ORIGINAL ARTICLE

# Once-Weekly Mazdutide in Chinese Adults with Obesity or Overweight

L. Ji,[1] H. Jiang,[2] Y. Bi,[3] H. Li,[4] J. Tian,[5] D. Liu,[6] Y. Zhao,[7] W. Qiu,[8] C. Huang,[9] L. Chen,[10] S. Zhong,[11] J. Han,[12] Y. Zhang,[13] Q. Lian,[14] P. Yang,[15] L. Lv,[16] J. Gu,[17] Z. Liu,[17] H. Deng,[17] Y. Wang,[17] L. Li,[17] L. Pei,[17] and L. Qian,[17] for the GLORY-1 Investigators*

## ABSTRACT

### BACKGROUND

Evidence suggests that incretin-based dual agonist pharmacotherapy is helpful in persons with obesity. Mazdutide, a glucagon-like peptide-1 and glucagon receptor dual agonist, may have efficacy in persons with overweight or obesity.

### METHODS

In a phase 3, double-blind, placebo-controlled trial in China, we randomly assigned, in a 1:1:1 ratio, adults 18 to 75 years of age who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 28 or had a BMI of 24 to less than 28 plus at least one weight-related coexisting condition to receive 4 mg of mazdutide, 6 mg of mazdutide, or placebo for 48 weeks. The two primary end points were the percentage change in body weight from baseline and a weight reduction of at least 5% at week 32, as assessed in a treatment-policy estimand analysis (which assessed effects regardless of early discontinuation of mazdutide or placebo and the initiation of new antiobesity therapies).

### RESULTS

Among 610 participants, the mean body weight was 87.2 kg and the mean BMI was 31.1 at baseline. At week 32, the mean percentage change in body weight from baseline was –10.09% (95% confidence interval [CI], –11.15 to –9.04) in the 4-mg mazdutide group, –12.55% (95% CI, –13.64 to –11.45) in the 6-mg mazdutide group, and 0.45% (95% CI, –0.61 to 1.52) in the placebo group, and 73.9%, 82.0%, and 10.5% of the participants, respectively, had a weight reduction of at least 5% ($P<0.001$ for all comparisons with placebo). At week 48, the mean percentage change in body weight from baseline was –11.00% (95% CI, –12.27 to –9.73) in the 4-mg mazdutide group, –14.01% (95% CI, –15.36 to –12.66) in the 6-mg mazdutide group, and 0.30% (95% CI, –0.98 to 1.58) in the placebo group, and 35.7%, 49.5%, and 2.0% of the participants, respectively, had a weight reduction of at least 15% ($P<0.001$ for all comparisons with placebo). Beneficial effects on all prespecified cardiometabolic measures were seen with mazdutide. The most frequently reported adverse events were gastrointestinal and mostly mild to moderate in severity. The incidence of adverse events leading to discontinuation of the trial regimen was 1.5% with the 4-mg mazdutide dose, 0.5% with the 6-mg mazdutide dose, and 1.0% with placebo.

### CONCLUSIONS

In Chinese adults with overweight or obesity, once-weekly mazdutide at a dose of 4 mg or 6 mg for 32 weeks led to clinically relevant reductions in body weight. (Funded by Innovent Biologics; GLORY-1 ClinicalTrials.gov number, NCT05607680.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Ji can be contacted at jiln@bjmu.edu.cn or at the Department of Endocrinology and Metabolism, Peking University People's Hospital, No. 11 Xizhimen S. St., Beijing, 100044, China. Dr. Qian can be contacted at cnradium@126.com or at Innovent Biologics, No. 999 Jinguang Rd., Minhang District, Shanghai, 201100, China.

*A complete list of the investigators in the GLORY-1 trial is provided in the Supplementary Appendix.

Drs. Ji and Jiang contributed equally to this article.

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Obesity is a growing worldwide pandemic.[1] According to Chinese criteria, approximately half the population in China lives with overweight (defined as a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of 24 to <28) or obesity (BMI, ≥28).[2] Obesity and overweight are well-recognized risk factors for a wide range of diseases, among which metabolic dysfunction–associated fatty liver disease (MAFLD), dyslipidemia, hypertension, and prediabetes have been most common in China.[2,3]

Chinese obesity guidelines recommend pharmacotherapy for adults with obesity or with overweight accompanied by weight-related coexisting conditions if lifestyle interventions fail to control body weight adequately.[4] In recent years, incretin-based pharmacotherapies for obesity have been associated with clinically relevant reductions in body weight, as well as with beneficial effects on cardiometabolic risks factors and cardiorenal outcomes.[5-7] To date, beinaglutide, liraglutide, semaglutide, and tirzepatide have been approved for the treatment of persons with obesity or overweight with coexisting conditions in China.[8-11]

Glucagon promotes hepatic glucose production and stimulates lipolysis and fatty acid oxidation.[12] Glucagon antagonism, although it effectively reduces the glucose level in persons with diabetes, is associated with dyslipidemia, weight gain, and increased hepatic fat content.[13] Such findings have led to speculation that glucagon agonism may promote weight loss and hepatic lipolysis, provided that the hyperglycemic effect of glucagon is effectively counteracted.[14] Participants with obesity or overweight in several preliminary studies of glucagon-like peptide-1 (GLP-1) and glucagon receptor coagonists have had marked body-weight reductions and metabolic benefits.[15-20]

Mazdutide (also known as IBI362 or LY3305677), a synthetic peptide analogue of mammalian oxyntomodulin, is a once-weekly GLP-1 and glucagon receptor dual agonist being developed for the treatment of obesity and type 2 diabetes. In phase 2 trials, mazdutide treatment in doses of up to 6 mg led to a marked reduction in body weight in Chinese adults with obesity or overweight and to both effective glycemic control and weight reduction in Chinese patients with type 2 diabetes.[18,21] In a 48-week, phase 3, double-blind, randomized, placebo-controlled trial of GLP-1 and glucagon receptor dual agonist therapy in persons with obesity or overweight (GLORY-1), we aimed to evaluate the efficacy and safety of mazdutide in long-term weight management. We evaluated the efficacy and safety of mazdutide as compared with placebo for reducing body weight and improving cardiometabolic risk factors in Chinese adults who had obesity or had overweight with at least one coexisting condition.

## METHODS

### TRIAL DESIGN

We conducted this trial at 23 hospitals in China. The sponsor (Innovent Biologics) and the first author designed and oversaw the conduct of the trial. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol, which is available with the full text of this article at NEJM.org, was approved by an independent ethics committee at each trial site. The investigators collected the data and worked under confidentiality agreements with the sponsor. The sponsor undertook trial-site monitoring and data collation and analysis. The authors had full access to the data and participated in the interpretation of the data. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first author and two other authors who are employees of the sponsor wrote the first draft of the manuscript. The authors, including those who are employees of the sponsor, made the decision to submit the manuscript for publication.

### PARTICIPANTS

Adult participants 18 to 75 years of age who had obesity or had overweight accompanied by at least one weight-related coexisting condition (prediabetes, hypertension, dyslipidemia, MAFLD, weight-bearing joint pain, obesity-related dyspnea, or obstructive sleep apnea syndrome) were eligible. Obesity and overweight were defined according to Chinese criteria (BMI of ≥28 and of 24 to <28, respectively). Participants were excluded if they reported a body weight that had fluctuated by more than 5% within the 12 weeks before screening. Participating women had to have a negative pregnancy test and not be breast-feeding at screening. The full inclusion and exclusion criteria are listed

in the Supplementary Appendix, available at NEJM .org. Written informed consent was obtained from all the participants.

### PROCEDURES

The trial included a 2-week screening period, a 48-week treatment period, and a 12-week off-treatment follow-up period (Fig. S1 in the Supplementary Appendix). Eligible participants were randomly assigned, in a 1:1:1 ratio, to receive 4 mg of mazdutide, 6 mg of mazdutide, or placebo, administered subcutaneously once weekly. Randomization was stratified according to the BMI at screening (<28 vs. ≥28).

Mazdutide was administered according to one of two dose schedules (starting at a low dose, with adjustment to the full dose). In the 4-mg group, the dose-adjustment schedule was as follows: 2 mg during weeks 1 to 4, with an increase to 4 mg during weeks 5 to 48. In the 6-mg group, the dose-adjustment schedule was as follows: 2 mg during weeks 1 to 4, with an increase to 4 mg during weeks 5 to 8 and then to 6 mg during weeks 9 to 48. All the participants received diet and exercise lifestyle-management instructions and received instructions and recommendations from the investigators throughout the trial.

### END POINTS AND ASSESSMENTS

The two primary end points were the percentage change in body weight from baseline to week 32 and a weight reduction of at least 5% by week 32. Key secondary end points were a weight reduction of at least 5% by week 48 and of at least 10% and at least 15% by weeks 32 and 48; the percentage change in body weight from baseline to week 48; the change in waist circumference from baseline to weeks 32 and 48; and changes from baseline to week 48 in systolic blood pressure and in levels of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, serum uric acid, and alanine aminotransferase in an analysis that pooled the two mazdutide dose groups. Definitions of other secondary efficacy end points (including the physical functioning score on the 36-Item Short Form Health Survey, version 2 [SF-36], and the physical function score on the Quality of Life–Lite Clinical Trials Version [IWQOL-Lite-CT] questionnaire) and exploratory end points (including liver-fat content in a subpopulation) are provided in the Supplementary Appendix.

Safety end points were assessed as reported adverse events, vital signs, electrocardiographic assessments, and laboratory results. Mental health was assessed with the use of the nine-item Patient Health Questionnaire (PHQ-9) and the Columbia–Suicide Severity Rating Scale (C-SSRS). Immunogenicity was assessed by detection of antimazdutide antibodies.

### STATISTICAL ANALYSIS

We calculated that a sample of 600 participants would provide the trial with more than 99% power to show the superiority of mazdutide (4 mg or 6 mg) to placebo with regard to the two primary end points, at a two-sided significance level of 0.025 for each dose level. Superiority would be met only if the results for both primary end points were significant.

Efficacy and safety end points were analyzed in all the participants who had undergone randomization (intention-to-treat principle). Two estimands (the treatment-policy estimand and efficacy estimand) were used to assess efficacy in order to account for intercurrent events (early discontinuation of the trial regimen and initiation of new antiobesity medication or bariatric surgery) differently. The treatment-policy estimand was used to evaluate efficacy regardless of intercurrent events, and results were estimated with the use of analysis of covariance for continuous end points and logistic regression for binary end points. Missing data were assumed to be missing not at random, since it was believed that participants who had a lack of efficacy or had an unacceptable level of adverse events with mazdutide or placebo would tend to withdraw from the trial prematurely. Therefore, missing data were imputed with the use of a hybrid multiple imputation method. Relative rates were calculated with the use of the estimates of marginal standardized rates from logistic models, and confidence intervals were estimated by bootstrap resampling.[22,23]

The type I error was strictly controlled for the two primary end points and key secondary end points with a graphical approach. Further details of the statistical analysis methods are provided in the Supplementary Appendix.

**Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Intention-to-Treat Population).***

| Characteristic | Mazdutide, 4 mg (N=203) | Mazdutide, 6 mg (N=202) | Placebo (N=205) | Overall (N=610) |
|---|---|---|---|---|
| Age — yr | 34.8±7.9 | 33.2±8.2 | 34.5±7.9 | 34.2±8.0 |
| Male sex — no. (%) | 101 (49.8) | 99 (49.0) | 99 (48.3) | 299 (49.0) |
| Body weight — kg | 87.9±14.8 | 87.2±14.1 | 86.5±13.0 | 87.2±13.9 |
| Waist circumference — cm | 101.7±10.0 | 101.7±10.1 | 101.1±9.4 | 101.5±9.8 |
| Body-mass index | 31.0±3.5 | 31.3±3.8 | 31.1±3.3 | 31.1±3.5 |
| Body-mass index category at screening — no. (%) | | | | |
| <28 | 31 (15.3) | 34 (16.8) | 38 (18.5) | 103 (16.9) |
| ≥28 | 172 (84.7) | 168 (83.2) | 167 (81.5) | 507 (83.1) |
| Systolic blood pressure — mm Hg | 122.0±11.4 | 122.2±12.0 | 122.8±12.1 | 122.3±11.8 |
| Diastolic blood pressure — mm Hg | 82.5±8.0 | 81.8±7.7 | 82.5±7.9 | 82.3±7.9 |
| Triglycerides — mmol/liter | 1.9±1.0 | 2.1±1.3 | 2.0±1.2 | 2.0±1.2 |
| Total cholesterol — mmol/liter | 4.7±0.8 | 4.8±0.9 | 4.9±0.9 | 4.8±0.9 |
| LDL cholesterol — mmol/liter | 3.2±0.7 | 3.2±0.7 | 3.2±0.7 | 3.2±0.7 |
| Serum uric acid — μmol/liter | 366.0±86.7 | 377.5±90.5 | 362.5±91.5 | 368.6±89.7 |
| Alanine aminotransferase — U/liter | 36.5±27.6 | 36.3±24.1 | 33.6±24.0 | 35.5±25.3 |

* Plus–minus values are means ±SD. The intention-to-treat population included all the participants who had undergone randomization. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for serum uric acid to milligrams per deciliter, divide by 59.48. LDL denotes low-density lipoprotein.

## RESULTS

### PARTICIPANTS

From November 2022 through January 2023, a total of 862 participants underwent screening, of whom 610 were enrolled and underwent randomization. All the participants who underwent randomization received mazdutide or placebo. Overall, 56 participants (9.2%) discontinued the trial regimen prematurely (23 participants [11.3%] in the 4-mg mazdutide group, 22 [10.9%] in the 6-mg mazdutide group, and 11 [5.4%] in the placebo group), and 567 participants (93.0%) completed the trial (187 [92.1%], 184 [91.1%], and 196 [95.6%], respectively) (Fig. S2).

The demographic and clinical characteristics of the participants at baseline were balanced across the trial groups (Table 1 and Table S1). Among all the participants at baseline, the mean age was 34.2 years, the mean body weight was 87.2 kg, and the mean BMI was 31.1. A total of 83.1% of the participants had a baseline BMI of at least 28 (indicating obesity), and 88.9% had at least one weight-related coexisting condition. The most common coexisting conditions were dyslipidemia (in 62.3% of the participants), MAFLD (in 48.9%), hyperuricemia (in 40.2%), and hypertension (in 22.8%). The trial population was representative of populations with obesity or overweight in China (Table S2).

### CHANGE IN BODY WEIGHT

Mazdutide therapy was associated with sustained reduction in body weight over a period of 32 weeks, with results extending up to 48 weeks (Fig. 1A and 1B, Figs. S3 and S5, and Tables S3 and S4). The least-squares mean percentage change in body weight from baseline to week 32 (first primary outcome) was –10.09% (95% confidence interval [CI], –11.15 to –9.04) in the 4-mg mazdutide group, –12.55% (95% CI, –13.64 to –11.45) in the 6-mg mazdutide group, and 0.45% (95% CI, –0.61 to 1.52) in the placebo group, with a difference as compared with placebo of –10.54 percentage points (95% CI, –11.83 to –9.26) in the 4-mg group and –13.00 percentage points (95% CI, –14.31 to –11.70) in the 6-mg group (P<0.001 for both comparisons) (Fig. 1B and Table 2).

The percentage of participants who met the

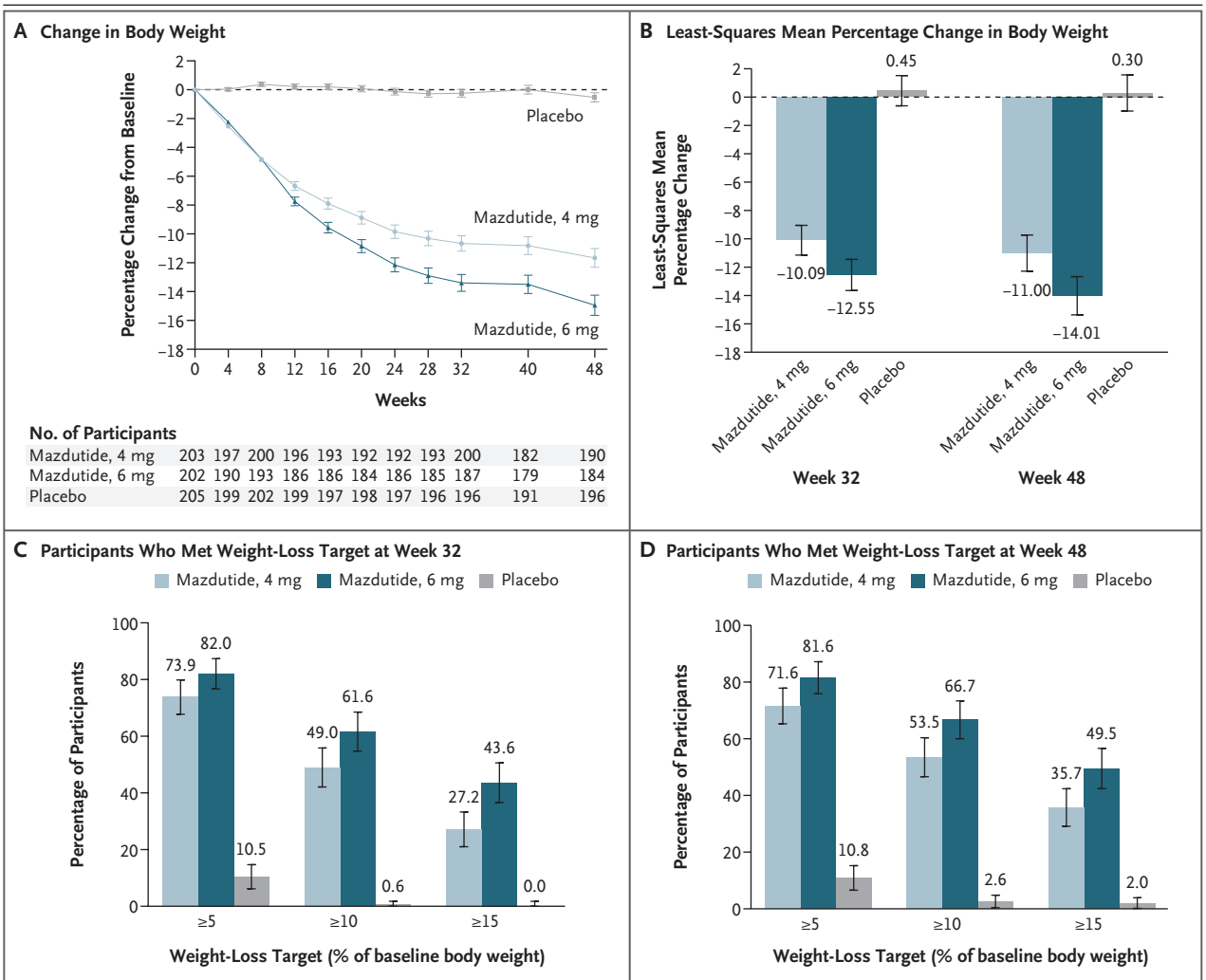


**Figure 1. Effect of Mazdutide on Body Weight (Treatment-Policy Estimand Analysis).**

Panel A shows the mean percentage change in body weight over time; I bars indicate the standard error. The numbers of participants with body-weight measurements at various time points are shown. Panel B shows the least-squares mean percentage change in body weight from baseline to week 32 (first primary outcome) and week 48 according to an analysis of covariance. The percentage of participants who had weight reduction of at least 5% at week 32 was the second primary outcome. Panel C shows the percentages of participants who met specified weight-loss targets at week 32, and Panel D at week 48. The treatment-policy estimand was used to assess effects regardless of early discontinuation of mazdutide or placebo and the initiation of new antiobesity therapies. Percentages were calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets, from a logistic-regression model. In Panels B, C, and D, I bars indicate 95% confidence intervals.

weight-loss target for the second primary outcome was higher with mazdutide than with placebo. A weight reduction of at least 5% at week 32 (second primary outcome) occurred in 73.9% (95% CI, 67.8 to 79.9) of the participants in the 4-mg mazdutide group and in 82.0% (95% CI, 76.7 to 87.4) of those in the 6-mg mazdutide group, as compared with 10.5% (95% CI, 6.2 to 14.7) of those in the placebo group (P<0.001 for both comparisons) (Table 2).

The least-squares mean percentage change in body weight from baseline to week 48 was –11.00% (95% CI, –12.27 to –9.73) in the 4-mg mazdutide group, –14.01% (95% CI, –15.36 to –12.66) in the 6-mg mazdutide group, and 0.30% (95% CI, –0.98 to 1.58) in the placebo group, with a difference as compared with placebo of –11.30 percentage points (95% CI, –12.84 to –9.76) in the 4-mg group and –14.31 percentage points (95% CI, –15.88 to –12.74) in the 6-mg group

**Table 2. Primary and Key Secondary End Points (Treatment-Policy Estimand Analysis).***

| Variable | Mazdutide, 4 mg (N=203) | Mazdutide, 6 mg (N=202) | Placebo (N=205) |
|---|---|---|---|
| No. of participants with body-weight and waist-circumference measures | | | |
| At wk 32 | 200 | 187 | 196 |
| At wk 48 | 190 | 184 | 196 |
| **Primary end points** | | | |
| Percentage change in body weight from baseline to wk 32 (95% CI) | −10.09 (−11.15 to −9.04) | −12.55 (−13.64 to −11.45) | 0.45 (−0.61 to 1.52) |
| Difference vs. placebo (95% CI) — percentage points | −10.54 (−11.83 to −9.26)† | −13.00 (−14.31 to −11.70)† | — |
| Weight reduction of ≥5% at wk 32 (95% CI) — %‡ | 73.9 (67.8 to 79.9) | 82.0 (76.7 to 87.4) | 10.5 (6.2 to 14.7) |
| Relative rate vs. placebo (95% CI) | 7.1 (4.6 to 11.0)† | 7.9 (5.1 to 12.2)† | — |
| **Key secondary end points** | | | |
| Percentage change in body weight from baseline to wk 48 (95% CI) — % | −11.00 (−12.27 to −9.73) | −14.01 (−15.36 to −12.66) | 0.30 (−0.98 to 1.58) |
| Difference vs. placebo (95% CI) — percentage points | −11.30 (−12.84 to −9.76)† | −14.31 (−15.88 to −12.74)† | — |
| Weight reduction of ≥10% at wk 32 (95% CI) — % | 49.0 (42.1 to 55.9) | 61.6 (54.8 to 68.5) | 0.6 (−0.5 to 1.8) |
| Relative rate vs. placebo (95% CI) | 81.7 (19.3 to 346.1)† | 101.7 (24.1 to 429.2)† | — |
| Weight reduction of ≥15% at wk 32 (95% CI) — %‡ | 27.2 (21.0 to 33.3) | 43.6 (36.6 to 50.6) | 0.0 (0.0 to 1.8) |
| Relative rate vs. placebo (95% CI) | 113.1 (88.7 to 144.1)† | 178.5 (145.8 to 218.6)† | — |
| Weight reduction of ≥5% at wk 48 (95% CI) — %‡ | 71.6 (65.3 to 77.9) | 81.6 (75.9 to 87.2) | 10.8 (6.5 to 15.2) |
| Relative rate vs. placebo (95% CI) | 6.7 (4.4 to 10.1)† | 7.6 (5.1 to 11.3)† | — |
| Weight reduction of ≥10% at wk 48 (95% CI) — %‡ | 53.5 (46.6 to 60.4) | 66.7 (60.0 to 73.4) | 2.6 (0.4 to 4.8) |
| Relative rate vs. placebo (95% CI) | 21.1 (7.6 to 58.2)† | 26.1 (9.4 to 72.0)† | — |
| Weight reduction of ≥15% at wk 48 (95% CI) — %‡ | 35.7 (29.1 to 42.4) | 49.5 (42.4 to 56.6) | 2.0 (0.1 to 3.9) |
| Relative rate vs. placebo (95% CI) | 18.5 (5.6 to 61.8)† | 25.3 (7.6 to 84.0)† | — |
| Change in waist circumference from baseline to wk 32 (95% CI) — cm | −7.86 (−8.69 to −7.03) | −9.27 (−10.12 to −8.42) | −0.99 (−1.82 to −0.16) |
| Difference vs. placebo (95% CI) | −6.87 (−7.88 to −5.86)† | −8.28 (−9.30 to −7.25)† | — |
| Change in waist circumference from baseline to wk 48 (95% CI) — cm | −9.12 (−10.11 to −8.12) | −10.72 (−11.76 to −9.68) | −1.41 (−2.41 to −0.42) |
| Difference vs. placebo (95% CI) | −7.70 (−8.91 to −6.50)† | −9.31 (−10.54 to −8.08)† | — |

* End-point data are least-squares means and differences with 95% confidence intervals. For continuous end points, analysis of covariance was used, and for binary end points, the logistic-regression model was used. The treatment-policy estimand was used to assess effects regardless of early discontinuation of mazdutide or placebo and the initiation of new antiobesity therapies. Trial group and stratification factor were fixed effects in the model, and the baseline value of the corresponding end-point variable was a covariate. The mean of the covariate and an equal weight of 0.5 for the stratification factor were applied to compute least-squares means. No data were missing for covariates, and multiple imputation was used for missing end-point data.

† P<0.001 for superiority as compared with placebo. The type I error was strictly controlled for the two primary end points and the key secondary end points with a graphical approach.

‡ Percentages were calculated with the use of Rubin's rules by combining the percentages of participants who met the weight-loss target in imputed data sets.

(P<0.001 for both comparisons). A total of 35.7% (95% CI, 29.1 to 42.4) of the participants in the 4-mg mazdutide group and 49.5% (95% CI, 42.4 to 56.6) of those in the 6-mg mazdutide group had a weight reduction of at least 15% at week 48, as compared with 2.0% (95% CI, 0.1 to 3.9) of those in the placebo group (P<0.001 for both comparisons).

**Table 3. Key Secondary End Points in the Pooled Mazdutide Group, as Compared with Placebo (Treatment-Policy Estimand Analysis).***

| Variable | Mazdutide, Pooled (N=405) | Placebo (N=205) | Difference |
|---|---|---|---|
| No. of participants with data at wk 48 | 374 | 196 | — |
| Change from baseline to wk 48 (95% CI) | | | |
| Systolic blood pressure — mm Hg | −8.56 (−9.90 to −7.23) | −2.13 (−3.78 to −0.48) | −6.44 (−8.22 to −4.65)† |
| Triglycerides — mmol/liter | −0.65 (−0.77 to −0.54) | −0.16 (−0.28 to −0.03) | −0.50 (−0.64 to −0.36)† |
| Total cholesterol — mmol/liter | −0.28 (−0.38 to −0.18) | 0.15 (0.04 to 0.27) | −0.43 (−0.56 to −0.31)† |
| LDL cholesterol — mmol/liter | −0.20 (−0.28 to −0.12) | 0.10 (0.02 to 0.19) | −0.31 (−0.41 to −0.20)† |
| Serum uric acid — μmol/liter | −36.70 (−46.01 to −27.39) | 7.91 (−2.76 to 18.58) | −44.61 (−56.56 to −32.65)† |
| Alanine aminotransferase — U/liter | −13.92 (−16.45 to −11.39) | −4.44 (−7.43 to −1.44) | −9.48 (−12.75 to −6.21)† |

* End-point data are least-squares means and differences with 95% confidence intervals. Data for the 4-mg and 6-mg mazdutide groups were pooled for these analyses. Analysis of covariance was used. The trial group and stratification factor were fixed effects in the model, and the baseline value of the corresponding outcome variable was a covariate. The mean of the covariate and an equal weight of 0.5 for the stratification factor were applied to compute least-squares means. Central laboratory measurements of triglycerides (in two participants), total cholesterol (in one), LDL cholesterol (in two), serum uric acid (in two), and alanine aminotransferase (in one) were missing at baseline. Missing data from the central laboratory were imputed with the use of their corresponding local measures, and multiple imputation was used for missing end-point data.

† P<0.001 for superiority as compared with placebo, with the analysis controlled for the type I error.

At week 48, participants had a mean change in body weight of −9.37 kg (95% CI, −10.47 to −8.27) in the 4-mg mazdutide group and −12.12 kg (95% CI, −13.28 to −10.96) in the 6-mg mazdutide group, with a mean weight gain of 0.08 kg (95% CI, −1.04 to 1.19) in the placebo group. Body weight rebounded during the 12-week off-treatment follow-up period (Table S6). For both doses of mazdutide, participants in different baseline BMI categories had similar magnitudes of weight loss (Fig. S4).

Overall, 114 participants had body-composition assessments performed by means of dual-energy x-ray absorptiometry at both baseline and week 48. In both mazdutide dose groups, the reduction in total fat mass appeared to be greater than the reduction in total lean mass (Fig. S6).

### CARDIOMETABOLIC RISK FACTORS AND PARTICIPANT-REPORTED OUTCOMES

Mazdutide treatment was associated with improvements in multiple cardiometabolic risk factors (Tables 2 and 3, Table S5, and Fig. S7). Reductions in the least-squares mean values were significantly greater with mazdutide than with placebo at week 48 with regard to waist circumference (−9.12 cm in the 4-mg mazdutide group and −10.72 cm in the 6-mg mazdutide group vs. −1.41 cm in the placebo group; P<0.001 for both comparisons) (Table 2). Significant differences in the changes from baseline to week 48 between the pooled mazdutide group and the placebo group were also seen with regard to systolic blood pressure (−8.56 mm Hg with mazdutide vs. −2.13 mm Hg with placebo), the triglyceride level (−0.65 vs. −0.16 mmol per liter [−58 vs. −14 mg per deciliter]), the total cholesterol level (−0.28 vs. 0.15 mmol per liter [−11 vs. 6 mg per deciliter]), the LDL cholesterol level (−0.20 vs. 0.10 mmol per liter [−8 vs. 4 mg per deciliter]), the serum uric acid level (−36.70 vs. 7.91 μmol per liter [−0.6 vs. 0.1 mg per deciliter]), and the alanine aminotransferase level (−13.92 vs. −4.44 U per liter) (P<0.001 for all comparisons) (Table 3). Beneficial effects with regard to hip circumference, neck circumference, diastolic blood pressure, and levels of aspartate aminotransferase, glycated hemoglobin, fasting glucose, fasting insulin, high-sensitivity C-reactive protein, total testosterone, and urinary albumin were observed with mazdutide (Tables S6 and S7).

In participants with liver steatosis, mazdutide treatment for 48 weeks appeared to be associated with a greater reduction in liver-fat content than placebo, and more participants who received mazdutide had relative reductions of 30% and 50% in liver-fat content and a liver-fat content of less than 5% at week 48 than those who received placebo (Fig. S8). SF-36 physical functioning scores and IWQOL-Lite-CT physical function scores increased with mazdutide therapy at weeks 32 and 48, with magnitudes greater than those observed with placebo.

**Table 4. Adverse Events (Safety Population).***

| Event | Mazdutide, 4 mg (N=203) | Mazdutide, 6 mg (N=202) | Placebo (N=205) |
|---|---|---|---|
| | | *number (percent)* | |
| Any adverse event | 195 (96.1) | 196 (97.0) | 183 (89.3) |
| Serious adverse event | 12 (5.9) | 8 (4.0) | 13 (6.3) |
| Death | 0 | 0 | 0 |
| Adverse event leading to discontinuation of mazdutide or placebo | 3 (1.5) | 1 (0.5) | 2 (1.0) |
| Adverse events occurring in ≥10% of participants in any group† | | | |
| Nausea | 66 (32.5) | 102 (50.5) | 12 (5.9) |
| Diarrhea | 71 (35.0) | 78 (38.6) | 13 (6.3) |
| Vomiting | 53 (26.1) | 87 (43.1) | 6 (2.9) |
| Decreased appetite | 70 (34.5) | 58 (28.7) | 10 (4.9) |
| Covid-19 | 39 (19.2) | 50 (24.8) | 40 (19.5) |
| Upper respiratory tract infection | 42 (20.7) | 45 (22.3) | 41 (20.0) |
| Urinary tract infection | 24 (11.8) | 25 (12.4) | 22 (10.7) |
| Hyperuricemia | 20 (9.9) | 22 (10.9) | 42 (20.5) |
| Abdominal distention | 13 (6.4) | 28 (13.9) | 4 (2.0) |
| Suspected Covid-19 | 21 (10.3) | 14 (6.9) | 27 (13.2) |
| Other adverse events of clinical interest | | | |
| Injection-site reaction‡ | 14 (6.9) | 17 (8.4) | 3 (1.5) |
| Allergic reaction§ | 6 (3.0) | 9 (4.5) | 3 (1.5) |
| Sinus tachycardia | 4 (2.0) | 9 (4.5) | 6 (2.9) |
| Hypoglycemia | 5 (2.5) | 5 (2.5) | 1 (0.5) |
| Acute cholecystitis | 1 (0.5) | 0 | 0 |
| Cholecystitis | 1 (0.5) | 0 | 1 (0.5) |
| Cholelithiasis | 2 (1.0) | 3 (1.5) | 0 |
| Obstructive pancreatitis | 1 (0.5) | 0 | 0 |

* The adverse events reported here are those that were reported for the first time or as a worsening of a preexisting event after receipt of the first dose and within 56 days after the last administration of mazdutide or placebo. The safety population included all the participants who received at least one dose of mazdutide or placebo. Covid-19 denotes coronavirus disease 2019.

† Adverse events that occurred in at least 10% of the participants in any group are reported according to *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.0, preferred terms.

‡ Injection-site reaction includes the MedDRA preferred terms of injection-site reaction, injection-site pruritus, injection-site erythema, injection-site pain, injection-site rash, injection-site hemorrhage, injection-site bruising, and injection-site hypersensitivity.

§ Allergic reaction includes the MedDRA preferred terms of urticaria, rash, hypersensitivity, dermatitis allergic, eczema, dermatitis, drug hypersensitivity, and anal eczema.

### SAFETY

Three participants (1.5%) in the 4-mg mazdutide group, one (0.5%) in the 6-mg mazdutide group, and two (1.0%) in the placebo group discontinued the trial regimen prematurely owing to adverse events (Table 4 and Table S9). Serious adverse events that were judged by the investigators as being related to mazdutide or placebo included anal fistula (in one participant in the 4-mg group), cholecystitis and obstructive pancreatitis (both in one in the 4-mg group), electrolyte imbalance (in one in the 6-mg group), panniculitis (in one in the 6-mg group), and cholecystitis (in one in the placebo group) (Table S10).

The most frequently reported adverse events were nausea (in 32.5% of the participants who received 4 mg of mazdutide, in 50.5% of those who received 6 mg of mazdutide, and in 5.9% of those who received placebo), diarrhea (in 35.0%, 38.6%, and 6.3%, respectively), and vomiting (in 26.1%, 43.1%, and 2.9%, respectively), with the incidence increasing with a higher mazdutide dose (Table 4 and Table S8). Nausea, diarrhea, and vomiting were mostly mild or moderate in severity and occurred during dose escalation (Fig. S9).

In the mazdutide groups, increases in the heart rate were observed, with the heart rate peaking during the dose-escalation period (mean increase, ≤4.6 beats per minute) and declining during the dose-maintenance period (Fig. S10). Sinus tachycardia was reported in 2.0% of the participants in the 4-mg mazdutide group, in 4.5% of those in the 6-mg mazdutide group, and in 2.9% of those in the placebo group (Table 4).

The incidence of marked elevations in post-baseline levels of alanine aminotransferase, aspartate aminotransferase, lipase, amylase, and calcitonin was low in the two mazdutide groups and the placebo group (Table S11). No case of medullary thyroid cancer or C-cell hyperplasia was reported during the trial.

No association between mazdutide therapy and mental health as assessed by the PHQ-9 questionnaire was observed. No suicidal ideation or behavior was reported on the basis of the C-SSRS assessment.

With regard to immunogenicity, antimazdutide antibodies developed during treatment in 45.0% of the participants in the 4-mg mazdutide group and in 43.7% of those in the 6-mg mazdutide group. The mean reduction in body weight was similar among participants with treatment-induced antimazdutide antibodies and those without.

## DISCUSSION

This trial showed that mazdutide therapy at doses of 4 mg and 6 mg induced clinically meaningful and significant reductions in body weight over a period of 32 weeks in Chinese adults with obesity or overweight. Significant reductions were also seen at 48 weeks. These reductions were accompanied by improvements in multiple cardiometabolic risk factors. Our findings provide robust clinical evidence regarding the applicability of GLP-1–based agonists as treatment in Chinese adults with obesity or overweight with coexisting conditions and support the use of mazdutide as a new treatment option for weight management in the Chinese population.

Our trial population differs from that of other trials to date. China adopted lower BMI cutoffs for overweight and obesity than those used by the World Health Organization.[2] Participants in our trial had a lower BMI and were younger than those in obesity trials involving predominantly White participants.[24,25] The younger age of the participants may reflect the high prevalence of overweight and obesity among young persons in China, which has probably been caused by the rapid increase in the prevalence of obesity among children and adolescents in China during the past three decades, coupled with unhealthy lifestyles in younger persons, although greater disease awareness and willingness to seek medical assistance have been observed in this age group than in older adults.[1,2] Our trial participants were relatively young with a high prevalence of weight-related cardiometabolic diseases, most notably dyslipidemia (in 62.3%), MAFLD (in 48.9%), hyperuricemia (in 40.2%), and hypertension (in 22.8%). Our results are consistent with results of a recent study involving young Chinese adults, which showed an alarmingly high prevalence of the same weight-related cardiometabolic conditions.[3] Such results underscore the importance of effective body-weight management in Chinese adults with obesity or overweight.

The weight-loss effect of mazdutide in our trial was similar to that reported in a phase 3 trial of tirzepatide in a Chinese population.[11] Weight loss occurred, regardless of the baseline BMI, which supports the use of mazdutide in weight management in Chinese adults with obesity or overweight. Furthermore, body-weight reduction and improvements in most cardiometabolic risk factors were dose-related in this trial, which implies greater benefits with higher doses of mazdutide. In a phase 2 trial involving Chinese adults with a BMI of at least 30, a 9-mg dose of mazdutide led to a placebo-adjusted reduction in body weight of 15.4% at 24 weeks and of 18.6% at 48 weeks.[26] A phase 3 trial evaluating the 9-mg dose of mazdutide in Chinese adults is ongoing (ClinicalTrials.gov number, NCT06164873).

The potential and unique metabolic effects of mazdutide that differentiate it from GLP-1 receptor agonists and other GLP-1–based dual agonists

appear to stem from glucagon agonism. Although a head-to-head comparison of mazdutide with GLP-1 receptor agonists is important for a firm conclusion, we speculate that the seemingly more-pronounced overall improvements in lipid metabolism, such as reductions in triglyceride and alanine aminotransferase levels and most notably in liver-fat content, may be attributable to glucagon-driven lipid oxidation in the liver and in adipose tissue.[12] These observations may be important, given the high prevalence of fatty liver and dyslipidemia among Chinese adults with obesity or overweight.[3] Furthermore, in phase 1 and 2 studies of treatment for these indications, mazdutide treatment was associated with marked reductions in serum uric acid levels,[18,27,28] a result that was confirmed in the present trial. Although clear clinical evidence regarding the effect of GLP-1 on reducing serum uric acid levels is lacking, the potential effects of glucagon on purine metabolism in the liver and urinary excretion of uric acid may underlie the observed reductions in serum uric acid levels with mazdutide therapy.[29-31] Results from an ongoing trial comparing mazdutide with semaglutide in persons with type 2 diabetes and obesity (NCT06184568) may help to elucidate the role of glucagon agonism.

The most common adverse events with mazdutide therapy were gastrointestinal; most of these events occurred during the dose-escalation period and were mild or moderate in severity and transient, resolving without intervention. To ensure effective communication between investigators and participants and to facilitate the timely management of adverse events, three additional visits (at weeks 1, 5, and 9) were scheduled 1 week after each dose-level change during the dose-escalation period. Thus, the incidence of adverse events leading to discontinuation of mazdutide and to dose reduction was relatively low, which indicated a generally favorable safety profile.

Owing to the cardiostimulatory effect of glucagon, a notable increase in the heart rate, as has been seen with several incretin-based polyagonists involving glucagon receptor agonism, was expected.[18-20,32] In this trial, the mean increase in the heart rate peaked during the dose-escalation period and declined during the dose-maintenance period; the mean increases in the heart rate were similar to those seen with other GLP-1 receptor agonists.[33] Apart from sinus tachycardia, the incidence of other cardiac events was low, with no clear association with mazdutide therapy. Nonetheless, the potential long-term cardiovascular benefits with GLP-1 and glucagon receptor dual agonists await further investigation.

This trial has several limitations. First, all the participants were Chinese, which limits the generalizability of the results to persons of other backgrounds. Second, the trial excluded persons with type 2 diabetes. Study of the efficacy and safety of mazdutide therapy in participants with overweight or obesity plus type 2 diabetes is warranted. Finally, the 12-week off-treatment follow-up period was relatively short for the evaluation of weight regain after the discontinuation of mazdutide or placebo.

In this trial involving Chinese adults with obesity or overweight, treatment with mazdutide at doses of 4 mg and 6 mg led to clinically meaningful reductions in body weight at 32 weeks.

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**AUTHOR INFORMATION**

Linong Ji, M.D.,[1] Hongwei Jiang, M.D.,[2] Yan Bi, M.D.,[3] Hua Li, M.D.,[4] Junhang Tian, M.D.,[5] Dexue Liu, M.D.,[6] Yuzhu Zhao, M.D.,[7] Wei Qiu, M.D.,[8] Chongbing Huang, M.D.,[9] Lei Chen, M.D.,[10] Shao Zhong, M.D.,[11] Jie Han, M.D.,[12] Yawei Zhang, M.D.,[13] Qiufang Lian, M.D.,[14] Ping Yang, M.D.,[15] Lingchun Lv, M.D.,[16] Jieyu Gu, M.D.,[17] Zihan Liu, M.D.,[17] Huan Deng, M.D.,[17] Yanqi Wang, M.Sc.,[17] Li Li, Ph.D.,[17] Lijuan Pei, Ph.D.,[17] and Lei Qian, M.D.[17]

[1] Department of Endocrinology and Metabolism, Peking University People's Hospital, Beijing; [2] Department of Endocrinology, First Affiliated Hospital and Clinical Medicine College, Henan University of Science and Technology, Luoyang, China; [3] Department of Endocrinology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China; [4] Department of Cardiology, Zibo Municipal Hospital, Zibo, China; [5] Department of Endocrinology, Luoyang Third People's Hospital, Luoyang, China; [6] Department of Endocrinology, First Affiliated Hospital of Nanyang Medical College, Nanyang, China; [7] Department of Endocrinology, Fifth People's Hospital of Shenyang, Shenyang, China; [8] Department of Endocrinology, Huzhou Central Hospital, Huzhou, China; [9] Department of Endocrinology, People's Hospital of Xuancheng, Xuancheng, China; [10] Department of Endocrinology, Suzhou Municipal Hospital, Suzhou, China; [11] Department of Endocrinology, First People's Hospital of Kunshan, Kunshan, China; [12] Department of Endocrinology, China National Petroleum Corporation Central Hospital, Langfang; [13] Department of Endocrinology, Pingxiang People's Hospital, Pingxiang, China; [14] Department of Cardiology, Yan'an University Xianyang Hospital, Xianyang, China; [15] Department of Cardiology, China–Japan Union Hospital of Jilin University, Changchun, China; [16] Department of Cardiology, Lishui Central Hospital, Lishui, China; [17] Innovent Biologics, Suzhou, China.

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