nature portfolio

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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	NA
Data analysis	All analytics and visualizations carried out in Python 3.11 with the following packages: numpy==1.26.4 pandas==2.2.3 scipy==1.12.0 statsmodels==0.14.2 plotly==5.23.0 gseapy==1.1.9 In addition see the custom `proteoclock` library (v 1.0.0) developed specifically for this submission: https://github.com/Insilico-org/proteoclock

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

Proteomic data generated in this study have been deposited in the China National Center for Bioinformation (CNCB) database under accession number OMIX008341 (https://ngdc.cncb.ac.cn/omix/release/OMIX008341). This dataset may be paired with anonymized predictions from Table S2 by following the instructions in the table legend.

This dataset was originally generated as part of the official phase-2a clinical trial NCT05938920. More information about the original trial is available in the published trial report paper: https://www.nature.com/articles/s41591-025-03743-2

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	Table S1 features the cohort-level description of the sex/gender composition of the 42 study participants.
Reporting on race, ethnicity, or other socially relevant groupings	All study participants are reported to be of Asian race, as per table S1. The trial has been conducted in 22 Chinese locations.
Population characteristics	Table S1 also provides cohort-level overview of age, BMI, and adverse events. Individual-level age is reported for all participants.
Recruitment	This phase 2a, multicenter, double-blind, placebo-controlled, randomized, multidose trial of rentosertib in adults with IPF was performed at 22 sites across China beginning 19 July 2023 and running through 11 June 2024. All patients satisfying the following criteria were included in the study: # Inclusion Criteria: - Male or female patients aged ≥40 years based on the date of the written informed consent form - Diagnosis of IPF as defined by American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines - In a stable condition and suitable for study participation based on the results of medical history, physical examination, vital signs, 12-lead ECG, and laboratory evaluation - Subjects with background pirfenidone or nintedanib may be enrolled if their regimen of antifibrotic therapy has been stable for > 8 weeks prior to Visit 1 - Meeting all of the following criteria during the screening period: a. FVC ≥40% predicted of normal b. DLCO corrected for Hgb ≥25% and ≤80% predicted of normal. c. forced expiratory volume in the first second/FVC (FEV1/FVC) ratio >0.7 based on pre-bronchodilator value # Exclusion Criteria: - Acute IPF exacerbation within 4 months prior to Visit 1 and/or during the screening period, as determined by the investigator - Patients who are unwilling to refrain from smoking within 3 months prior to screening and until the end of the study - Female patients who are pregnant or nursing - Abnormal ECG findings See full details of trial recruitment here: https://clinicaltrials.gov/study/NCT05938920
Ethics oversight	The trial was conducted following the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice guidelines. Institutional review boards at participating centers approved the protocol, and all patients provided written informed consent. Trial management and data processing were conducted by Fortrea Clinical Pharmacology Services (Leeds, UK). All participants, investigators, and analysts remained blinded to treatment assignments until data freeze. See full details on trial design in the original trial report [https://www.nature.com/articles/s41591-025-03743-2] The following ethics committees and review boards at recruiting institutions approved this trial: The Drug Clinical Trials Ethic Review Committee of Peking Union Medical College Hospital; The Medical Ethic Committee of Sichuan University; The Dug Research Ethic Committee of The Second Hospital of Anhui Medical University; The Ethic Committee of Shanghai Chest Hospital; The Ethic Committee of Shengjing Hospital of China Medical University; The Drug, Device and New Medical Technology Ethic Committee of The First Affiliated Hospital, Sun Yat-sen University; The Ethic Committee of Tianjin Medical University General Hospital; The Ethic Committee of Shanghai Pulmonary Hospital; The Medical Ethic Committee of Jiangxi Provincial People's Hospital; The Life Ethic Committee of Beijing Friendship Hospital, Capital Medical University; The Medical Ethic Committee of Nanfang Hospital of Southern Medical University; The Scientific Research and Clinical Trials Ethic Committee of First Affiliated Hospital of Zhengzhou University; The Medical Ethic Committee of Xiangya Hospital, Central South University; The Registration Popurse Clinical Trials Ethic Committee of The First Affiliated Hospital - Zhejiang University

School of Medicine; The Medical Ethic Committee of Zhongshan Hospital Fudan University; The Medical Ethic Committee of Hainan General Hospital; The Medical Ethic Committee of Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School; The Medical Ethic Committee of Peking University Shougang Hospital; The Clinical Trials Ethic Committee of Anhui Medical University - Anhui Chest Hospital; The Clinical Trials Medical Ethic Committee of Shanxi Academy of Medical Sciences - Shanxi Bethune Hospital (Shanxi Dayi Hospital); The Drug Clinical Trials Medical Ethic Committee of Qilu Hospital of Shandong University; The Medical Ethic Committee of The Second Xiangya Hospital of Central South University.

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	Adults with IPF were randomly assigned in a 1:1:1:1 ratio via interactive response technology to receive oral rentosertib at doses of 30 mg once daily (QD), 30 mg twice daily (BID), 60 mg once daily (QD), or placebo (QD) for 12 weeks, along with continued standard-of-care medications. An informed consent form for the proteomic assessment was offered to all 55 participants who completed the trial after its end. Among them, 43 signed the form in person and agreed to have their data included in the proteomic substudy. One participant was excluded from this study due to missing proteomic measurements at week-12 (end of trial). Full summary statistics (including sex, age, BMI, and adverse events) of the cohort are available in Table S1. This sample size was considered adequate after exploratory data analytics with multiple corrections passing statistical significance thresholds.
Data exclusions	The single exclusion from the OMIX008341 dataset is a patient from the 60 mg QD group with a missing week-12 OLINK measurement. This patient was excluded due to this incomplete entry not being directly comparable to all other included participants.
Replication	The validity of proteomic aging clock implementations was confirmed by using author-provided datasets and code review by members of corresponding research teams. Statistical tests were confirmed by multiple team members with various methodologies, including ANOVA for between-group pace-of-aging differences, LMEMs implemented in R. GSEA analytics were additionally carried out in GSEA App 4.4.0 for Windows desktop application, the software freely available on MSigDB website (https://www.gsea-msigdb.org/gsea/downloads.jsp). The methodology presented in the submission reflect the format deemed the most accessible to a general Nature reader by most authors. Python packages were selected as the primary reported methodology due to better compatibility with the used visualization solution, Plotly — a Python library.
Randomization	The participants of the original NCT05938920 trial were assigned to treatment arms at random.
Blinding	Participant group allocation was not hidden from investigators since treatment arm was the key studied covariate.

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	NCT05938920
Study protocol	https://cdn.clinicaltrials.gov/large-docs/20/NCT05938920/Prot_000.pdf
Data collection	The trial was conducted at 21 sites across China from July 19, 2023, through June 11, 2024. Adults with IPF were randomly assigned in a 1:1:1:1 ratio via interactive response technology to receive oral rentosertib at doses of 30 mg once daily (QD), 30 mg twice daily (BID), 60 mg once daily (QD), or placebo (QD) for 12 weeks, along with continued standard-of-care medications. Proteomic data to be submitted to CNCB was collected at baseline, week-2 and -4 of the trial, as well as at the end-of-trial (week-12).
Outcomes	Original outcome measures for this trial included the incidence of treatment-emergent adverse events and changes in lungs' forced vital capacity (FVC). The submitted study, however, constitutes an ancillary exploration of changes to participants' proteome in response to rentosertib.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*