

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 Data were collected using InForm Electronic Data Capture platform version 6.2.

Data analysis SAS version 9.4

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](#)

Data from the analyses in this study cannot be publicly available due to the sponsor's (Eli Lilly and Company) contractual obligations. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for

this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, 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 www.vivli.org.

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender	Sex was collected as a baseline variable and was captured from the InForm EDC platform. Subgroup analyses by baseline sex were conducted for efficacy and safety endpoints. The results from subgroups were consistent with the overall population, and no treatment-by-subgroup interaction was observed. As sex is not associated with treatment for type 2 diabetes, the subgroup analyses results are not included in the manuscript.
Population characteristics	Eligible patients were insulin-naïve adults (≥ 18 years of age) with T2D inadequately controlled (HbA1c $\geq 7.5\%$ and $\leq 11.0\%$) despite stable treatment with metformin, with or without a sulphonylurea, for ≥ 2 months. Patients were also required to have a body mass index (BMI) of ≥ 23 kg/m ² and stable bodyweight during the previous three months before enrollment. Key exclusion criteria included: type 1 diabetes; , estimated glomerular filtration rate ≤ 45 mL/min/1.73 m ² ; , history of pancreatitis, proliferative diabetic retinopathy, diabetic maculopathy, and non-proliferative diabetic retinopathy requiring acute treatment.
Recruitment	Patients were recruited at the study sites (addresses for each study site are provided in Supplementary Table 9) by investigators. The patients were enrolled between Dec 31, 2019 and Jan 27, 2021 using eligibility criteria pre-specified in the study protocol (supplementary information pages 14–18). The patients were required to sign an informed consent form before any study procedures. The study incorporated randomization to minimize bias. Treatment group assignment was determined by computer-generated random sequence using an interactive web-response system (IWRS). To avoid bias on this open-label study, the sponsor did not analyze the data based on actual treatments before database lock.
Ethics oversight	Ethics Review Boards at each study site approved the protocol, a full list can be found in Supplementary Table 9. The trial was conducted in accordance with the principles of international ethics guidelines, including the Declaration of Helsinki, and applicable laws and regulations.

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 calculation assumed at least a 0.45% superior HbA1c reduction with tirzepatide 10 and 15 mg versus insulin glargine, a common standard deviation of 1.2%, and no more than 25% initiation of rescue therapy or discontinuation from study drug. Given these assumptions, enrolment of approximately 956 patients would provide 90% power to demonstrate the superiority of all tirzepatide doses compared to insulin glargine at a two-sided significance level of 0.05. This sample size calculation provided a >99% power for the non-inferiority comparison with a NIM of 0.4%. A graphical multiple-testing procedure was employed to control the type I error for the primary and key secondary endpoint analyses.
Data exclusions	Efficacy and safety were assessed using the modified intent-to-treat (mITT) population, which consists of all randomly assigned patients who were exposed to at least one dose of study drug. No data were excluded from the analyses.
Replication	As this was a clinical study, measurements were not replicated for each patient. In addition, patients were not permitted to have received previous treatment with tirzepatide, which precludes repeated measurements.
Randomization	Patients were enrolled by investigators and randomly assigned 1:1:1:1 to tirzepatide 5 mg, 10 mg, 15 mg, or insulin glargine using a computer-generated randomization sequence, which was implemented via an interactive web-response system (IWRS). Randomization was stratified according to baseline HbA1c ($\leq 8.5\%$ vs $>8.5\%$), country, and OAM use (metformin alone vs metformin plus a sulphonylurea).
Blinding	An open-label design was chosen due to the different dosing frequencies, titration schemes and injection devices of insulin glargine compared to tirzepatide, which precluded masking of treatment allocation.

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

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	NCT04093752
Study protocol	Study protocol is available on clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT04093752?id=04093752&draw=2&rank=1 , under study details - study documents (full-text) section.
Data collection	Patients were enrolled between Dec 31, 2019 and Jan 27, 2021 at 66 medical research centers and hospitals in China (n=43), Korea (n=13), Australia (n=6), and India (n=4). The addresses for each research center are provided in Supplementary Table 9. All samples were collected at the participating medical research centers.
Outcomes	The study outcomes were predefined in the protocol and statistical analysis plan before the study database lock. The primary study objective was non-inferiority of tirzepatide 10 mg or 15 mg, or both, compared with insulin glargine, for mean change in HbA1c from baseline at Week 40 at a non-inferiority margin (NIM) of 0.4%. Key secondary objectives, controlled for type I error, were to demonstrate: non-inferiority of tirzepatide 5 mg vs insulin glargine for mean change in HbA1c from baseline at Week 40; superiority of each tirzepatide dose vs insulin glargine for weight loss from baseline at Week 40; superiority of each tirzepatide dose vs insulin glargine for mean change in HbA1c from baseline at Week 40; and superiority of each tirzepatide dose vs insulin glargine for the proportion of patients achieving HbA1c <7.0% at Week 40. HbA1c was analyzed using BioRad Variant II. Fasting serum glucose, lipids, pancreatic amylase, lipase and hepatic enzymes were analyzed using Roche Cobas c501. All of these tests were performed by central laboratories (Q Squared Solutions, Beijing, China, for samples collected from China, and Q Squared Solutions, Singapore, for samples collected from the other countries). Weight and waist circumference were measured at fasting visits at the research centers.