

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- | | | |
|-------------------------------------|-------------------------------------|--|
| ☐ | ☒ | The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ | The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ | A description of all covariates tested |
| ☐ | ☒ | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ | For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☐ | ☒ | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☒ | ☐ | Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection No specific software or code was used in the study. All data were collected using TrialMaster Electronic Data Capture 5.0 platform (online access).

Data analysis All statistical analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

De-identified data supporting this study's findings are available to other qualified researchers upon request. Interested parties may contact the corresponding authors (Dalong Zhu [zhudalong@nju.edu.cn], Jiajun Zhao [jjzhao@sdu.edu.cn], or Lei Qian [cnradium@126.com]). Request will be reviewed and approved access

requires an ethics committee endorsement of the proposed data use and execution of a data access agreement with Innovent Biologics. The clinical study protocol and statistical analysis plan are provided as Supplementary Protocol and Supplementary Statistical Analysis Plan, respectively.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	Of 319 participants randomised, 204 (63.9%) were male and 115 (36.1%) were female.
Reporting on race, ethnicity, or other socially relevant groupings	This study was conducted in China and all participants were Asian.
Population characteristics	This study enrolled Chinese adults (aged 18–75 years, both inclusive) with overweight (body mass index [BMI] $>23 \text{ kg/m}^2$) and a diagnosis of T2D inadequately controlled by diet and exercise alone (baseline glycated hemoglobin A1c [HbA1c] of 7.5% or more [$\geq 58 \text{ mmol/mol}$] to 10.5% or less [$\leq 91 \text{ mmol/mol}$] at screening) for at least 2 months before screening. Eligible participants had a mean HbA1c of 8.2% (66.6 mmol/mol), mean FPG of 9.7 mmol/L (174.6 mg/dL), mean body weight of 77.7 kg, mean BMI of 28.20 kg/m^2, and mean diabetes duration of 1.9 years at baseline.
Recruitment	During the Screening period, Investigator enrolled participants by the following steps: 1. Obtaining an informed consent form (ICF) signed by the participant prior to any study-related procedures. 2. Formally confirming the participants' eligibility by the Principal Investigator or trained designee after reviewing the inclusion/exclusion criteria. Note: Sponsor monitors the enrollment of each treatment group to ensure that the sample size of each group meets the study requirements. Re-screening rules: Participants who do not meet the relevant criteria of this study (screen failure) may be re-screened. If re-screening of a participant is considered, Investigator must contact Sponsor's medical monitor. Each participant can be re-screened once. Participants must sign the ICF again and receive a new identification number when they are re-screened. Participants who have failed to enter the lead-in period are not allowed to be re-screened or re-lead-in. If Investigator believes that the examination/measurement results that do not meet the inclusion/exclusion criteria (including vital signs, BMI, ECG, ophthalmoscopy, and laboratory tests, etc.) are caused by examination/measurement errors or other objective reasons that can be explained (except subjectively speculated reasons) and need to be retested, these indicators can only be retested once (must be performed during the screening period), and this situation is not considered re-screening; those who fail the screening because HbA1c does not meet the inclusion criteria cannot be retested or re-screened. If the body weight, FSG, or FPG that do not meet the randomization criteria during the lead-in period are considered by Investigator to be caused by examination/measurement errors or other objective reasons that can be explained (except for subjectively speculated reasons) and need to be retested, this parameter can only be retested once (must be performed during the lead-in period), and this situation is not considered as re-screening or re-run; HbA1c that fails to meet the randomization criteria and thus fails the lead-in, cannot be retested. Participants who withdraw from the study for any reason are not allowed to be re-screened. Screened eligible participants will enter the Lead-In period. During this period, if any participant uses hypoglycemic agents prohibited by the study protocol (See SI), they were deemed ineligible and withdrawn from the trial before randomisation. Throughout the Lead-In period, participants received trainings covering disease monitoring (e.g., self-monitoring of blood glucose, SMBG), disease management procedures, study diary card usage, and general study protocols. In the last week of the lead-in period, participants must return to the hospital for repeat measurements of HbA1c, fasting plasma glucose (FPG) or fasting serum glucose (FSG), body weight, and other relevant parameters. During this visit, they also underwent assessment against randomization criteria to determine eligibility for the next trial period.
Ethics oversight	This trial was conducted in accordance with International Conference on Harmonization guidelines on Good Clinical Practice, the principles of the Declaration of Helsinki, and China National Medical Products Administration regulations and guidelines. The study protocol and all related regulatory documents were reviewed and approved by Independent Ethics Committee (IEC) (Supplementary Information). All participants provided informed consent prior to initiating any study procedures.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size of 330 participants was estimated to provide at least 95% power to show the superiority of optimal mazdutide dose to placebo in terms of HbA1c change from baseline to week 24, at a two-sided significance level of 0.05. In the calculation of the sample size, it was assumed the mean percentage change in HbA1c from baseline to week 24 of 0.3% with placebo, 1.6% with mazdutide 4 mg, and 1.7% with mazdutide 6 mg, a common standard deviation of approximately 1.2%.
Data exclusions	“Treatment-policy estimand” was defined as the primary estimand in the study protocol. It aimed to evaluate the efficacy regardless of any intercurrent events, reflecting the clinical practice of target population in the real world. All observed data collected during the study were utilized for model fitting. Missing data were assumed to be missing not at random (MNAR) and a series of predefined sensitivity analyses were performed to assess result robustness. For the primary analysis, an ANCOVA model was employed, with missing data imputed via multiple imputation. “Efficacy estimand” aimed to estimate the treatment effect under a hypothetical scenario where all participants adhere to the planned treatment regimen without rescue therapy. A hypothetical strategy was applied to handle intercurrent events (i.e., premature treatment discontinuation or rescue therapy), assuming participants experiencing intercurrent events would still maintain their previous visits’ treatment effect trends. Data collected for all randomized patients before intercurrent events would be remained for modeling fitting. Missing data were implicitly imputed by an MMRM model, assuming that participants’ treatment effects would have followed their previous visits’ trend. The two estimands addressed different clinical questions and served different purposes. Results for the “treatment-policy estimand” are presented in the main text of the manuscript, whereas most results for the “efficacy estimand” have been relocated to Extended Data figures or tables or SI.
Replication	The data in this manuscript are derived from the Phase 3 DREAMS-1 clinical trial, where results were collected and analysed across different treatment groups. A total of A total of 320 participants were randomised and 319 participants (mazdutide 4 mg: n = 106; 6 mg: n = 106; placebo: n = 107) received at least one dose of study treatment. Given the clinical trial design, reporting experimental repetition (as typical in basic science) is not directly applicable here.
Randomization	A block randomisation method with a block size of 6 was used to randomly assign eligible participants 1:1:1 to receive mazdutide 4 mg, 6 mg or matching placebo using an interactive web response system, stratified by pre-randomisation HbA1c levels at screening, dichotomized as <8.5% or ≥8.5%. Randomisation list was generated by an independent statistician who was not involved in the clinical operations of the study.
Blinding	The study drugs and placebo were identically labelled and indistinguishable in appearance. The participants, investigators, study site personnel involved in treating and assessing participants and sponsor personnel in contact with the investigators and participants were masked to treatment allocation until the database lock.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems	Methods
n/a	n/a
Involved in the study	Involved in the study
☒ ☐ Antibodies	☒ ☐ ChIP-seq
☒ ☐ Eukaryotic cell lines	☒ ☐ Flow cytometry
☒ ☐ Palaeontology and archaeology	☒ ☐ MRI-based neuroimaging
☒ ☐ Animals and other organisms	
☐ ☒ Clinical data	
☒ ☐ Dual use research of concern	
☒ ☐ Plants	

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	This trial was registered with ClinicalTrials.gov (NCT05628311).
Study protocol	The full clinical study protocol was supplemented in the supplementary information (SI) file.
Data collection	Between Nov 20, 2022 and May 10, 2023, participants were enrolled and data were collected from the 48 study centers. The full

Data collection	study sites information were provided in the supplementary information document.
Outcomes	The primary endpoint was the change in HbA1c from baseline to week 24. The key secondary endpoints included the proportions of participants with HbA1c <7.0%, body weight loss ≥5%, both HbA1c <7.0% and body weight loss ≥5%, as well as the percentage change in body weight from baseline to week 24. Other secondary efficacy endpoints in glycemic measurements included the proportions of participants achieving HbA1c ≤6.5%, HbA1c <5.7%, the changes in FPG from baseline, 1,5-anhydroglucitol (1,5-AG), and SMBG profiles at week 24. The proportion of participants achieving weight loss ≥10%, the absolute change in body weight from baseline, the changes in circumference and BMI at week 24 were also included in secondary endpoints. The cardiorenal/metabolic measurements further included the changes in systolic and diastolic blood pressure, blood lipids (total cholesterol [TC], low density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C] and triglyceride [TG]) levels, blood uric acid (UA) levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, urine albumin/creatinine ratio (UACR), HOMA2-B, and HOMA2-IR. Patient report outcome (PRO) questionnaire were also included, such as the Diabetes Treatment Satisfaction Questionnaire (DTSQ) score and the European Quality of Life Five-Dimensions Five-Levels Scale (EQ-5D-5L). Secondary efficacy endpoints also included above-mentioned indicators at week 48. Safety outcomes included incidence of adverse events, as well as the abnormalities in vital signs, laboratory tests, and electrocardiograms (ECGs). Hypoglycemia was graded using the American Diabetes Association (ADA) 2022 classification, with severity designated as level 1 (≥54 mg/dL [3.0 mmol/L] or <70 mg/dL [3.9 mmol/L]), level 2 (<54 mg/dL [3.0 mmol/L]), and level 3 (severe). The complete study endpoints were provided in supplementary files.

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.