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Reporting Summary

Nature Research 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 Research 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 software was used to collect data
Data analysis	Graphpad Prism v9.2, R v4.05

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 Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

All data are available upon request to the corresponding author.

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 primary objective of the study was to identify a safe and infectious dose of wild type SARS-CoV-2 in healthy volunteers, suitable for future intervention studies. No formal sample size calculation was therefore performed for this early-stage dose finding study. However, a sample size of up to an expected 30 subjects for a dose level and treatment regimen was felt sufficient to meet the primary objective of escalating/expanding the dose in a safe manner whilst providing information on the attack rate.
Data exclusions	Two virology datapoints were invalidated due to laboratory error. These are indicated in the manuscript. No other data were excluded from the analysis
Replication	The study took place over 5 distinct quarantine groups with similar findings across all studies
Randomization	None; all subjects enrolled into the study were inoculated with challenge virus in this open-label study
Blinding	Study participants, laboratory and clinical staff were blinded to virological outcome where possible until results or protocol-defined procedures made this apparent.

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
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

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

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Vero cells purchased from the European collection of authenticated cell cultures (ECACC)
Authentication	Vero cells were authenticated and quality controlled by the supplier
Mycoplasma contamination	Vero cells were tested negative for Mycoplasma by culture isolation, Hoechst DNA staining and PCR
Commonly misidentified lines (See ICLAC register)	N/A

Human research participants

Policy information about studies involving human research participants

Population characteristics	Sero-suitable (no evidence of COVID 19 infection or previous vaccination) healthy male and female volunteers 18-30 years of age (inclusive) with no known risk factors for severe COVID-19
Recruitment	Screening of potential participants took place in two stages with an initial screening visit, followed by a study specific remote consultation to go through the full study participant information following adequate time for the informed consent form (ICF)

and participation in the study to be considered. Screening visits took place between Day -90 to Day -2. Potential participants were screened under a separate study-specific screening protocol using a screening ICF and advertising material that was approved by the Research Ethics Committee (REC) and Health Research Authority (HRA). Screening activities under the separate screening protocol continued up until subjects sign the study specific consent. Recruitment was done through a number of channels:
- Approved advertising, including social media
- hVIVO volunteer database (Volunteers already registered with any other hVIVO database may be contacted to determine their interest in participating in SARS-CoV-2 research.)
- Referral
- Organic search (e.g. via Google or other search engines)

Ethics oversight

This study was conducted in accordance with the protocol, the Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable ICH Good Clinical Practice guidelines, applicable laws and regulations. The screening protocol and main study were approved by the UK Health Research Authority – Ad Hoc Specialist Ethics Committee (reference: 20/UK/2001 and 20/UK/0002).

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

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

Clinicaltrials.gov NCT04865237

Study protocol

Following acceptance of the manuscript we will upload the protocol to the protocol exchange portal

Data collection

The study was conducted in one locale
Data collection occurred at:
Study specific screening Day -90 to Day -2
Quarantine Phase Day -2 to Day 14 (+ extended days)
Follow up visits Day 28 (+/-3 days), Day 90 (+/- 7 days), Day 180 (+/- 14 days), Day 270 (+/- 14 days) and Day 360 (+/- 14 days)

Outcomes

Primary Objective /Endpoint
- To identify a safe and infectious dose of wild type SARS-CoV-2 in healthy volunteers, suitable for future intervention studies, that:
- has an acceptable safety profile as measured by:
  - o Occurrence of Adverse Events (AEs) within 30 days post-viral challenge (Day 0) up to Day 28 follow up.
  - o Occurrence of Serious Adverse Events (SAEs) from the viral challenge (Day 0) up to Day 28 follow up.
- induces laboratory confirmed infection in ≥50% of participants (ideally between 50% and 70%). Laboratory confirmed infection is defined by:
  - o Two quantifiable greater than lower limit of quantification (viral load ≥LLOQ) RT-PCR measurements from mid turbinate and/or throat samples, reported on 2 or more consecutive timepoints, starting from 24 hours post-inoculation and up to discharge from quarantine.

Secondary
Objectives/endpoint
- To further assess SARS-CoV-2 viral infection rates in upper respiratory samples by qRT-PCR and cell culture
- To assess the incidence of symptomatic SARS-CoV-2 infection
- To assess the SARS-CoV-2 viral dynamics in upper respiratory samples (AUC, peak, duration, incubation period)
- To assess the SARS-CoV-2 induced symptoms (Sum, AUC, peak, peak daily, frequency)
- To assess the incidence of SARS-CoV-2 illness (Upper Respiratory Tract illness [URTI], Lower Respiratory Tract illness [LRTI], Systemic Illness (SI), Febrile Illness [FI], grade 1, 2 & 3 symptoms)

Exploratory/Tertiary
Objectives /
Endpoints
- To explore the safety of the wild type SARS-CoV-2 human challenge model (smell, cognition, pulmonary changes [CT, spirometry, FOT], safety laboratory tests, blood type, concomitant medications)
- To explore SARS-CoV-2 viral infection rates in saliva, by qRTPCR and cell culture

- To explore the SARS-CoV-2 viral dynamics in saliva, by qRT-PCR and cell culture (AUC, peak, duration, incubation period)
- To explore the host-pathogen relationship in the SARS-CoV-2 human challenge model (including humoral and cellular immunity, proteomics, transcriptomics, host and viral genomics, microbiome and systems biology)
- To explore the Minimal Clinically Important Difference (MCID) in instrument change (e.g. Symptom diary cards)
- To explore environmental contamination in the SARS-CoV-2 human challenge model (quantitation and detection of virus in air sampling, exhaled breath and surface swabbing)