (0·28)	32·9 (0·81)	–0·3 (0·28)	32·9 (0·79)	–1·7 (0·27)†‡	32·6 (0·82)	–3·1 (0·28)†§	32·2 (0·81)	–4·1 (0·31)†§	32·4 (0·80)	–1·0 (0·27)*
Mean waist circumference (cm)	107·7 (2·06)	–1·3 (0·91)	109·9 (2·04)	–2·1 (0·89)	110·1 (2·00)	–5·1 (0·86)*‡	109·6 (2·04)	–7·4 (0·88)†§	107·6 (2·17)	–10·2 (1·00)†§	108·5 (2·02)	–2·5 (0·87)

Data are LS mean (SE) from MMRM on treatment data analyses. Exact p values are given in the appendix. BMI=body-mass index. CFB=change from baseline at 26 weeks. HOMA2-B=homeostatic model assessment of β-cell function. HOMA2-IR=homeostatic model assessment of insulin resistance. *p<0·05 versus placebo. †p<0·001 versus placebo. ‡p<0·05 versus 1·5 mg dulaglutide. §p<0·001 versus 1·5 mg dulaglutide. ¶p<0·05 estimated treatment ratio LY3298176 versus dulaglutide. ‖p<0·001 estimated treatment ratio LY3298176 versus dulaglutide.

Table 2: **CFB for other glycaemic and bodyweight outcomes**

10 mg, p=0·0061 for 15 mg; table 2, appendix). Glucagon concentrations adjusted by fasting glucose decreased at 5 mg (p=0·0385), 10 mg (p=0·0001), and 15 mg (p=0·0003) LY3298176 compared with dulaglutide at week 26 (appendix).

Changes in mean bodyweight from baseline to week 26 ranged from –0·9 kg to –11·3 kg for the LY3298176 groups (*vs* –0·4 kg for placebo, –2·7 kg for dulaglutide; appendix). All doses of LY3298176 reduced bodyweight relative to placebo in a dose-dependent manner (figure 3A, appendix). The reduction in bodyweight was greater for 5 mg, 10 mg, and 15 mg LY3298176 than for dulaglutide (posterior mean differences in the mITT without postrescue dataset: –2·1 for 5 mg, –4·4 for 10 mg, and –6·2 kg for 15 mg). The bodyweight results for LY3298176 versus placebo and dulaglutide were consistent in all supportive analyses (appendix). Consistent with the observed HbA_{1c} reductions, patients who received 10 mg or 15 mg LY3298176 lost the most weight.

More patients treated with 5 mg, 10 mg, and 15 mg LY3298176 reached bodyweight targets (≥5%, ≥10%, and ≥15% weight loss from baseline) than did those treated with placebo and dulaglutide (figure 3B, appendix). At 26 weeks, 14–71% of those treated with LY3298176 achieved the weight loss target of at least 5% (*vs* 22% with dulaglutide, 0% with placebo) and 6–39% achieved the weight loss target of at least 10% (*vs* 9% with dulaglutide, 0% with placebo; figure 3B, appendix). Changes in mean waist circumference from baseline to week 26 ranged from –2·1 cm to –10·2 cm for the LY3298176 groups (*vs* –1·3 cm for placebo, –2·5 cm for dulaglutide; appendix). At week 26, mean waist circumference decreased with the 5 mg, 10 mg, and 15 mg doses of LY3298176 compared with placebo and dulaglutide (*vs* placebo: p=0·0013 for 5 mg, p<0·0001 for 10 mg and 15 mg; *vs* dulaglutide: p=0·0245 for 5 mg, p<0·0001 for 10 mg and 15 mg; table 2, appendix).

Changes in mean total cholesterol from baseline to week 26 ranged from 0·2 mmol/L to –0·3 mmol/L for LY3298176 (vs 0·3 mmol/L for placebo, –0·2 mmol/L for dulaglutide; appendix). At week 26, mean total cholesterol was reduced for 5 mg, 10 mg, and 15 mg LY3298176

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compared with placebo (p=0·0099 for 5 mg, p=0·0012 for 10 mg, and p=0·0006 for 15 mg LY3298176). No significant changes were observed versus dulaglutide. At week 26, the LY3298176 groups and placebo did not differ in terms of changes in the concentrations of HDL or LDL cholesterol (appendix).

Changes in mean triglyceride concentrations from baseline to week 26 ranged from 0 mmol/L to –0·8 mmol/L for LY3298176 (*vs* 0·3 mmol/L for placebo, –0·3 mmol/L for dulaglutide; appendix). At week 26, triglyceride concentrations decreased from baseline for the 5 mg, 10 mg, and 15 mg doses of LY3298176 and for dulaglutide, compared with placebo (p=0·0002 for 5 mg, p<0·0001 for 10 mg and 15 mg, p=0·0074 for dulaglutide; appendix). Reductions were greater for the 10 mg and 15 mg LY3298176 groups compared with dulaglutide (p=0·0325 for 10 mg, p=0·0097 for 15 mg; appendix).

The number of adverse events in the LY3298176 groups increased in a dose-dependent manner, which was largely driven by the increasing incidence of gastrointestinal adverse events. The incidence of treatment-emergent adverse events with 5 mg and 10 mg LY3298176 was similar to that of dulaglutide and lower than that of the 15 mg LY3298176 dose (table 3). 13 (4%) of 316 participants across the six treatment groups had 23 serious adverse events in total. Discontinuation of study treatment because of an adverse event was more common in the 5 mg, 10 mg, and 15 mg LY3298176 groups and dulaglutide group than it was in the 1 mg LY3298176 dose and placebo, with the highest rate in the 15 mg LY3298176 group. Most discontinuations in the 15 mg LY3298176 group were during the 6-week titration phase. One participant in the placebo group died from stage IV lung adenocarcinoma, which was unrelated to study treatment.

Gastrointestinal events (nausea, diarrhoea, and vomiting) and decreased appetite were the most common treatment-emergent adverse events (table 3); the incidence of these events was higher for the LY3298176 and dulaglutide groups than for the placebo group. The incidence of nausea, diarrhoea and vomiting were 15·4% for 1 mg LY3298176, 25·5% for 5 mg LY3298176, 39·2% for 10 mg LY3298176, 60·4% for 15 mg LY3298176, 35·2% for dulaglutide, and 5·9% for placebo. The gastrointestinal events generally occurred early in the course of therapy, were transient, and most were mild to moderate in intensity (appendix). When compared with dulaglutide, the frequency of nausea and vomiting in the 5 mg and 10 mg LY3298176 groups was similar, but these adverse events were most common in the 15 mg LY3298176 group (table 3). Diarrhoea was more common in the 5 mg, 10 mg, and 15 mg LY3298176 groups than in the other three groups. The proportion of patients discontinuing study treatment prematurely because of adverse events was higher with 15 mg LY3298176 than with dulaglutide, with variability observed in the lower dose range that precludes definitive conclusion on treatment comparisons with the 5 mg and 10 mg LY3298176 doses.

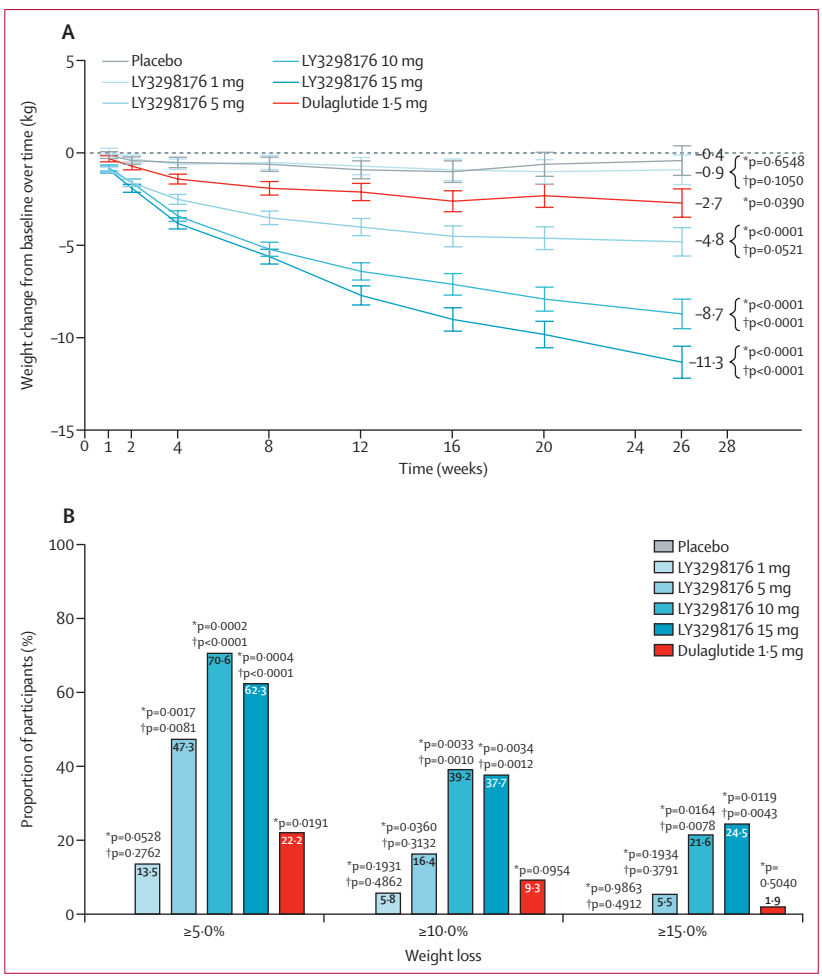

Figure 3: **Bodyweight outcomes of treatment with LY3298176 at week 26**
(A) Mixed-effect model for repeated measures analysis of the mITT on treatment dataset. Data are least squares mean, with SE error bars.B) Last observation carried forward endpoint data of the mITT on treatment dataset. mITT=modified intention-to-treat. *p values versus placebo. †p values versus dulaglutide 1·5 mg. HbA_{1c}=glycated haemoglobin A_{1c}.

Overall, the incidence of hypoglycaemic episodes (ie, documented symptomatic, probable, and asymptomatic events) was similar across all treatment groups (table 3). There were no reports of severe hypoglycaemia.

At week 26, changes from baseline in mean systolic blood pressure, diastolic blood pressure, and pulse rate did not differ between any of the groups (appendix). The incidence of cardiovascular adverse events did not differ among the groups. The incidence of cardiac events did not differ among the groups (placebo [two patients], 1 mg LY3298176 [two patients], 5 mg LY3298176 [one patient], 10 mg LY3298176 [no patients], 15 mg LY3298176 [two patients], and dulaglutide [three patients].

Two participants treated with 5 mg LY3298176 (table 3) had pancreatitis. Two other participants (one each in the 10 mg LY3298176 and dulaglutide groups) had elevated

Ex. 2014-009

	Placebo (n=51)	1 mg LY3298176 (n=52)	5 mg LY3298176 (n=55)	10 mg LY3298176 (n=51)	15 mg LY3298176 (n=53)	1·5 mg dulaglutide (n=54)
Any treatment-emergent adverse events	27 (52·9%)	26 (50·0%)	40 (72·7%)	40 (78·4%)	45 (84·9%)	40 (74·1%)
Participants with at least one treatment-emergent adverse event						
Mild	15 (29·4%)	15 (28·8%)	18 (32·7%)	15 (29·4%)	20 (37·7%)	23 (42·6%)
Moderate	11 (21·6%)	7 (13·5%)	18 (32·7%)	22 (43·1%)	17 (32·1%)	11 (20·4%)
Severe	1 (2·0%)	4 (7·7%)	4 (7·3%)	3 (5·9%)	8 (15·1%)	6 (11·1%)
Serious adverse events	2 (3·9%)	2 (3·8%)	1 (1·8%)	3 (5·9%)	2 (3·8%)	3 (5·6%)
Fatal adverse events	1 (2·0%)	0	0	0	0	0
Adverse events leading to treatment discontinuation	2 (3·9%)	2 (3·8%)	5 (9·1%)	3 (5·9%)	13 (24·5%)	6 (11·1%)
Adverse events leading to study discontinuation	1 (2·0%)	1 (1·9%)	0	1 (2·0%)	2 (3·8%)	2 (3·7%)
Adverse events occurring in at least 5% of participants in one or more treatment groups, by MedDRA (version 21.0) preferred term						
All gastrointestinal adverse events	5 (9·8%)	12 (23·1%)	18 (32·7%)	26 (51·0%)	35 (66·0%)	23 (42·6%)
Nausea	3 (5·9%)	2 (3·8%)	11 (20·0%)	11 (21·6%)	21 (39·6%)	16 (29·6%)
Diarrhoea	2 (3·9%)	7 (13·5%)	13 (23·6%)	12 (23·5%)	17 (32·1%)	9 (16·7%)
Vomiting	1 (2·0%)	2 (3·8%)	4 (7·3%)	8 (15·7%)	14 (26·4%)	5 (9·3%)
Decreased appetite	1 (2·0%)	2 (3·8%)	11 (20·0%)	13 (25·5%)	10 (18·9%)	3 (5·6%)
Nasopharyngitis	2 (3·9%)	1 (1·9%)	3 (5·5%)	2 (3·9%)	3 (5·7%)	6 (11·1%)
Dizziness	2 (3·9%)	4 (7·7%)	2 (3·6%)	2 (3·9%)	5 (9·4%)	1 (1·9%)
Abdominal distension	1 (2·0%)	0	2 (3·6%)	5 (9·8%)	4 (7·5%)	3 (5·6%)
Constipation	0	1 (1·9%)	2 (3·6%)	6 (11·8%)	2 (3·8%)	3 (5·6%)
Upper respiratory tract infection	3 (5·9%)	1 (1·9%)	3 (5·5%)	2 (3·9%)	1 (1·9%)	4 (7·4%)
Headache	2 (3·9%)	2 (3·8%)	2 (3·6%)	1 (2·0%)	5 (9·4%)	1 (1·9%)
Influenza	1 (2·0%)	2 (3·8%)	2 (3·6%)	4 (7·8%)	1 (1·9%)	2 (3·7%)
Increased lipase	1 (2·0%)	1 (1·9%)	3 (5·5%)	4 (7·8%)	2 (3·8%)	1 (1·9%)
Dyspepsia	0	0	1 (1·8%)	6 (11·8%)	2 (3·8%)	2 (3·7%)
Decreased weight	0	2 (3·8%)	2 (3·6%)	5 (9·8%)	2 (3·8%)	0
Bronchitis	3 (5·9%)	1 (1·9%)	1 (1·8%)	3 (5·9%)	0	2 (3·7%)
Urinary tract infection	0	2 (3·8%)	2 (3·6%)	1 (2·0%)	4 (7·5%)	0
Abdominal discomfort	2 (3·9%)	0	1 (1·8%)	1 (2·0%)	4 (7·5%)	0
Amylase increased	1 (2·0%)	0	2 (3·6%)	4 (7·8%)	1 (1·9%)	0
Cough	1 (2·0%)	1 (1·9%)	1 (1·8%)	0	3 (5·7%)	1 (1·9%)
Abdominal pain upper	1 (2·0%)	0	1 (1·8%)	0	3 (5·7%)	1 (1·9%)
Contusion	2 (3·9%)	0	3 (5·5%)	0	0	1 (1·9%)
Hypertension	1 (2·0%)	0	0	0	1 (1·9%)	3 (5·6%)
Other adverse events						
Total hypoglycaemia (plasma glucose ≤70 mg/dL)	2 (3·9%)	1 (1·9%)	4 (7·3%)	5 (9·8%)	4 (7·5%)	2 (3·7%)
Severe hypoglycaemia	0	0	0	0	0	0
Cholecystitis	0	0	0	1 (2·0%)	0	1 (1·9%)
Acute pancreatitis (adjudicated)	0	0	2 (3·6%)	0	0	0
Injection site reaction	2 (3·9%)	1 (1·9%)	3 (5·5%)	4 (7·8%)	1 (1·9%)	6 (11·1%)
Hypersensitivity	5 (9·8%)	0	2 (3·6%)	2 (3·9%)	2 (3·8%)	0

Data are n (%). Safety population.

Table 3: **Adverse events**

concentrations of pancreatic enzymes without symptoms and without radiological signs of acute pancreatitis at a follow-up abdominal computed tomography scan. One participant had asymptomatic acalculous cholecystitis (dulaglutide group) and another had acute cholecystitis due to calculus (10 mg LY3298176 group). Similar

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increases from baseline in mean values of amylase and lipase were seen in the LY3298176 and dulaglutide groups (appendix). No cases of retinopathy were reported. There were no clinically significant changes in calcitonin concentrations across treatment groups and no thyroid-related adverse events.

The incidence of possible or probable hypersensitivity reactions did not differ between treatment groups, with dermatitis, hypersensitivity (unspecified), and rash as the most commonly reported. The number of patients with anti-drug antibodies ranged from 16 (31·4%) to 26 (49·1%) across the four LY3298176 groups (appendix). 74 (87%) of 85 treatment-emergent anti-drug antibody-positive participants had low titres of anti-drug antibodies (defined as 1:20 to 1:320). There was no evidence of diminished effect of LY3298176 in HbA_{1c} lowering, bodyweight reduction, or LY3298176 pharmacokinetics in patients with anti-drug antibodies (data not shown). There was no association between treatment-emergent hypersensitivity events and development of anti-drug antibodies (data not shown).

Discussion

This randomised, double-blind, controlled phase 2b study showed that use of the novel dual GIP and GLP-1 receptor agonist, LY3298176, caused dose-dependent reductions in HbA_{1c} and bodyweight at 26 weeks across the dose range studied (1 mg to 15 mg) compared with placebo. Compared with a selective GLP-1 receptor agonist, dulaglutide, which we used as an active comparator, reductions in HbA_{1c} and bodyweight with 5 mg, 10 mg, and 15 mg LY3298176 were of greater magnitude. We believe that the observed differences are clinically meaningful. Gastrointestinal adverse events with LY3298176 treatment versus dulaglutide were similar, except for an increased frequency with 15-mg LY3298176. The safety findings of LY3298176 were consistent with the safety profile of GLP-1 receptor agonists.[23]

We tested various doses of LY3298176 with a relatively long 26-week treatment period, compared with a typical phase 2 study in type 2 diabetes, to assess the effects on glycaemic control and bodyweight more accurately. Once-weekly LY3298176 led to clinically meaningful and dose-dependent improvements in HbA_{1c}. The differences in glycaemic efficacy versus dulaglutide were statistically significant and clinically meaningful across a broad dose range (5 mg to 15 mg), with the largest difference versus dulaglutide observed in the 15 mg LY3298176 group. In addition to a greater proportion of patients in the LY3298176 groups being able to reach the standard near-normoglycaemic target of less than 7% than in the placebo and dulaglutide groups, about one-fifth of patients in the 10 mg LY3298176 group, and one-third of patients in the 15 mg LY3298176 group, achieved normoglycaemia (indicated by a HbA_{1c} value of <5·7%). Near-normalisation or complete normalisation of glucose concentrations without increasing hypoglycaemia risk has been shown to further reduce the risk of microvascular complications.[24]

Use of LY3298176 also caused a dose-dependent reduction in bodyweight across the dose range included in this study, with clinically meaningful differences versus dulaglutide, and decreases in waist circumference—indicating a potential reduction in visceral adipose tissue. Notably, many patients in the LY3298176 groups lost more than 5% of their bodyweight; and 21·6% and 24·5% in the 10 mg and 15 mg dose group, respectively, lost >15%. Weight loss of 5–10% is clinically meaningful and influences cardiovascular risk factors, such as hypertension and dyslipidemia.[25,26] More pronounced weight loss (>15%) is associated with decreased mortality and other clinical benefits (eg, improvements in sleep apnea and non-alcoholic steatohepatitis).[27] In this study, LY3298176 treatment resulted in a small decrease in diastolic and systolic blood pressure despite baseline values in the normotensive range. The reductions in triglyceride concentrations were greater in the LY3298176 groups than in the dulaglutide group. This finding is consistent with preclinical evidence showing a substantial reduction in concentrations of triglycerides with a dual agonist, but not with a selective GLP-1 receptor agonist, liraglutide.[21] The GIP receptor is highly expressed in human adipose tissue, suggesting that GIP receptor signalling might have a role in the regulation of lipolysis and lipogenesis.[11,13] Further studies are needed to characterise the effect of LY3298176 on bodyweight, cardiovascular risk factors, and relevant cardiovascular outcomes in patients with type 2 diabetes and individuals who are obese but not diabetic.[27,28]

Our study included an assessment of various biomarkers to develop a better understanding of the potential differences versus selective GLP-1 receptor stimulation with dulaglutide. The dual agonist improved HOMA2-IR and reduced insulin concentrations, whereas dulaglutide did not have significant effects on these measures, suggesting a possible insulin-sensitising effect of LY3298176. This effect could be secondary to visceral fat reduction, since visceral fat mass correlates strongly with the magnitude of insulin resistance in patients with type 2 diabetes.[29] Direct actions of GIP on adipose tissue, such as increased insulin-dependent glucose uptake into adipose tissue, might also play a role.

LY3298176 also increased HOMA2-B more than did dulaglutide. Although the observed results should be interpreted with caution because the measurements were obtained on treatment, they suggest that LY3298176 improved β-cell function. These observations are consistent with our preclinical data[22] for LY3298176 and preclinical data on co-agonism reported by Finan and colleagues,[20] which showed the additive actions of GIP and GLP-1 on insulin secretion. What effect the co-agonist had on the responsiveness of β-cells to GIP remains an important question, and is one that we did

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not study here. It has been hypothesised that β-cells can regain their sensitivity to GIP under near-normoglycaemia attained with GLP-1-related actions, thus allowing GIP to further improve β-cell function and provide additional glucose-lowering efficacy beyond the GLP-1 component.[11,13] This hypothesis could explain the high proportion of patients with normoglycaemia in the LY3298176 groups.

Treatment with GLP-1 receptor agonists decreases glucagon concentrations despite decreases in glucose concentrations.[30] LY3298176 had a similar effect, but the magnitude was greater than it was with dulaglutide. This finding was surprising, given that acute infusion of GIP raises glucagon concentrations;[31] however, the effects of chronic GIP activation in the context of GLP-1 co-agonism are yet to be determined. An important question is whether the glucagonostatic effect of the dual agonist affects the response to hypoglycaemia. We did not see any clinically relevant differences in the incidence of hypoglycaemia between the treatment groups, suggesting that the counter-regulatory response was preserved in patients treated with the dual agonist.

We did not assess the effect of LY3298176 and dulaglutide on appetite and food intake. Decreased appetite was more common in the LY3298176 groups than in the dulaglutide group. This finding suggests that decreased food intake contributes to the reduction in weight seen in patients treated with LY3298176 and is consistent with our preclinical findings,[19] indicating a more profound effect on food intake compared with a selective GLP-1 receptor agonist.[20] LY3298176 might engage GIP-responsive appetite-regulatory neurons and GLP-1 pathways, or might preferentially access and activate neurons that are not activated by single GLP-1 receptor agonists, or both.[32] Our preclinical studies[19,20] also showed a potential contributing effect of increased energy expenditure to the negative energy balance and increased weight loss with chronic GLP-1 and GIP receptor co-stimulation.

Our findings suggest that dual agonism might improve key abnormalities in patients with type 2 diabetes. An important question is whether the clinical profile of LY3298176 is due to the combined GIP and GLP-1 receptor co-signalling or to other LY3298176-specific mechanisms. The observed qualitative effects of LY3298176 on the clinical outcomes and biomarkers of interest could be attributed exclusively to GLP-1 receptor signalling. However, given the magnitude of the effect, the observed differences are probably related to GIP-related actions via pathways shared by both incretin hormones. In the SUSTAIN-7 trial,[33] 1 mg semaglutide was superior to 1·5 mg dulaglutide at reducing HbA_{1c} and bodyweight, suggesting that the clinical potency that is achievable via the GLP-1 R pathway is not maximised with 1·5 mg dulaglutide. Therefore, semaglutide would have been a better comparator than dulaglutide in our study for the understanding of the contribution of the GIP component of the dual agonist; however, it was not marketed during the conduct of this study. A greater separation versus dulaglutide for the key clinical outcomes was seen in patients treated with more than 5 mg LY3298176 in our study, compared with the differences between semaglutide and dulaglutide in the SUSTAIN-7 trial.[33] This indirect comparison is not appropriate for making conclusions, and supports the need for a definitive head-to-head study of LY3298176 and semaglutide to provide data on their comparative efficacy and mechanisms of action. This research is even more important because substantial variability between these molecules, with regards to their in vivo binding properties, biodistribution in the body, and in vitro potency, might also contribute to their differences in efficacy.

Clinical experience with other dual GIP and GLP-1 receptor agonists is limited and does not provide substantial additional information on their mechanism of action. A pegylated dual agonist enhanced insulin secretion, improved glycaemic control, and induced weight loss without causing relevant gastrointestinal side-effects in people with type 2 diabetes.[21] The authors suggest that these results show the potential of GIP to enhance the pharmacology of selective GLP-1 receptor agonists by strengthening the inherent efficacy and broadening their therapeutic range. Another dual agonist, RG7697, investigated in a single ascending dose study[34] of healthy participants, and a 14-day multiple ascending dose study[35] of patients with type 2 diabetes, showed glycaemic improvement and weight loss. Finally, NNC0090-2746 had glucose-lowering and bodyweight-lowering effects that did not differentiate against liraglutide in a clinically meaningful way.[36] LY3298176 has greater potency at the GIP receptor relative to a GLP-1 receptor agonist than does NNC0090-2746, which is one possible explanation for the differences in their clinical efficacy.

The safety characteristics of LY3298176 were similar to that of dulaglutide. The most common adverse events were nausea, vomiting, and diarrhoea. In general, these events were mild or moderate, with few severe episodes, and transient. Differences between the 5 mg and 10 mg LY3298176 doses and dulaglutide were not clinically meaningful in terms of the frequency of gastrointestinal adverse events or treatment discontinuations, despite their superior glycaemic and bodyweight efficacy. 15 mg LY3298176 was associated with more gastrointestinal adverse events and an increased frequency of patients discontinuing study treatment early after a relatively short titration period. Slower up-titration and smaller dose increments might improve tolerability. This finding could be relevant to further clinical development of LY3298176, since the 15-mg dose might provide an additional therapeutic benefit versus the 10-mg dose in patients who adhere to treatment, as suggested by our sensitivity analyses. A separate titration study (NCT03311724) is underway to further address this hypothesis.

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Two patients treated with LY3298176 had acute pancreatitis, but our sample size was too small for any conclusions to be made; more data are needed in the phase 3 programme to assess the risk of this event. As is seen other incretin and non-incretin drugs for diabetes, we observed increases in mean concentrations of lipase and amylase with the dual agonist and with dulaglutide, but the clinical relevance remains unclear.[37] Treatment-emergent anti-drug antibodies were frequently seen in patients treated with LY3298176, but titres were mostly low and non-progressive, without clinical consequences.

The limitations of this study are its small size and homogenous patient population, such that our results might not be generalisable to other populations with more advanced type 2 diabetes. Exposure was restricted to 26 weeks, which does not allow for full evaluation of the glycaemic and weight loss potential of LY3298176. Data on gastrointestinal side-effects was only collected via spontaneous reporting and more information could have been gathered with a validated triggered data collection.[38] Furthermore, titration steps were not optimised and titration time was short, which probably led to increased study discontinuation in the 15 mg LY3298176 group during the titration period. The trial design did not enable a broad understanding of mechanistic differences between dual agonism and selective GLP-1 agonism and, as such, is only hypothesis generating.

In summary, this phase 2b study established a wide dose range of a dual GIP and GLP-1 receptor agonist, LY3298176, which showed clinically meaningful and superior HbA_{1c} control with greater weight loss and an acceptable tolerability profile compared with dulaglutide. LY3298176 has the potential to become a treatment option for patients with type 2 diabetes. The results of this study warrant a thorough evaluation of efficacy and safety in a phase 3 programme with an optimised administration regimen.

Contributors

JPF, JV, and MEK collected and interpreted the data. MAN and REG interpreted the data. As the study statistician, XC analysed and interpreted the data. CB, SU, ZM, AH, and DR designed the study and analysed and interpreted the data. DR was also responsible for patient enrolment and helped to collect data. All authors prepared this manuscript and approved the final version. All authors take responsibility for the accuracy and completeness of data and data analyses.

Declaration of interests

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Data sharing

Eli Lilly provides access to all individual participant data collected during this trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request in a timely fashion after the indication studied has been approved in the USA and EU and after primary publication acceptance. No expiration date of data requests is currently set once they 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 up to 2 years per proposal. Details on submitting a request can be found online.

To **submit a request** see https://www.clinicalstudydatarequest.com

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