nature portfolio

Corresponding author(s): Dalong Zhu and Hai Pan

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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 *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	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 *Give P values as exact values whenever suitable.*
☒	☐	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 code was used for data collection
Data analysis	Statistical analyses were completed using the statistical software SAS version 9.4 or above.

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

The data supporting this Article are available within the Article, Supplementary Information, and Source Data file. The full dataset and code are not publicly available.

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	Male and female participants were enrolled in the study (67.9 and 52.8% male for ecnoglutide and placebo groups, respectively). Participant gender was self-reported.
Reporting on race, ethnicity, or other socially relevant groupings	This study was conducted in China. The majority of participants were Han ethnicity.
Population characteristics	Eligible male and female (non-pregnant and non-lactating) participants were 18-65 years of age inclusive and with a diagnosis of T2DM according to WHO criteria. In the three months prior to screening, they were to have been treated with diet and/or exercise alone or with one oral hypoglycemic agent.
Recruitment	The IRB-approved recruitment ad was distributed throughout China via flyers at clinics/hospitals/community centers, on public websites of clinics/hospitals/community centers, or digital news/social media including WeChat, which is the most popular and accessible media platform. No potential self-selection bias is evident, although willingness to participate in a clinical trial and compliance with study procedures may not be homogenous.
Ethics oversight	The trial was conducted per the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. All the participants provided written informed consent before participating. The study protocol was approved by ethics committees at the following institutions, Nanjing Drum Tower Hospital, Nanjing First Hospital, Beijing Luhe Hospital Capital Medical University, The First Affiliated Hospital of Henan University of Science and Technology, Central Hospital Affiliated to Shan Dong First Medical University, The Fourth Affiliated Hospital of Harbin Medical University, Emergency General Hospital, The Affiliated Hospital of Xuzhou Medical University, Changde First People's Hospital, The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Nanjing Jiangning Hospital, Luoyang Third People's Hospital, Zaozhuang Centre Hospital Of Shandong Yiyang Health Group, Binzhou Medical University Hospital, Heibei Petro China Centre Hospital, The First Hospital of Handan, Genertec Liaoyou Gem Flower Hospital, Shijiazhuang People's Hospital, Nanyang First People's Hospital, and Daqing People's Hospital.

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

Life sciences study design

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

Sample size	The enrollment of at least 36 subjects in each group provided 80% power of detecting a 1.0% difference of mean change from baseline in HbA1c between ecnoglutide and placebo (superiority margin was 0.3), with a one-sided significance level of 0.025, a common SD of 0.9%, and a dropout rate of 20%.
Data exclusions	The intention-to-treat set (ITT) was all randomized subjects who follow the ITT principle. The safety set included all subjects who received investigational drug or placebo at least once. Pharmacokinetic analysis set included all subjects who had at least one post-medication PK data available.
Replication	The study enrolled 145 adult subjects with T2DM.
Randomization	Subjects were randomly assigned in a 1:1:1:1 ratio to receive once-weekly subcutaneous (SC) injections of ecnoglutide at target dose of 0.4 mg (cohort [C]1), 0.8 mg (C2), or 1.2 mg (C3), or placebo (ecnoglutide vehicle).
Blinding	Study was double blinded

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

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

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	Chinese Clinical Trial Registry number CTR20211014
Study protocol	The study protocol is not publicly available.
Data collection	The study was conducted in China at 21 hospital-based certified study centers. The study enrolled 145 adult subjects with T2DM, whose disease was inadequately controlled through lifestyle management or single oral antidiabetic therapy.
Outcomes	The primary efficacy endpoint of the study was the change from the baseline in the glycosylated hemoglobin (HbA1c) tested by the central laboratory at Week 20 of treatment. Secondary endpoints included FPG, SMBG, lipids, body weight, PK and safety/tolerability endpoints.