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<br>*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<br>*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 software used to collect data. |
| Data analysis | Custom code to analyze proteomics data at https://codeocean.com/capsule/4095438/tree/v1.; PandaOmics (commercially available), R (v4.4.2), clusterProfiler R package (v4.13.4), lme4 R package (v1.1-35.5) |

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

Complete de-identified Olink proteomics data, demographics, and FVC data is deposited at the OMIX database at https://ngdc.cncb.ac.cn/omix/release/OMIX008341.

## 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 | Study cohort consisted of self-reported males and females, as listed in Table 1. Any bias in sex composition is reflective of incidence of IPF in the population. No sex- or gender-based analyses are reported. |
| Reporting on race, ethnicity, or other socially relevant groupings | The study participants are all of self-reported Asian race due to the study being conducted exclusively in China. This is listed in Table 1. |
| Population characteristics | Trial participants were all previously diagnosed with IPF as a criteria for inclusion. Patients were not excluded or included based on prior SOC antifibrotic therapy administration, but any concomitant antifibrotic use must have been stable for >8 weeks prior to screening. Patient mean age 66.7 (min 52, max 81, SD 6.7). Patient population was 90.1% male. Mean BMI 25.36 (min 16.3, max 33.9, SD 3.4). |
| Recruitment | Patients were recruited to the trial by site investigators. Prior to patient participation in the study, written informed consent was otained from each patient (or the patient's legally accepted representative) according to ICH-GCP standards and to the regulatory and legal requirements of the participating country. The investigator or delegate gave a full explanation to study patients based on the patient information form. A language understandable to the patient was chosen, technical terms and expressions avoided, if possible. Translation was provided where needed. The patient was given sufficient time to consider participation in the study. No self-selection or other bias was expected. |
| Ethics oversight | Each participating study institution was required to get approval from their Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international 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

# Life sciences study design

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

| | |
|---|---|
| Sample size | A target of 15 subjects was assigned to each treatment arm. . Approximately 70 patients will be enrolled to ensure approximately 60 patients complete treatment of 12 weeks. Given an approximate sample size of 15 subjects per treatment arm, there exists a 90% probability of observing at least 1 AE if the true population rate is approximately 15%, which is sufficient to assess the feasibility of safety parameters, the primary study objective. |
| Data exclusions | No data was excluded. One efficacy (FVC) analysis excluded n=1 patient from the placebo group and n=1 patient from the ISM001-055 30 mg QD group who exhibited >600 mL difference between screening and baseline FVC measurements, making uncertain the baseline FVC values in those patients. This is made clear in the Extended Data figure in which the analysis is shown. |
| Replication | Not applicable to phase 2a clinical trial data. Exploratory proteomics analyses not repeated due to limited biological material and cohort size. |
| Randomization | Patients were randomized 1:1:1:1 to each treatment arm. |
| Blinding | Subjects, investigators, site study staff, reviewers, and everyone involved in study conduct or analysis, were blinded with regard to the randomized treatment assignments until after data freeze. Bioanalytics staff were allowed to identify samples from subjects assigned to placebo treatment but did not disclose randomization until trial unblinding. |

# 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 | Study protocol will be made available with publication. |
| Data collection | The trial was conducted at 21 sites across China beginning July 19, 2023, and running through June 11, 2024.<br>Participating study sites:<br>Anhui Chest Hospital, Hefei, Anhui, China, 230031<br>The Second Affiliated Hospital of Anhui Medical University,Hefei, Anhui, China, 230601<br>Peking University Shougang Hospital, Beijing, Beijing, China, 100041<br>Beijing Friendship Hospital, Capital Medical University, Beijing, Beijing, China, 100050<br>Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, Beijing, China, 100730<br>The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China, 510080<br>Nanfang Hospital of Southern Medical University, Guangzhou, Guangdong, China, 510515<br>Hainan General Hoapital, Haikou, Hainan, China, 570311<br>The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China, 450052<br>Xiangya Hospital of Central South University, Changsha, Hunan, China, 410008<br>The Second Xiangya Hospital of Central South University, Changsha, Hunan, China, 410011<br>Nanjing Drum Tower Hospital, Nanjing, Jiangsu, China, 210008<br>Jiangxi Provincial People's Hospital, Nanchang, Jiangxi, China, 330006<br>The Shengjing Hospital of China medical university, Shenyang, Liaoning, China, 110004<br>Qilu Hospital of Shandong University, Jinan, Shandong, China, 250013<br>Shanghai Chest Hospital, Shanghai, Shanghai, China, 200030<br>Zhongshan hospital Fudan University, Shanghai, Shanghai, China, 200032<br>Shanghai Pulmonary Hospital, Shanghai, Shanghai, China, 201800<br>Shanxi Bethune Hospital, Taiyuan, Shanxi, China, 030032<br>The West China Hospital of Sichuan University, Chengdu, Sichuan, China, 610041<br>General Hospital of Tianjin Medical University, Tianjin, Tianjin, China, 300052<br>The First Affiliated Hospital - Zhejiang University School of Medicine, Hangzhou, Zhejiang, China, 310006 |
| Outcomes | The primary objective of this study was to evaluate the safety and tolerability of orally administered ISM001-055 for up to 12 weeks in adult patients with IPF compared to placebo. The primary end point for this study was the percentage of patients who have at least 1 treatment-emergent adverse event (TEAE). Patients were continually monitored for AEs during the 12 weeks of rentosertib treatment and for one week following administration of the final dose, with study drug-related SAE and AESI collected if they occurred beyond the study period. Medical judgement of the site investigators was used to determine whether there was a reasonable possibility of a causal relationship between an AE and the given study treatment.<br><br>The secondary efficacy endpoints measured the relative and percent change in FVC from week 0/visit 2 up to week 12. The absolute and relative change in FVC % predicted from week 0/visit 2 up to week 12 was also measured. The change in DLCO % predicted from week 0/visit up to week 12 and, the change in Leicester Cough Questionnaire (LCQ) from week 0 to weeks 4, 8, and 12 were also analyzed. The change in 6-minute walk distance (6MWD) in meters from week 0 to week 12 was also evaluated. FVC and FEV1 measured at baseline/randomization with centrally sourced SpiroSphere devices (Clario) provided by the sponsor with study-specific training and proficiency tests to the operating staff to meet the 2019 ATS/ERS guideline criteria with central overread. DLCO measurements were all assessed with devices from each site according to the ATS/ERS guidelines, and all measurements were conducted with the same equipment for each site.<br><br>Other secondary end points included pharmacokinetic parameters of ISM001-055 and related metabolites following the first dose at visit 2 and the last dose at visit 6 (EOT) from blood samples drawn at weeks 0, 2, 4, 8, and 12. This study also collected data on the number of acute IPF exacerbations and the number of days hospitalized following acute IPF exacerbations from week 0 through week 12.<br><br>The Leicester Cough Questionnaire (LCQ) is a 19-item questionnaire that assesses cough related QOL taken at weeks 0, 4, 8, and 12.<br><br>The exploratory end points analyzed include the change in IPF blood biomarkers following ISM001-055 treatment at weeks 0, 2, 4, 8, |

and 12. Changes in the blood proteome in treated patients were also measured at these time points.

## 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.*