Efficacy and safety of mazdutide in adults with obesity or overweight: a US-based, multicentre, phase 2, randomised, placebo-controlled clinical trial

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Summary

Background Therapies targeting GLP-1 or glucose-dependent insulinotropic polypeptide (GIP) receptors have provided efficacious weight reduction in adults with obesity. Mazdutide, a glucagon and GLP-1 receptor dual agonist, presents a novel opportunity for differentiated weight reduction. We aimed to evaluate the efficacy, safety, and tolerability of once-weekly mazdutide across a dose range up to 16 mg in adults with obesity or overweight without type 2 diabetes in the USA.

Methods In this randomised, double-blind, placebo-controlled phase 2 trial at 24 centres in the USA, adults aged 18–75 years without type 2 diabetes and with a BMI of 30 kg/m² and higher—or of 27 kg/m² to less than 30 kg/m² with at least one weight-related comorbidity—were randomly allocated (3:2:3:3) to receive once-weekly subcutaneous injections of placebo or mazdutide (3–6 mg, 10 mg, or 16 mg) for 48 weeks. Participants assigned to 3–6 mg mazdutide maintained 3 mg from week 4 to week 32 before escalating to 6 mg at 32 weeks to assess 3 mg and 6 mg as potential maintenance doses. The primary endpoint was percentage change in bodyweight from baseline to 32 weeks, evaluated using the efficacy (hypothetical) estimand. Efficacy analyses included all randomly allocated participants, and safety analyses included all randomly allocated participants who received at least one treatment dose. This study is registered at ClinicalTrials.gov, NCT06124807, and is completed.

Findings Between Nov 17, 2023, and July 9, 2025, 179 participants were randomly allocated to receive mazdutide (32 participants to 3–6 mg, 48 to 10 mg, and 51 to 16 mg) or placebo (48 participants). The mean age was 47·7 years (SD 12·3), and 118 (66%) participants were female and 61 (34%) were male. At 32 weeks, the least-squares mean percentage change from baseline in bodyweight was –7·3% (SE 0·9) with mazdutide 3–6 mg, –15·6% (0·7) with 10 mg, and –18·1% (1·0) with 16 mg, versus –0·9% (0·8) with placebo. Estimated treatment differences versus placebo ranged from –6·5% to –17·2% (p<0·0001, all comparisons). Additional bodyweight reductions were observed at 48 weeks. The most common adverse events with mazdutide were gastrointestinal-related and mostly mild to moderate in severity; discontinuation of study treatment due to adverse events occurred most frequently with 16 mg (20%), associated primarily with gastrointestinal disorders.

Interpretation Once-weekly, subcutaneous mazdutide showed clinically meaningful bodyweight reduction in adults with obesity or overweight across all studied doses, with higher doses (10 mg and 16 mg) showing additional weight reduction.

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Introduction

Glucagon receptor agonism has been previously highlighted as a potential therapeutic option for the treatment of type 2 diabetes and obesity, most often in combination with a GLP-1 receptor agonist in the form of a multihormone receptor modulator.[1–4] Activation of the glucagon receptor modulates carbohydrate, lipid, and protein metabolism to regulate fuel storage and use.[5] Acute exogenous glucagon administration suppresses food intake and enhances energy expenditure; chronic coadministration with GLP-1 synergistically improves glucose clearance and bodyweight reduction while potentially maintaining the energy expenditure effects of glucagon receptor agonism, thus augmenting its therapeutic benefit.[6,7] Several GLP-1 and glucagon multihormone receptor modulators are being developed to treat obesity, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease.[8–10]

Mazdutide (LY3305677) is a long-acting synthetic peptide containing a fatty acyl side chain to extend its time of action to bind to and activate both glucagon and GLP-1 receptors, thus allowing for once-weekly dosing by subcutaneous injection. Mazdutide has potent binding

Research in context

Evidence before this study

We searched MELINE and Embase via Ovid on Jan 23, 2026, for all available research articles to identify references to mazdutide (or other dual or triple GLP-1–glucagon receptor agonists) or tirzepatide (or other dual glucose-dependent insulinotropic polypeptide [GIP]–GLP-1 receptor agonists) in obesity. A complete listing of search terms can be found in the appendix (p 5). Phase 2 trials involving participants with obesity have reported meaningful weight reductions with dual or triple agonists that include action at glucagon receptors. Using on-treatment data, treatment with the GLP-1–glucagon receptor dual agonist survodutide resulted in up to 16·4% placebo-adjusted bodyweight reduction after 46 weeks of treatment, whereas treatment with retatrutide 12 mg, a GIP–GLP-1–glucagon receptor triple agonist, resulted in a placebo-adjusted change in bodyweight of –22·1% after 48 weeks. Survodutide and retatrutide have ongoing phase 3 programmes in weight management. Clinical investigations with other unimolecular GLP-1–glucagon receptor dual agonists—such as cotadutide, efinopegdutide, and pemvidutide—have also shown improvements in glycaemic control and bodyweight reduction. UBT251, a GIP–GLP-1–glucagon receptor triple agonist, has also shown improvements in bodyweight. Previous phase 1–2 trials in Chinese individuals with overweight or obesity showed placebo-adjusted bodyweight changes of up to –12·6% with mazdutide 6 mg weekly after 24 weeks using all available data in exposed participants (regardless of treatment status), and phase 3 results showed bodyweight changes of up to –14·8% after 48 weeks using on-treatment data.

Added value of this study

Mazdutide (2 mg, 4 mg, and 6 mg doses) received approval in China for use, in combination with lifestyle interventions, in long-term weight management in adults with a BMI of 28 kg/m² or more—or with a BMI of 24 kg/m² or more together with one or more weight-related comorbidities—in June, 2025, and then for glycaemic control in adults with type 2 diabetes in September, 2025. In this phase 2 study in adults with obesity or overweight, dose-dependent reductions in bodyweight at 32 weeks were observed across the once-weekly mazdutide dose range studied compared with placebo. Changes in lipid and glycaemic parameters were also observed. Adverse events were predominantly gastrointestinal and mostly mild to moderate in severity, with treatment discontinuation due to adverse events more frequent at higher doses than with lower doses or placebo.

Implications of all the available evidence

Emerging data suggest that multihormone receptor modulators that include glucagon receptor agonism—such as mazdutide—could provide novel and effective alternatives for weight management, further expanding the options available for optimisation of treatment for individuals with obesity.

affinity to human and mouse GLP-1 and glucagon receptors.[11]

Mazdutide has been evaluated among Chinese participants with overweight or obesity. After encouraging results from phase 1 and 2 studies,[12–14] a phase 3 trial among people with obesity without type 2 diabetes showed that 6 mg mazdutide treatment versus placebo reduced bodyweight by 13·4% at 32 weeks and by 14·8% at 48 weeks (efficacy [hypothetical] estimand), and by 12·6% at 32 weeks and by 14·0% at 48 weeks (treatment-regimen estimand, consistent with intention to treat).[15] In June, 2025, mazdutide (2 mg, 4 mg, and 6 mg doses) was approved in China for the management of overweight and obesity.[16]

With the intent of further dose exploration, we previously did a phase 1, placebo-controlled dose escalation trial of mazdutide that explored the safety and efficacy of doses up to 16 mg.[17] After 20 weeks of treatment, participants with obesity or overweight had placebo-adjusted changes in bodyweight of up to –20·9%.[17] These findings suggest that mazdutide doses higher than those previously evaluated in phase 3 studies could provide weight reduction efficacy similar to that of other multihormone receptor modulators. In this phase 2 dose-finding trial, we aimed to investigate the efficacy, tolerability and safety of doses up to 16 mg of once-weekly mazdutide in people with obesity or overweight without type 2 diabetes in the USA.

See Online for appendix

Methods

Study design and participants

In this randomised, double-blind, placebo-controlled, parallel-group, phase 2 study at 24 centres in the USA, we recruited adults aged 18–75 years without type 2 diabetes and with either a BMI of 30 kg/m² and higher or a BMI between 27 and less than 30 kg/m² accompanied by at least one weight-related comorbidity. Participants were also required to have maintained a stable bodyweight (<5% gain or loss) for the 3 months before randomisation. Individuals were excluded if they had any previous diagnosis of diabetes (other than gestational diabetes), previous or planned surgical treatment for obesity, or treatment with any medication that promotes weight loss or gain within 3 months before screening. A full list of eligibility criteria is provided in the appendix (pp 88–90, 224–29).

The study protocol and informed consent forms were approved by a central ethics review board (appendix p 4). The study was done in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each participant at study entry before any study

procedures. This study is registered at ClinicalTrials.gov, NCT06124807.

Randomisation and masking

Participants were randomly allocated (3:2:3:3) to one of four treatment groups: placebo, mazdutide 3–6 mg, mazdutide 10 mg, or mazdutide 16 mg (appendix p 9). Treatment groups were assigned randomly using a centralised interactive web-response system; enrolled participants were stratified by baseline BMI (≤30 kg/m² or >30 kg/m²) and sex (male or female). Enrolment was actively monitored to ensure a sufficiently large sample of men in the study. In a double-blinded manner, participants randomly allocated to placebo followed the same injection dose schedule and with matching injection volume as those assigned to mazdutide treatment groups. Additional details on the database, data handling, and randomisation can be found in the appendix (p 8).

Procedures

The study had a 6-week screening and lead-in period, a 48-week treatment period, and a post-treatment follow-up period of approximately 8 weeks after the last treatment period visit (appendix p 9). During the treatment period, participants subcutaneously self-administered either mazdutide or matching placebo once weekly using a syringe. Participants were trained to use the syringe and injected the study treatments on site at randomisation. Study treatment compliance was assessed at each visit via study visit adherence, diary recording of study intervention administration, and the return of used and unused study drug at study visits. There were four maintenance doses of mazdutide: 3 mg, 6 mg, 10 mg, and 16 mg (appendix p 9). With the exception of the mazdutide 3–6 mg group, mazdutide dose was increased every 4 weeks starting from 1·5 mg until the maintenance dose was reached. For the 3–6 mg group, the dose was increased from 1·5 to 3 mg after 4 weeks, kept at 3 mg until the primary endpoint at 32 weeks, and then escalated to a maintenance dose of 6 mg for the remaining 16 weeks. This schedule was designed to assess both 3 mg and 6 mg as potential maintenance doses within a single group; accordingly, the 32-week primary endpoint for this group reflects exposure to 3 mg, with the subsequent 16 weeks allowing assessment of effects at the higher 6 mg maintenance dose. All participants received individualised dietary and physical activity counselling from site personnel, including nutrition and hydration recommendations, with intake and activity reviewed as per protocol. Participants who discontinued treatment early were encouraged to remain in the study throughout the follow-up period.

The MRI acquisition protocol included sequences for measurements of liver fat content, as well as muscle and fat volumes. Scans were done on 1·5 T and 3 T MRI scanners at each site across three manufacturers (GE HealthCare [Chicago, IL, USA], Siemens Healthineers [Erlangen, Germany], and Philips Healthcare [Amsterdam, Netherlands]). The same scanner and imaging acquisition parameters were used for baseline and post-baseline measurements for each participant. Imaging centres participating in this study were provided with a standardised imaging acquisition protocol; scans were reviewed centrally by a contract research organisation (ICON, Dublin, Ireland). Abdominal visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (SAT), and muscle volume analyses were done using AMRA Researcher (AMRA Medical, Linköping, Sweden).[18] VAT analysis consisted of the measurement of the adipose tissue within the abdominal cavity, excluding adipose tissue outside the abdominal skeletal muscles and posterior to the spine and back muscles. SAT analysis consisted of the measurement of the subcutaneous adipose tissue in the abdomen from the top of the femoral head to the top of the thoracic vertebra T9.

Outcomes

The primary efficacy outcome was the percentage change in bodyweight from baseline to 32 weeks. Secondary efficacy outcomes were the percentage change in bodyweight from baseline to 48 weeks, the absolute change from baseline in bodyweight and BMI, and the percentage of participants with weight reductions of 5% and greater and of 10% and greater at 32 weeks and 48 weeks. Additional secondary outcomes were the assessment of treatment-emergent antidrug antibodies and pharmacokinetic parameters. Safety assessments included adverse events, treatment-emergent adverse events, serious adverse events, and laboratory assessments. Prespecified exploratory outcomes were assessed at 32 weeks and 48 weeks and included the proportion of participants reaching additional weight reduction targets of 15% and greater, 20% and greater, 25% and greater, and 30% and greater; the changes from baseline in waist circumference, systolic blood pressure, and diastolic blood pressure; subgroup analyses based on baseline BMI and sex; and the percentage change from baseline in lipid parameters. Additional prespecified exploratory outcomes were the change from baseline in glucose regulation, longitudinal and endpoint biomarkers, body composition measures, and health-related quality of life (assessed using the Short Form 36 version 2 acute form).

Statistical analysis

We estimated that a sample size of 165 participants would provide at least 91% power to show the superiority of each of the three mazdutide groups to placebo at a two-sided significance level of 0·05. Sample size was estimated with a two-sample t-test by assuming a 20% dropout rate, an 8 percentage-point difference in mean percentage weight change from baseline to 32 weeks between mazdutide groups and placebo, and a common SD of 10 percentage points in percentage

weight change. An 8 percentage-point difference was chosen as the target effect, reflecting the anticipated placebo-adjusted response in the mazdutide 3–6 mg group at 32 weeks on the 3 mg dose.

Efficacy analyses included all randomly allocated participants (full analysis set), whereas safety analyses included all participants who received at least one dose of mazdutide or placebo (safety analysis set). Unless otherwise specified, results reflect the efficacy estimand, which uses a hypothetical strategy to account for the intercurrent event of treatment discontinuation, estimating the treatment effect if all participants had remained on their assigned regimen throughout the study. Data were analysed from randomisation throughout the treatment period up to the occurrence of permanent discontinuation of study drug. Dose modifications and temporary interruptions were not considered intercurrent events because they are part of the treatment condition. Results based on the treatment-regimen estimand, which evaluates outcomes regardless of treatment discontinuation and is consistent with the intention-to-treat principle, are also presented for primary and key secondary endpoints.

For continuous endpoints assessed over time, mixed models for repeated measures (MMRM) or constrained MMRM (cMMRM)[19] were used, with the latter allowing pooling of treatment groups during shared titration periods. For continuous endpoints with only one post-baseline assessment, ANCOVA was used. Binary efficacy outcomes were analysed using logistic regression. Missing data under the efficacy (hypothetical) estimand were handled using multiple imputation under the missing-at-random assumption for ANCOVA and logistic regression models, with final estimates combined using

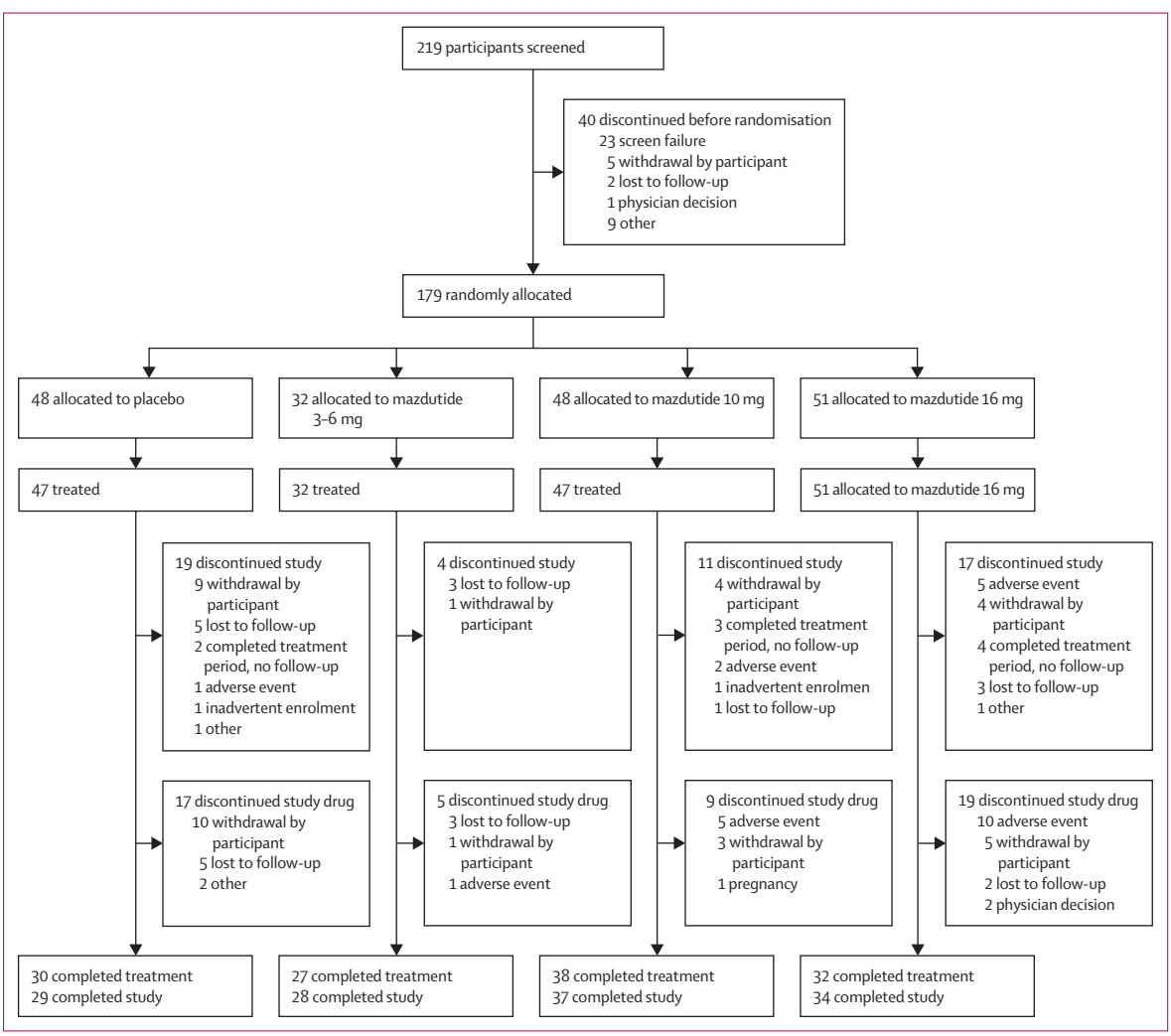

Figure 1: **Trial profile**
Abbreviated trial profile, 48 weeks. Participants who discontinued the study with the reason "completed treatment period, no follow-up" reached the end of the treatment period but did not return for the scheduled safety follow-up. No specific reason for the missed follow-up was documented, because the relevant case report form was not generated.

Rubin's rules.[20] MMRM and cMMRM addressed missingness implicitly via likelihood-based methods. Details on the missing data imputation strategy under the treatment-regimen estimand (consistent with intention to treat) are provided in the statistical analysis plan (appendix pp 173–74). Briefly, due to insufficient retrieved dropouts to support a reliable imputation model, the prespecified fallback of jump-to-reference imputation was applied, with missing values imputed using observed data from the placebo group across 100 imputed datasets.

Summary statistics for continuous measures were presented as means and SDs, and changes from baseline were presented as least-squares means with SEs, along with differences between treatment groups and corresponding 95% CIs and p values. Safety endpoints were analysed for all participants who received at least one dose of study intervention, and treatment comparisons of proportions in safety analyses were examined using Fisher's exact test, with 95% CIs estimated via the Newcombe score method. No adjustments for multiplicity were applied for sample size determination or analyses of results.

Covariates for all models are summarised in the statistical analysis plans (appendix pp 169–73, 326–29). One deviation from the planned analyses is noted: due to the low number of participants (seven) with a baseline BMI of less than 30 kg/m², only MMRM used a combined strata covariate of sex and baseline BMI category (≤30 kg/m² and >30 kg/m²). Logistic regression and ANCOVA models used a strata covariate of sex only.

Statistical analyses were done using R (version 4.4.2) and SAS (version 9.4).

Role of the funding source

The study funder was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Nov 17, 2023, and July 9, 2025, 179 participants were randomly allocated (32 to mazdutide 3–6 mg, 48 to 10 mg, 51 to 16 mg, and 48 to placebo; figure 1). Demographic and baseline clinical characteristics were generally balanced (table 1). 118 (66%) participants were female and 61 (34%) were male. The mean age was 47·7 years (SD 12·3) and bodyweight ranged from 103·1 kg (SD 21·2) to 109·8 kg (17·7) across the treatment groups. Median BMI ranged from 35·3 kg/m² (IQR 32·4–40·1) to 39·2 kg/m² (34·6–44·0) across the treatment groups, and 62 (35%) participants had a BMI of 40 kg/m² or higher.

Two participants (one in the placebo group and one in the 10 mg group) were randomly assigned but not dosed and were therefore excluded from safety analyses, resulting in 177 participants in safety analyses. Overall, 128 (72%) of the 179 randomly allocated participants completed the trial, and 127 (71%) completed treatment (mazdutide or placebo; figure 1). Missing outcome data arose primarily from treatment discontinuation, which differed in categorisation across groups. Discontinuations from study drug due to adverse events increased with mazdutide dose (one [3%] participant in the 3–6 mg group, five [11%] in the 10 mg group, and ten [20%] in the 16 mg group) and was absent in the placebo group, whereas placebo discontinuation was driven largely by participant withdrawal (ten [21%] participants) and loss to follow-up (five [10%] participants). Treatment was completed by 27 (84%) participants in the 3–6 mg group, 38 (79%) in the 10 mg group, 32 (63%) in the 16 mg group, and 30 (63%) in the placebo group.

	Placebo (n=48)	Mazdutide 3–6 mg (n=32)	Mazdutide 10 mg (n=48)	Mazdutide 16 mg (n=51)
Age, years	45·7 (12·5)	48·6 (13·8)	48·4 (10·1)	48·3 (13·3)
Sex				
Female	32 (67%)	21 (66%)	32 (67%)	33 (65%)
Male	16 (33%)	11 (34%)	16 (33%)	18 (35%)
Ethnicity*				
Hispanic or Latino	14 (29%)	9 (28%)	7 (15%)	11 (22%)
Not Hispanic or Latino	34 (71%)	23 (72%)	40 (85%)	38 (78%)
Race†				
American Indian or Alaska Native	0	0	1 (2%)	0
Asian	2 (4%)	3 (10%)	2 (4%)	2 (4%)
Black or African American	9 (19%)	7 (23%)	11 (23%)	7 (14%)
White	34 (71%)	20 (67%)	33 (69%)	38 (78%)
Multiple	3 (6%)	0	1 (2%)	2 (4%)
Bodyweight, kg	103·1 (21·2)	109·8 (17·7)	108·5 (21·7)	109·7 (20·7)
Waist circumference, cm	112·7 (15·4)	119·4 (14·4)	117·0 (12·2)	115·8 (12·2)
Ratio of waist to height	0·68 (0·09)	0·72 (0·09)	0·70 (0·07)	0·69 (0·07)
BMI, kg/m²	35·3 (32·4, 40·1)	39·2 (34·6, 44·0)	35·9 (34·2, 41·4)	37·5 (33·9, 42·3)
<30 kg/m²	3 (6%)	0	2 (4%)	2 (4%)
30 to <35 kg/m²	18 (38%)	8 (25%)	18 (38%)	13 (25%)
35 to <40 kg/m²	14 (29%)	9 (28%)	12 (25%)	18 (35%)
≥40 kg/m²	13 (27%)	15 (47%)	16 (33%)	18 (35%)
Glycaemic status‡				
Normoglycaemia	28 (61%)	18 (56%)	32 (68%)	32 (63%)
Prediabetes	18 (39%)	12 (38%)	15 (32%)	19 (37%)
Diabetes	0	2 (6%)	0	0
Hypertension	10 (21%)	8 (25%)	20 (42%)	20 (39%)
Dyslipidaemia	10 (21%)	10 (31%)	15 (31%)	20 (39%)
Estimated glomerular filtration rate, mL/min per 1·73 m²§	90·4 (18·9)	90·4 (17·9)	91·7 (18·3)	90·0 (18·3)
Urine albumin to creatinine ratio, g/kg	8·3 (100·0)	7·8 (97·7)	8·2 (71·7)	9·9 (178·8)

Data are mean (SD), n (%), median (IQR), or geometric mean (coefficient of variation %). The full analysis set and safety analysis set differ by only two participants (1% of the 179-participant full analysis set); baseline characteristics are therefore reported for the full analysis set only, as a separate table for the safety population is not expected to yield meaningful differences. *Missing responses for one participant in the 10 mg group and two participants in the 16 mg group. †Missing responses for two participants in the 3–6 mg group and two participants in the 16 mg group. ‡Normoglycaemia (HbA_{1c} <5·7% [<39 mmol/mol]), prediabetes (HbA_{1c} 5·7% to <6·5% [39 to <48 mmol/mol]), and diabetes (HbA_{1c} ≥6·5% [≥48 mmol/mol]); missing responses for two participants in the placebo group and one participant in the mazdutide 10 mg group. §Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation based on cystatin C and normalised to body surface area.[21]

Table 1: **Demographic and clinical characteristics of participants at baseline (full analysis set)**

For the primary endpoint assessed at 32 weeks under the efficacy (hypothetical) estimand, the estimated mean percentage change in bodyweight from baseline was –7·3% in the 3–6 mg treatment group (reflecting the effect of 3 mg mazdutide), –15·6% in the 10 mg group, and –18·1% in the 16 mg group, compared with –0·9% in the placebo group; placebo-adjusted differences were –6·5% (95% CI –8·9 to –4·1) in the 3–6 mg group, –14·7% (–16·9 to –12·6) in the 10 mg group, and –17·2% (–19·8 to –14·7) in the 16 mg group (table 2, figure 2). At 48 weeks, the estimated mean percentage change from baseline was –10·5% in the 3–6 mg group (participants had been on 6 mg for 16 weeks at this timepoint), –19·2% in the 10 mg group, and –22·3% in the 16 mg group, compared with –0·05% in the placebo group; placebo-adjusted differences were –10·5% (95% CI –14·1 to –6·9) in the 3–6 mg group, –19·2% (–22·2 to –16·2) in the 10 mg group, and –22·3% (–25·9 to –18·7) in the 16 mg group. Results for mean absolute change in bodyweight from baseline are provided in table 2.

	Placebo (n=48)	Mazdutide 3–6 mg (n=32)	Mazdutide 10 mg (n=48)	Mazdutide 16 mg (n=51)
Percentage change in bodyweight, % (baseline to 32 weeks)*	n=31	n=28	n=39	n=37
Percentage change	–0·9% (0·8)	–7·3% (0·9)	–15·6% (0·7)	–18·1% (1·0)
Versus placebo	..	–6·5% (–8·9 to –4·1; p<0·0001)	–14·7% (–16·9 to –12·6; p<0·0001)	–17·2% (–19·8 to –14·7; p<0·0001)
Percentage change in bodyweight, % (baseline to 48 weeks)*	n=29	n=27	n=38	n=32
Percentage change	–0·05% (1·1)	–10·5% (1·5)	–19·2% (1·1)	–22·3% (1·4)
Versus placebo	..	–10·5% (–14·1 to –6·9; p<0·0001)	–19·2% (–22·2 to –16·2; p<0·0001)	–22·3% (–25·9 to –18·7; p<0·0001)
Weight loss thresholds (32 weeks)†	n=31	n=28	n=39	n=37
≥5% weight loss	6 (24·0%)	19 (67·6%)	38 (96·1%)	36 (92·2%)
Risk difference	..	43·7 (21·7 to 65·6; p=0·0001)	72·1 (56·8 to 87·5; p<0·0001)	68·3 (52·0 to 84·5; p<0·0001)
≥10% weight loss	2 (8·7%)	12 (45·4%)	34 (86·0%)	30 (77·1%)
Risk difference	..	36·7 (16·4 to 57·0; p=0·0005)	77·2 (62·8 to 91·7; p<0·0001)	68·4 (52·9 to 83·8; p<0·0001)
Weight loss thresholds (48 weeks)†	n=29	n=27	n=38	n=32
≥5% weight loss	5 (26·0%)	20 (74·8%)	37 (95·9%)	32 (91·9%)
Risk difference	..	48·8 (27·2 to 70·5; p<0·0001)	70·0 (54·5 to 85·4; p<0·0001)	65·9 (49·1 to 82·7; p<0·0001)
≥10% weight loss	2 (13·8%)	16 (57·9%)	32 (84·0%)	28 (80·7%)
Risk difference	..	44·1 (22·6 to 65·6; p<0·0001)	70·2 (54·1 to 86·3; p<0·0001)	67·0 (50·2 to 83·8; p<0·0001)
Change in bodyweight, kg (baseline to 32 weeks)*	n=31	n=28	n=39	n=37
Absolute change	–1·0 (0·9)	–7·8 (1·0)	–16·1 (0·8)	–19·2 (1·0)
Versus placebo	..	–6·8 (–9·5 to –4·2; p<0·0001)	–15·1 (–17·5 to –12·8; p<0·0001)	–18·2 (–21·0 to –15·5; p<0·0001)
Change in bodyweight, kg (baseline to 48 weeks)*	n=29	n=27	n=38	n=32
Absolute change	–0·2 (1·2)	–11·2 (1·6)	–19·7 (1·1)	–23·9 (1·5)
Versus placebo	..	–11·0 (–14·9 to –7·1; p<0·0001)	–19·6 (–22·8 to –16·3; p<0·0001)	–23·8 (–27·7 to –19·8; p<0·0001)
Change in BMI, kg/m² (baseline to 32 weeks)*	n=31	n=28	n=39	n=37
Absolute change	–0·3 (0·3)	–2·8 (0·4)	–5·8 (0·3)	–6·9 (0·4)
Versus placebo	..	–2·5 (–3·5 to –1·6; p<0·0001)	–5·5 (–6·3 to –4·7; p<0·0001)	–6·5 (–7·5 to –5·6; p<0·0001)
Change in BMI, kg/m² (baseline to 48 weeks)*	n=29	n=27	n=38	n=32
Absolute change	–0·02 (0·4)	–4·1 (0·6)	–7·2 (0·4)	–8·5 (0·6)
Versus placebo	..	–4·1 (–5·5 to –2·6; p<0·0001)	–7·1 (–8·3 to –6·0; p<0·0001)	–8·5 (–9·9 to –7·1; p<0·0001)

Data are mean (SE), mean (95% CI; p), or n (%). Endpoints were analysed under the efficacy (hypothetical) estimand (appendix p 8). *Model-based estimates were derived using a constrained mixed model for repeated measures, which enables the pooling of treatment groups during shared titration periods. †Logistic regression models were fit to binarised data, where missing continuous values were imputed under a missing-at-random assumption using within-group, within-visit data before binarisation based on whether percentage change from baseline met the specified threshold. Unconditional average treatment effects were estimated via G-computation and pooled across 100 imputed datasets using Rubin's rules.

Table 2: **Primary and secondary endpoints (efficacy [hypothetical] estimand)**

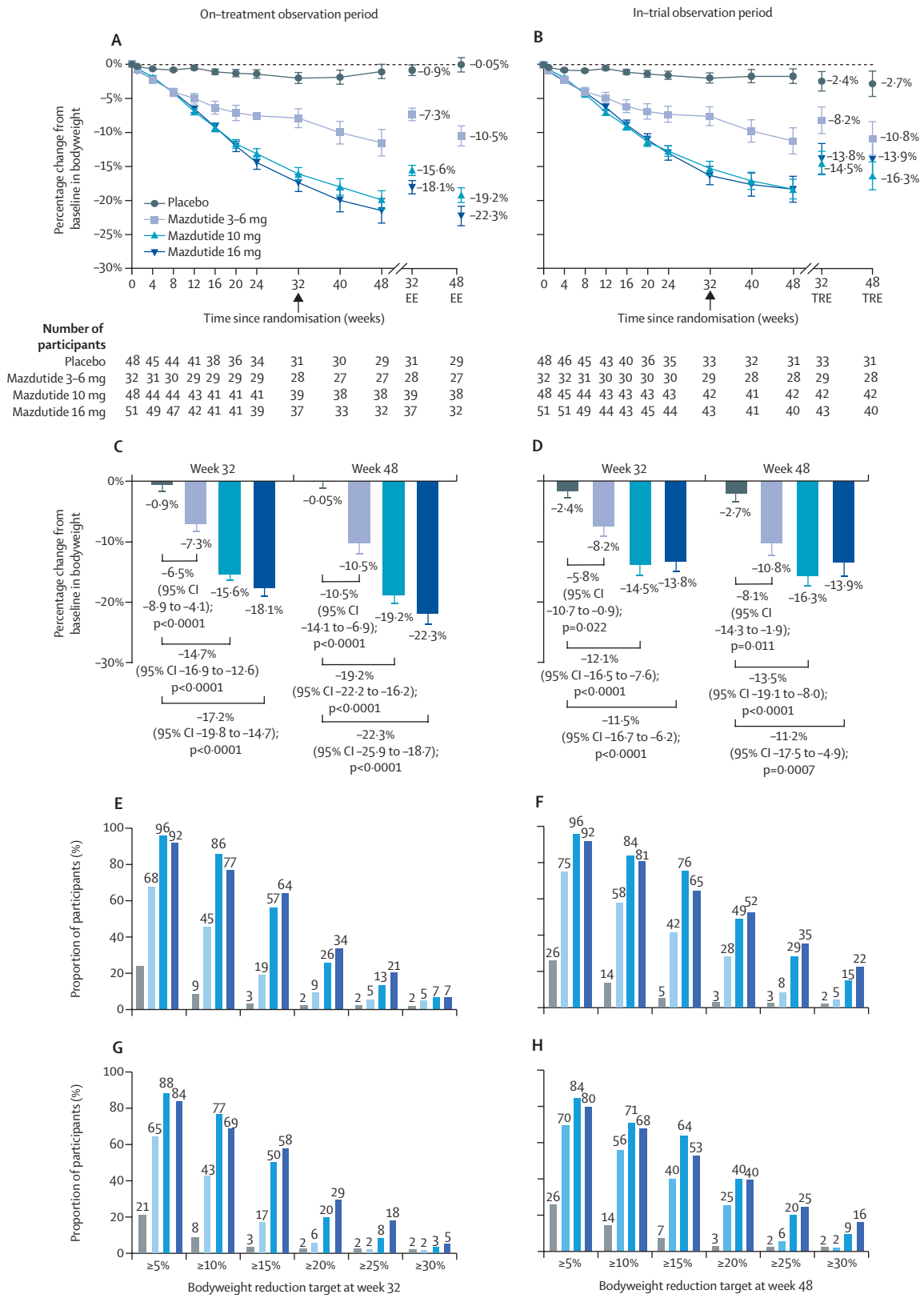

Figure 2: **Effects of mazdutide on bodyweight compared with placebo**
Upward-facing arrow indicates the timepoint (week 32) at which participants in the 3–6 mg treatment group escalated from 3 mg to 6 mg. (A, B) Lines denote observed means with error bars indicating SEs. Points at right show model-based estimates at weeks 32 and 48. (C, D) Bars denote model-based estimates with error bars indicating SEs. Brackets show treatment differences versus placebo with 95% CIs and p values. (E, F) Estimated from logistic regression with multiple imputation under a missing-at-random assumption. (G, H) Estimated from logistic regression with multiple imputation using jump to reference. EE=efficacy (hypothetical) estimand. MMRM=mixed model for repeated measures. TRE=treatment-regimen estimand.

Under the treatment-regimen estimand, mean percentage changes in bodyweight from baseline to 48 weeks ranged from –10·8% to –16·3% in the mazdutide treatment groups compared with –2·7% with placebo (figure 2, table 3). The estimated mean percentage change at 48 weeks in the 10 mg treatment group (–16·3%) exceeded that observed in the 16 mg group (–13·9%). This reversal probably reflects higher discontinuation rates in the 16 mg group, where post-discontinuation trajectories (both observed and imputed) attenuated the dose group mean.

At 32 weeks, 68–96% of participants in the mazdutide treatment groups had bodyweight reductions of 5% or more, compared with 24% of participants in the placebo group (figure 2, table 2; efficacy [hypothetical] estimand). Similarly, at 48 weeks, 75–96% of participants in the mazdutide treatment groups had bodyweight reductions of 5% or more, compared with 26% of participants in the placebo group. At both 32 weeks and 48 weeks, higher proportions of participants treated with mazdutide had bodyweight reduction thresholds of 10% or more, 15% or more, 20% or more, 25% or more, and 30% or more compared with placebo (figure 2). Approximately 50% of participants on mazdutide 10 mg or 16 mg had bodyweight loss of 20% or more at 48 weeks (figure 2). In general, the proportions of participants reaching reduction targets remained stable or increased between 32 weeks and 48 weeks.

Compared with placebo, participants treated with mazdutide had statistically significant reductions in BMI (p<0·0001, all comparisons; table 2) and waist circumference (p<0·05, all comparisons; appendix pp 19–20) at 32 weeks and 48 weeks. Approximately 40% of participants on mazdutide 10 mg or 16 mg improved by two or more BMI categories (appendix p 10). In prespecified subgroup analyses, there was no statistical evidence that the treatment effect differed by baseline BMI category or sex (appendix pp 11, 21). Additionally, treatment with mazdutide resulted in a greater shift toward lower waist-to-height ratio categories at week 48 compared with placebo, with seven (22%) of 32 participants in the 3–6 mg group, 16 (33%) of 48 in the 10 mg group, and nine (18%) of 51 in the 16 mg group shifting from the high central adiposity category (>0·59) to the increased central adiposity category (>0·49 to 0·59), versus only one (2%) of 48 participants with placebo (appendix p 22).

	Placebo (n=48)	Mazdutide 3–6 mg (n=32)	Mazdutide 10 mg (n=48)	Mazdutide 16 mg (n=51)
Percentage change in bodyweight, % (baseline to 32 weeks)*	n=33	n=29	n=42	n=43
Percentage change	–2·4% (1·4)	–8·2% (2·0)	–14·5% (1·7)	–13·8% (2·2)
Versus placebo	..	–5·8% (–10·7 to –0·9; p=0·022)	–12·1% (–16·5 to –7·6; p<0·0001)	–11·5% (–16·7 to –6·2; p<0·0001)
Percentage change in bodyweight, % (baseline to 48 weeks)*	n=31	n=28	n=42	n=40
Percentage change	–2·7% (1·9)	–10·8% (2·5)	–16·3% (2·0)	–13·9% (2·8)
Versus placebo	..	–8·1% (–14·3 to –1·9; p=0·011)	–13·5% (–19·1 to –8·0; p<0·0001)	–11·2% (–17·5 to –4·9; p=0·0007)
Weight loss thresholds (32 weeks)†	n=33	n=29	n=42	n=43
≥5% weight loss	6 (21·2%)	19 (64·6%)	39 (87·9%)	39 (83·8%)
≥10% weight loss	2 (8·5%)	12 (42·6%)	34 (76·7%)	32 (68·8%)
Weight loss thresholds (48 weeks)†	n=31	n=28	n=42	n=40
≥5% weight loss	6 (25·6%)	20 (69·6%)	38 (84·5%)	36 (79·8%)
≥10% weight loss	3 (14·3%)	16 (55·9%)	32 (71·0%)	31 (67·8%)
Change in bodyweight, kg (baseline to 32 weeks)*	n=33	n=29	n=42	n=43
Absolute change	–3·5 (1·8)	–8·7 (2·4)	–15·3 (2·0)	–15·1 (2·2)
Versus placebo	..	–5·2 (–11·2 to 0·8; p=0·091)	–11·9 (–17·1 to –6·6; p<0·0001)	–11·6 (–17·2 to –6·1; p<0·0001)
Change in bodyweight, kg (baseline to 48 weeks)*	n=31	n=28	n=42	n=40
Absolute change	–3·9 (2·3)	–11·3 (2·7)	–16·8 (2·2)	–15·5 (2·7)
Versus placebo	..	–7·4 (–14·6 to –0·1; p=0·046)	–12·9 (–19·4 to –6·5; p=0·0001)	–11·6 (–18·3 to –5·0; p=0·0007)

Data are mean (SE), mean (95% CI; p), or n (%). Endpoints were analysed under the treatment-regimen estimand, consistent with intention to treat (appendix p 8). *Model-based estimates were derived from an ANCOVA model, with missing data addressed via jump-to-reference multiple imputation across 100 datasets and estimates pooled using Rubin's rules. †Logistic regression models were fit to binarised data, where missing continuous values were imputed using placebo-group observed data as the reference (jump to reference), then binarised based on whether the percentage change from baseline met the specified threshold. Unconditional average treatment effects were estimated via G-computation and pooled across 100 imputed datasets using Rubin's rules.

Table 3: **Primary and secondary endpoints (treatment-regimen estimand)**

At 48 weeks, mazdutide treatment at all doses was associated with statistically significant reductions in MRI-derived adipose tissue volumes from baseline compared with placebo (appendix pp 23–26). Mean percentage changes versus placebo at 48 weeks were generally dose-related across the three adipose compartments: VAT was –16·4% (95% CI –24·2 to –7·9) for 3–6 mg, –32·4% (–37·9 to –26·3) for 10 mg, and –32·1% (–38·9 to –24·4) for 16 mg; SAT was –18·4% (–26·4 to –9·5) for 3–6 mg, –29·8% (–36·2 to –22·9) for 10 mg, and –31·1% (–38·8 to –22·5) for 16 mg; and total abdominal fat was –19·0% (–26·7 to –10·5) for 3–6 mg, –31·7% (–37·6 to –25·3) for 10 mg, and –32·7% (–39·9 to –24·6) for 16 mg (appendix pp 23–26). Reductions in total lean tissue volume versus placebo reached –13% with the 10 mg and 16 mg doses by 32 weeks and did not progress meaningfully thereafter (maximum –14·1% with 10 mg at 48 weeks; appendix pp 23–26). At 48 weeks, the maximum reductions versus placebo in total spinal erector and total thigh fat-free muscle volumes were –14·4% (95% CI –17·2 to –11·5) for 10 mg and –15·9% (–19·4 to –12·2) for 16 mg (appendix pp 23–26). Anterior thigh and spinal muscle fat infiltration (a marker of muscle quality)[22] showed non-statistically significant changes at 48 weeks across all mazdutide doses.

From an overall mean baseline HbA_{1c} of 5·5%, mazdutide treatment was associated with statistically significant placebo-adjusted reductions at 48 weeks in HbA_{1c} of –0·34% to –0·45% (p<0·0001, all comparisons; appendix pp 19–20), in fasting glucose of –4·9 to –10·1 mg/dL (p<0·01, all comparisons; appendix pp 19–20), and in fasting glucagon of –69·9% to –86·7% (p<0·0001, all comparisons; appendix pp 27–30). Categorical shifts in glycaemic status were also observed: among participants with prediabetes at baseline who had a non-missing post-baseline measurement at week 48, the proportions shifting to normoglycaemia were nine (100%) of nine participants in the 3–6 mg group, 11 (100%) of 11 in the 10 mg group, and 12 (92%) of 13 in the 16 mg group, compared with six (60%) of ten with placebo (appendix p 31). Baseline and endpoint values for glycaemic endpoints are provided in the appendix (pp 19–20, 27–30).

Mazdutide treatment was associated with statistically significant placebo-adjusted reductions at 48 weeks in total cholesterol (up to –13·0% [95% CI –18·2 to –7·4]), LDL cholesterol (up to –16·0% [–23·5 to –7·8]), non-HDL cholesterol (up to –16·4% [–22·8 to –9·5]), and triglycerides (up to –23·6% [–33·5 to –12·2]). HDL cholesterol did not change meaningfully across treatment groups. Modestly elevated baseline high-sensitivity C-reactive protein (hsCRP; 3–4 mg/L) declined with mazdutide treatment, with statistically significant placebo-adjusted reductions of up to –31·3% (95% CI –52·0 to –1·8) with 16 mg at 32 weeks (appendix pp 12, 27–30, 32–34).

A population pharmacokinetic model for mazdutide was developed with measured mazdutide concentrations via a nonlinear mixed effects modelling approach to describe mazdutide pharmacokinetic exposures. Model-predicted steady-state mean peak, trough concentrations, and area under the plasma concentration–time curve over a 168-h dosing interval for 3 mg once weekly to 16 mg once weekly are reported in the appendix (p 35). The population mean half-life was estimated to be approximately 9·1 days.

At baseline, out of the 175 participants who were evaluable for treatment-emergent antidrug antibodies, 27 (15%) had pre-existing antidrug antibodies against mazdutide and three (2%) had crossreactive antibodies to native oxyntomodulin (appendix p 36). After baseline, out of the 129 participants treated with mazdutide who were evaluable for treatment-emergent antidrug antibodies, 24 (19%) had treatment-emergent antidrug antibodies and 12 (9%) were positive for crossreactive antibodies to native oxyntomodulin. Participants positive for treatment-emergent antidrug antibodies generally had low antidrug antibody titres (range 1:20 to 1:2560; median 1:80). No apparent association was observed between the presence of treatment-emergent antidrug antibodies and hypersensitivity reactions, injection site reactions, and related adverse events. Antidrug antibody status and titre values were evaluated for impact on mazdutide pharmacokinetic exposures and apparent clearance but were not found to have any significant effects on mazdutide pharmacokinetics. Although treatment with mazdutide was associated with treatment-emergent antidrug antibodies in some participants in this study, the presence of antidrug antibodies had no apparent effect on safety or efficacy of mazdutide.

Survey tools assessing self-reported impact on health-related quality of life indicated improved scores on the Physical Functioning domain of the Short Form 36 version 2 acute form at 48 weeks in the mazdutide 10 mg treatment group compared with placebo, whereas no statistically significant differences were noted for other domains (appendix p 13).

At least one treatment-emergent adverse event, irrespective of investigator-reported causality, was reported in 37 (79%) of 47 participants in the placebo group, 30 (94%) of 32 in the 3–6 mg group, 40 (85%) of 47 in the 10 mg group, and 47 (92%) of 51 in the 16 mg mazdutide group (table 4). Treatment discontinuation due to adverse events occurred in one (3%) of 32 participants in the 3–6 mg group, five (11%) of 47 in the 10 mg group, and ten (20%) of 51 in the 16 mg mazdutide group, and in no participants in the placebo group. The most frequently reported treatment-emergent adverse events were gastrointestinal in nature and included nausea, constipation, diarrhoea, and vomiting (appendix pp 37–38). Gastrointestinal events were also the most common reason for treatment discontinuation (table 5) and occurred more frequently among participants treated

	Participants with one or more adverse events				Risk difference*		
	Placebo (n=47)	Mazdutide 3–6 mg (n=32)	Mazdutide 10 mg (n=47)	Mazdutide 16 mg (n=51)	Mazdutide 3–6 mg *vs* placebo	Mazdutide 10 mg *vs* placebo	Mazdutide 16 mg *vs* placebo
Treatment-emergent adverse events	37 (79%)	30 (94%)	40 (85%)	47 (92%)	15·0 (–1·7 to 29·4)	6·4 (–9·4 to 21·9)	13·4 (–0·7 to 27·9)
Of which adverse events of special interest	3 (6%)	4 (13%)	8 (17%)	15 (29%)	6·1 (–7·0 to 22·2)	10·6 (–2·9 to 24·4)	23·0 (7·8 to 37·3)
Serious adverse events†	1 (2%)	1 (3%)	1 (2%)	2 (4%)	1·0 (–8·4 to 13·7)	0·0 (–9·2 to 9·2)	1·8 (–7·6 to 11·3)
Of which adverse events of special interest	0	0	0	1 (2%)	0·0 (–7·6 to 10·7)	0·0 (–7·6 to 7·6)	2·0 (–5·8 to 10·3)
Deaths	0	0	0	0	0·0 (–7·6 to 10·7)	0·0 (–7·6 to 7·6)	0·0 (–7·6 to 7·0)
Adverse events leading to study discontinuation	1 (2%)	0	2 (4%)	5 (10%)	–2·1 (–11·1 to 8·7)	2·1 (–7·4 to 12·3)	7·7 (–2·9 to 19·0)
Of which adverse events of special interest	0	0	0	0	0·0 (–7·6 to 10·7)	0·0 (–7·6 to 7·6)	0·0 (–7·6 to 7·0)
Adverse events leading to study drug discontinuation	0	1 (3%)	5 (11%)	10 (20%)	3·1 (–4·9 to 15·7)	10·6 (1·0 to 22·6)	19·6 (8·2 to 32·5)
Of which adverse events of special interest	0	0	0	1 (2%)	0·0 (–7·6 to 10·7)	0·0 (–7·6 to 7·6)	2·0 (–5·8 to 10·3)

Data are n (%) or risk difference (95% CI). Participants may be counted in more than one category. Adverse events of special interest are listed in the protocol.*CIs for risk differences were estimated using the Newcombe score method, which is more appropriate for sparse counts. †One participant in the mazdutide 3–6 mg group had a kidney stone, one participant in the mazdutide 16 mg group had acute calculous cholecystitis, one participant in the mazdutide 16 mg group had intermittent dizziness, one participant in the mazdutide 10 mg group had epilepsy, and one participant in the placebo group had hepatic necrosis.

Table 4: **Overview of adverse events (safety analysis set)**

	Placebo (n=47)	Participants with one or more adverse events		
		Mazdutide 3–6 mg (n=32)	Mazdutide 10 mg (n=47)	Mazdutide 16 mg (n=51)
Gastrointestinal disorders	0	0	2 (4%)	6 (12%)
Vomiting	0	0	1 (2%)	3 (6%)
Diarrhoea	0	0	1 (2%)	1 (2%)
Nausea	0	0	0	2 (4%)
Gastro-oesophageal reflux disease	0	0	1 (2%)	0
Nervous system disorders	0	0	2 (4%)	1 (2%)
Dizziness	0	0	0	1 (2%)
Epilepsy	0	0	1 (2%)	0
Headache	0	0	1 (2%)	0
Ear and labyrinth disorders	0	0	1 (2%)	0
Tinnitus	0	0	1 (2%)	0
Hepatobiliary disorders	0	0	0	1 (2%)
Cholelithiasis	0	0	0	1 (2%)
Musculoskeletal and connective tissue disorders	0	1 (3%)	0	0
Arthralgia	0	1 (3%)	0	0
Neoplasms, benign, malignant, and unspecified (including cysts and polyps)	0	0	0	1 (2%)
Prostate cancer*	0	0	0	1 (6%)
Renal and urinary disorders	0	0	0	1 (2%)
Urinary incontinence	0	0	0	1 (2%)
Skin and subcutaneous tissue disorders	0	0	1 (2%)	0
Rash	0	0	1 (2%)	0

Data are n (%). Participants can be counted in more than one category. Data are presented by preferred term within system organ class. *Denominator adjusted because prostate cancer is a male sex-specific event: 16 participants in the placebo group, 11 in the mazdutide 3–6 mg group, 16 in the mazdutide 10 mg group, and 18 in the mazdutide 16 mg group.

Table 5: **Adverse events reported as the primary reason for study drug discontinuation (safety analysis set)**

with mazdutide than with placebo, particularly at the higher doses. The majority of the gastrointestinal adverse events were mild to moderate in severity (appendix pp 14–16). Five participants reported a total of five serious adverse events (one participant each in the placebo, mazdutide 3–6 mg, and mazdutide 10 mg groups, and two participants in the mazdutide 16 mg group; table 4); none were considered related to study drug by the reporting investigator. No deaths were reported in the study. In terms of cardiovascular safety measures, no consistent trend was observed for diastolic blood pressure; placebo-adjusted reductions in mean systolic blood pressure were observed for the mazdutide 10 mg and 16 mg treatment groups at 32 weeks (10 mg: –6·8 mm Hg [95% CI –11·0 to –2·6], p=0·0018; 16 mg: –9·4 mm Hg [–13·9 to –5·0], p<0·0001), and at 48 weeks (10 mg: –6·8 mm Hg [–11·6 to –1·9], p=0·0064; 16 mg: –5·9 mm Hg [–10·7 to –1·1], p=0·017; appendix pp 39–40). Mazdutide resulted in dose-dependent increases in estimated pulse rate, with peaks observed at 8 weeks (3–6 mg group [on 3 mg at this timepoint]; 4·9 bpm), 40 weeks (10 mg; 8·0 bpm), and 24 weeks (16 mg; 9·1 bpm), followed by declines across all treatment groups (appendix pp 17, 39–40). Mean estimated blood pressure and pulse rates remained within normal ranges at weeks 32 and 48 for the placebo and mazdutide-treated groups. Treatment-emergent pulse rate increases of more than 10 bpm from baseline were observed across all mazdutide dose groups at any visit (3–6 mg: 15 [47%] of 32 participants; 10 mg: 26 [55%] of 47; and 16 mg: 25 [49%] of 51) and at a notably lower rate in the placebo group (12 [26%] of 47 participants). Sustained elevations at two or more consecutive visits appeared dose-dependent, rising from eight (25%) of 32 participants treated with mazdutide 3–6 mg to 18 (38%) of 47 with 10 mg and 25 (49%) of 51 with 16 mg, compared with four (9%) of 47 with placebo (appendix p 41). Treatment-emergent increases in pulse rate exceeding 10 bpm from baseline at any visit were observed in 66 (51%) of 130 participants treated with mazdutide versus 12 (26%) of 47 in the placebo group; increases exceeding 10 bpm at two or more consecutive visits occurred in 51 (39%) participants treated with mazdutide versus four (9%) treated with placebo (appendix p 41). Skin burning sensations and related adverse events (hyperaesthesia, paraesthesia, sensitive skin, and skin burning sensation) were reported in eight (6%) of 130 participants who received mazdutide and in none of the 47 participants who received placebo.

Laboratory safety assessments showed that liver transaminases (alanine aminotransferase and aspartate aminotransferase) had decreased or remained unchanged versus placebo at 48 weeks (appendix pp 42–45). Two participants had maximum post-baseline alanine aminotransferase values of three to less than five times the upper limit of normal, one receiving 10 mg and one receiving 16 mg mazdutide. In both participants, alanine aminotransferase elevation occurred at 24 weeks (125 IU/L and 145 IU/L). Both elevations were transient and resolved without treatment interruption. No participant had a maximum post-baseline aspartate aminotransferase value of three or more times the upper limit of normal. Mean increases in pancreatic amylase and lipase levels were observed from baseline to 48 weeks in mazdutide treatment groups compared with placebo (appendix pp 42–45) and no cases of pancreatitis were reported. No cases of clinically significant hypoglycaemia, retinopathy, medullary thyroid cancer, or C-cell hyperplasia were reported. There were no investigator-reported or investigator-adjudicated major cardiovascular adverse events, and no participant developed diabetes during the study.

Discussion

In this randomised, double-blind, placebo-controlled, phase 2 dose-ranging study among adults with overweight or obesity, we explored higher doses of mazdutide than those used in previous studies. All mazdutide doses produced statistically significant, dose-dependent reductions in bodyweight relative to placebo. At the primary endpoint of 32 weeks, estimated mean percentage change in bodyweight under the efficacy (hypothetical) estimand was –15·6% with mazdutide 10 mg and –18·1% with 16 mg, compared with –0·9% with placebo, with continued reductions to –19·2% with 10 mg and –22·3% with 16 mg by 48 weeks. Improved BMI and waist circumference were also observed across all mazdutide doses compared with placebo, with approximately 40% of participants on mazdutide 10 mg or 16 mg improving by two or more BMI categories. The weight loss trajectory in all mazdutide treatment groups had not reached a plateau by the end of the 48-week treatment period, suggesting that further weight reduction is possible with continued treatment. Results from the 3–6 mg group offered additional insight into the dose–response relationship: the steeper decline in bodyweight observed after week 32 in this group was probably attributable to the dose escalation from 3 mg to 6 mg at that timepoint. At week 32, when participants in this group were still receiving 3 mg, the mean percentage weight change in the 3–6 mg group was –7·3%, slightly below the prespecified placebo-adjusted target of –8% (appendix p 8) and nearly identical to the –7·2% reported for 3 mg mazdutide at 24 weeks in a phase 2 trial among Chinese participants with obesity or overweight (modified intention-to-treat population).[14] Taken together, these findings highlight the potential of mazdutide across the dose range explored, with the higher doses in particular suggesting efficacy similar to that of currently available multihormone receptor modulators.

The safety and tolerability profile of mazdutide was generally consistent with that of incretin-based therapies, with mostly mild to moderate gastrointestinal events

occurring most frequently. Although the cohort was 66% female, prespecified subgroup analyses under the efficacy (hypothetical) estimand showed no statistical evidence that the treatment effect on bodyweight differed by sex (treatment by sex interaction p=0·49) or by baseline BMI category (treatment by BMI interaction p=0·81) at week 32 (appendix pp 11, 21). Although female participants lost more weight overall than male participants (subgroup main effect p=0·023; appendix p 21), this difference was present across all groups including placebo (–1·8% in female *vs* 0·2% in male participants; appendix p 21), indicating a background sex difference in weight change rather than a differential response to mazdutide; placebo-adjusted effects were therefore broadly consistent across sexes, particularly at the 3–6 mg dose. Although the phase 2 sample size restricts the power of these subgroup tests, the consistency of the placebo-adjusted treatment effect across baseline BMI and sex supports the generalisability of the dose–response observed here to the broader population that would be enrolled in phase 3.

GLP-1 receptor agonists are effective for the treatment of obesity, promoting sustained and clinically relevant reductions in bodyweight. Semaglutide 2·4 mg weekly produced mean bodyweight changes of –16·9% at 68 weeks under the trial product estimand (analogous to the efficacy [hypothetical] estimand used here) and –14·9% under the treatment policy estimand (analogous to the treatment-regimen estimand used here).[23] In the recent STEP UP phase 3b trial, semaglutide 7·2 mg produced mean changes in bodyweight of –18·7% at 72 weeks versus –3·9% with placebo (treatment policy estimand).[24] Tirzepatide (a glucose-dependent insulinotropic polypeptide–GLP-1 receptor dual agonist) 15 mg has shown mean changes of –22·5% at 72 weeks (efficacy [hypothetical] estimand; –20·9% under the treatment-regimen estimand).[25] The potential enhancement of bodyweight reduction through targeting both glucagon and GLP-1 receptors has been previously shown in phase 1 and phase 2 trials in people living with obesity or overweight without diabetes. For example, phase 1 studies testing a wide range of mazdutide doses have shown mean changes in bodyweight of up to –20·9% in 20 weeks.[12,13,17] In a phase 2 study, treatment with survodutide (4·8 mg), a GLP-1–glucagon receptor dual agonist, resulted in a maximum mean bodyweight change of –18·7% at 46 weeks.[26] Additionally, in a phase 2 study of retatrutide, a GLP-1– glucose-dependent insulinotropic polypeptide–glucagon receptor triple agonist, administration of 12 mg for 48 weeks resulted in a mean change in bodyweight of –24·2%, with 83% of participants reaching at least 15% weight reduction.[27]

Weight reduction with mazdutide was accompanied by changes in glycaemic parameters and lipids, and by reductions in hsCRP, VAT, and SAT. Despite glucagon receptor co-agonism, hyperglycaemia was not observed; instead, mean HbA_{1c} and fasting glucose decreased modestly from a near-normal baseline. These reductions in HbA_{1c} were accompanied by categorical shifts from prediabetes to normoglycaemia in 32 (97%) of 33 participants treated with mazdutide with a non-missing baseline and week 48 measurement (appendix p 31). Reductions in endogenous glucagon were also observed, probably reflecting pancreatic α cell response to glucagon receptor engagement.[28] At 48 weeks, mazdutide was associated with placebo-adjusted reductions of up to –16·0% in LDL cholesterol, –23·6% in triglycerides, and –29·4% in hsCRP at the 16 mg dose, with little evidence of change in HDL cholesterol (appendix pp 27–30, 32–34). The potential clinical implications of these biomarker changes for future changes in cardiovascular risk would require evaluation in dedicated prospective outcome trials.

These results support the potential for therapies targeting multiple pathways to promote weight reduction in obesity, in particular with the addition of glucagon action. The magnitude of weight reduction observed with mazdutide 10 mg and 16 mg in the current trial is consistent with the notion that the addition of glucagon receptor agonism could augment weight loss effects from GLP-1 receptor agonism. No head-to-head comparisons of mazdutide with other agents were done in this trial, and the results cited above are drawn from separate independent studies with differing populations, durations, and analytical approaches. Therefore, these comparisons are focused on interpreting the current results in the context of rapidly expanding treatment options for weight management.

Although energy expenditure and metabolic flexibility were not assessed in this trial, the cardiometabolic profile observed with mazdutide might reflect contributions from hepatic glucagon receptor signalling to modulate lipid and carbohydrate metabolism. In preclinical models, hepatic glucagon receptor activation has been linked to fatty acid oxidation, suppression of de novo lipogenesis, and mitochondrial uncoupling.[29] The reductions in LDL cholesterol, triglycerides, hsCRP, and VAT observed here are directionally consistent with engagement of these pathways. Available human data with GLP-1–glucagon multihormone receptor modulators are limited in scope, with reported pharmacodynamic results that vary across compounds, populations, and estimands. The absence of hyperglycaemia in this trial, together with the observed reduction in endogenous glucagon, is compatible with the hypothesis that hepatic glucose production is counter-regulated through combining GLP-1 receptor and glucagon receptor agonism.

Whereas most previous weight reduction studies have assessed body composition using dual-energy X-ray absorptiometry, this study used MRI, which provides precise measurements and direct delineation of VAT from SAT.[30] Visceral fat has been linked to derangements of glucose and lipid metabolism. Abnormal VAT reflects a more pathogenic adipose tissue distribution pattern

and might contribute to cardiovascular risk through adipokines and other mediators of obesity-related chronic inflammation.[31] In this study, mazdutide treatment was associated with statistically significant reductions in visceral and subcutaneous adipose tissue, with potentially favourable implications for cardiovascular risk. Analyses of liver fat and its associations with metabolic parameters are ongoing to further characterise the effects of mazdutide on body composition and metabolic health. The observed reductions in total lean tissue volume are consistent with the proportional lean mass loss reported for incretin-based therapies.[32,33] Notably, dual-energy X-ray absorptiometry-derived total lean body mass and MRI-derived lean tissue and fat-free muscle volumes capture overlapping but non-identical compartments. Direct quantitative comparison of lean-mass changes across body-composition modalities is therefore not possible. The implications of these compositional changes for physical function and longer-term outcomes warrant prospective evaluation in future trials.

The most commonly reported adverse events with mazdutide were gastrointestinal in nature, which were mostly mild to moderate in severity. Treatment discontinuation due to these events was most common in the 16 mg group, where 20% of participants discontinued treatment due to adverse events and 12% discontinued due to gastrointestinal-related disorders, specifically. For context on tolerability of multihormone receptor modulators (although direct comparisons cannot be made across trials), treatment discontinuation due to adverse events has been reported at 29% with survodutide 4·8 mg[26] and at 16% with retatrutide 12 mg.[27] The results observed with mazdutide could be attributed to the titration strategy used in this phase 2 study and suggest that further adjustments to the dose-escalation approach could help balance the enhanced efficacy of higher doses while minimising rates of gastrointestinal events and treatment discontinuation. In the STEP UP phase 3b trial of semaglutide 7·2 mg, gastrointestinal adverse events were reported by 71% of participants (versus 61% with semaglutide 2·4 mg and 43% with placebo), with 3% discontinuing due to these events, probably reflecting tolerability management and enrichment through sequential dose-escalation strategies.[24] Gradual dose escalation appeared to improve gastrointestinal tolerability: fewer participants in the 3–6 mg group reported moderate to severe gastrointestinal adverse events at the 6 mg dose level after 28 weeks at 3 mg, compared with those in the 10 mg and 16 mg groups, who escalated to 6 mg at week 8 before continuing to the higher dose (appendix p 14).

Pulse rate increased with mazdutide to a greater extent than that reported in clinical trials with some incretin-based therapies, but the pattern was consistent with known class-related haemodynamic effects and could partly reflect glucagon receptor activation. Despite observed increases from baseline of more than 10 bpm with mazdutide compared with placebo (including at two or more consecutive visits), mean pulse remained within the physiological range, and no clinically meaningful arrhythmic or cardiovascular safety signal emerged in this phase 2 trial. The long-term clinical implications of sustained pulse rate elevations remain uncertain and cannot be fully characterised from the present data alone. Treatment-emergent antidrug antibodies were detected in 19% of participants treated with mazdutide but were generally low-titre and were not associated with hypersensitivity reactions, injection-site reactions, related adverse events, or measurable changes in mazdutide pharmacokinetics, and the presence of antidrug antibodies appeared to have no effect on the safety or efficacy of mazdutide in this study.

This study has limitations. Early treatment discontinuation reduced representation in the placebo and 16 mg groups, hampering precision for longer-term estimates and contributing to differences between the efficacy and treatment-regimen estimands. The apparent greater efficacy of 16 mg was attenuated under the treatment-regimen estimand (–14·5% for 10 mg *vs* –13·8% for 16 mg) and paralleled the higher discontinuation at 16 mg, which was in part due to the gastrointestinal adverse event burden observed at that dose. This pattern is likely to reflect two contributing factors: the two doses approaching equivalent maximal efficacy near the plateau of the dose–response curve, and downward pull on the 16 mg estimate from jump-to-reference imputation, which replaces missing values with placebo data and therefore has greater impact in the 16 mg group given its higher withdrawal rate. A sensitivity analysis comparing on-treatment weight loss trajectories between completers and discontinuers (appendix p 18) showed that the two groups tracked closely through the on-treatment visits in the higher-dose groups, indicating that dropout was not systematically related to weight loss trajectory. Together, these analyses suggest that the true treatment effect of 16 mg is likely to fall between the treatment-regimen and efficacy (hypothetical) estimands, with the treatment-regimen result representing a conservative lower bound and the efficacy (hypothetical) estimand an upper bound (appendix p 46). Because the treatment-regimen estimand more closely approximates real-world effectiveness, where patients who discontinue do not continue to accrue benefit, these data suggest that the net population-level advantage of 16 mg over 10 mg is more modest than the efficacy (hypothetical) estimand alone implies. Whereas the lower-dose range is already established in previous phase 3 work, the primary contribution of this study lies in characterising the higher-dose range and the role of tolerability in realising its potential benefit. Advancing both 10 mg and 16 mg, with a slower titration schedule informed by the lower gastrointestinal burden observed after 28 weeks on 3 mg, would allow the efficacy ceiling of 16 mg to be tested while retaining 10 mg as an alternative dose.

Additional limitations of this trial include differences in exposure to target doses between groups by design, particularly in the 3–6 mg group; no assessment of efficacy in people with type 2 diabetes; and, as is typical for phase 2 trials, a sample size permitting systematic evaluation of common but not rare safety events. No formal control of the type I error rate was applied across efficacy endpoints, and results should therefore be considered hypothesis generating.

In summary, in this phase 2 trial, once-weekly mazdutide treatment resulted in dose-dependent, statistically significant weight reduction among adults with obesity or overweight across a range of doses, with a gastrointestinal-related adverse event profile generally consistent with that of other incretin-based therapies. The findings from this study highlight the potential of therapies targeting multiple pathways for improved weight loss efficacy over current GLP-1 receptor agonists.

Contributors

AMKW, KJM, AH, MKT, LST, WN, and OFGDA contributed to the conception of the work. AMKW, KJM, TC, MKT, LST, WN, and OFGDA contributed to the design of the work. SHH and WN contributed to the acquisition of data. AMKW and LST accessed and verified the raw data and oversaw the programming for analysis of these data. SHH, HEB, LKB, AMKW, KJM, TC, AH, MKT, LST, BC, and OFGDA contributed to the interpretation of data. AMKW, MKT, and OFGDA contributed to the drafting of the work. All authors contributed to the critical revision of the work for important intellectual content. All authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, had full access to all of the data in the study, take responsibility for the integrity of the work as a whole, and were responsible for the final decision to submit for publication.

Declaration of interests

OFGDA, AMKW, KJM, TC, AH, LST, BC, WN, and MKT report being employees of and stockholders in Eli Lilly. LKB reports research support, consultant fees, or serving on advisory panels for Bayer, Dexcom, Endogenex, Eli Lilly, Novo Nordisk, Sanofi, Pfizer, and Xeris. SHH reports research funding to their research site from Eli Lilly. HEB reports research grants to their institution from 89bio, Allergan, Alon Medtech (Epitomee), Aligos, Altimmune, Amgen, Anji Pharma, AbbVie, AstraZeneca, BioAge, Biohaven, Bionime, Boehringer Ingelheim, Carmot, Chorus–BioAge, Eli Lilly, Esperion, Evidera, Fractyl, GSK, HighTide, Home Access, Horizon, Ionis, Kallyope, LG Chem, Madrigal, Merck, Mineralys, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Satsuma, Selecta, Shionogi, Skye (Bird Rock), TIMI, Veru, Viking, Vivus, and Zomagen; and consultancy for 89bio, Altimmune, Amgen, Boehringer Ingelheim, Eli Lilly, Eva Pharma, Kiniksa, HighTide, Novo Nordisk, Regeneron, Rivus, Veru, Zomagen, and ZyVersa.

Data sharing

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, except for 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 have been 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 clinical study report and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at https://www.vivli.org.

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