nature portfolio

Corresponding author(s): Jonathan Li

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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 software was used for data collection.
Data analysis	Statistical analysis was performed using GraphPad Prism 9.1.1. The following software was used for sequence assembly and minority variant analysis: PaSeq v1.4 (paseq.org), Trimmomatic v0.30, BBSplit v35.76, pear v0.9.6, and Bowtie2 v2.1.0. Pharmacokinetic parameter estimation was performed using WinNonLin. Mathematical modeling of resistance mutant fitness was performed using the R programming language.

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 authors confirm that all data underlying the findings are fully available. Due to ethical restrictions, study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group and the manufacturer of the investigational product.

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 current study includes all participants of the phase 2 bamlanivimab protocol of A5401/ACTIV-2. Sample size determination is detailed in the study protocol, which is included as a supplement to this manuscript.
Data exclusions	*Describe any data exclusions. If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*
Replication	Sequencing and viral load results from respiratory samples were confirmed through sampling both nasopharyngeal swabs and anterior nasal swabs. Serum samples were run in duplicate for detection of IgG antibodies. The quantitative viral load assay is EUA authorized and passed all external proficiency testing. All attempts at replication were successful.
Randomization	The 7000mg treatment group was enrolled first, followed by the 700mg treatment group. After enrollment, participants were randomly assigned by a web-based interactive response system in a 1:1 ratio to receive either bamlanivimab or placebo. Randomization was stratified by time from symptom onset (<= or >5 days) and risk of progression to severe COVID-19 ("higher" vs "lower"). "Higher" risk was defined in the protocol as meeting any of the following: age >=55 years or having a comorbidity (chronic lung disease or moderate to severe asthma, body mass index >35 kg/m2, hypertension, cardiovascular disease, diabetes, or chronic kidney or liver disease).
Blinding	Investigators were blinded during the sample collection and assay performance.

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

Antibodies

Antibodies used	The MSD SULFO-TAG anti-Human IgG antibody (Meso Scale Diagnostics, Rockville, MD; catalog # K15359U) was used to detect anti-SARS-CoV-2 spike, receptor binding domain, N-terminal domain, and nucleocapsid IgG. MSD SULFO-TAG anti-IgG antibody is provided as a 200X stock solution that is diluted to a 1X solution.
Validation	The MSD SULFO-TAG anti-Human IgG was reported by the manufacturer (Meso Scale Diagnostics, Rockville, MD) to be validated for use in their V-Plex SARS-CoV-2 serology panels (catalog # K15359U). Serology reference standard 1 for assay calibration and three control serums consisting of specific concentrations of human IgG recognizing antigens in the multiplex assay (lot-specific certifications at www.msd.com) are provided with the MSD kit. References using this technology: Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans Galit Alter, Jingyou Yu, Jinyan Liu, Abishek Chandrashekar, Erica N Borducchi, Lisa H Tostanoski, Katherine McMahan, Catherine Jacob-Dolan, David R Martinez, Aiquan Chang, Tochi Anioke, Michelle Lifton, Joseph Nkolola, Kathryn E Stephenson, Caroline Atyeo, Sally Shin, Paul Fields, Ian Kaplan, Harlan Robins, Fatima Amanat, Florian Krammer, Ralph S Baric, Mathieu Le Gars, Jerald Sadoff, Anne Marit de Groot, Dirk Heerwegh, Frank Struyf, Macaya Douoguih, Johan van Hoof, Hanneke Schuitemaker, Dan H Barouch

Evaluation of a novel multiplexed assay for determining IgG levels and functional activity to SARS-CoV-2
Marina Johnson, Helen R. Wagstaffe, Kimberly C. Gilmour, Annabelle Lea Mai, Joanna Lewis, Adam Hunt, Jake Sirr, Christopher Bengt, Louis Grandjean, David Goldblatt
Journal of Clinical Virology
2020
Nature
2021
Two doses of SARS-CoV-2 vaccination induce robust immune responses to emerging SARS-CoV-2 variants of concern
Donal T. Skelly, Adam C. Harding, Javier Gilbert-Jaramillo, Michael L. Knight, Stephanie Longet, Anthony Brown, Sandra Adele, Emily Adland, Helen Brown, Medawar Laboratory Team, Tom Tipton, Lizzie Stafford, Alexander J. Mentzer, Síle A. Johnson, Ali Amini, OPTIC (Oxford Protective T cell Immunology for COVID-19) Clinical Group, Tiong Kit Tan, Lisa Schimanski, Kuan-Ying A. Huang, Pramila Rijal, PITCH (Protective Immunity T cells in Health Care Worker) Study Group, C-MORE/PHOSP-C Group, John Frater, Philip Goulder, Christopher P. Conlon, Katie Jeffery, Christina Dold, Andrew J. Pollard, Alex Sigal, Tulio de Oliveira, Alain R. Townsend, Paul Klenerman, Susanna J. Dunachie, Eleanor Barnes, Miles W. Carroll & William S. James

Coronavirus-Specific Antibody Cross Reactivity in Rhesus Macaques Following SARS-CoV-2 Vaccination and Infection
Catherine Jacob-Dolan, Jared Feldman, Katherine McMahan, Jingyou Yu, Roland Zahn, Frank Wegmann, Hanneke Schuitemaker, Aaron G Schmidt, Dan H Barouch
Journal of Virology
2021

Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans
Galit Alter, Jingyou Yu, Jinyan Liu, Abishek Chandrashekar, Erica N Borducchi, Lisa H Tostanoski, Katherine McMahan, Catherine Jacob-Dolan, David R Martinez, Aiquan Chang, Tochi Anioke, Michelle Lifton, Joseph Nkolola, Kathryn E Stephenson, Caroline Atyeo, Sally Shin, Paul Fields, Ian Kaplan, Harlan Robins, Fatima Amanat, Florian Krammer, Ralph S Baric, Mathieu Le Gars, Jerald Sadoff, Anne Marit de Groot, Dirk Heerwegh, Frank Struyf, Macaya Douoguih, Johan van Hoof, Hanneke Schuitemaker, Dan H Barouch
Nature
2021
Nature Communications
2021

Human research participants

Policy information about studies involving human research participants

Population characteristics	Participant characteristics are described in Table 1.
Recruitment	Participants were recruited through a variety of mechanisms including a study-specific website with IRB-approved content describing the study. The website listed a telephone number that connected to a 24 hour call center staffed by English and Spanish speaking operators who followed an IRB-approved script to pre-screen callers for basic eligibility (e.g., recent diagnosis of COVID-19, age of 18 and older) and then connected callers to the nearest study site. In addition, digital marketing was conducted using the paid search services of the Google search engine such that IRB-approved advertisements for the trial were displayed when searching key words (e.g., COVID-19 treatment, COVID-19 treatment trial). IRB-approved study advertisements were also placed periodically on Facebook and Instagram. Persons testing COVID-19 positive at testing venues associated with the clinical laboratories Covance and Quest, operated by eTrueNorth Inc, or partnered with Verily Life Sciences or the PPD Accelerated Enrollment Solutions (AES) and who opted-in to receive information regarding research opportunities received IRB-approved messages or calls describing the study. Study sites also conducted their own outreach including the circulation of IRB-approved brochures, postcards, and flyers at COVID-19 testing centers. Lastly, the trial was listed on the NIH-operated public access website www.clinicaltrials.gov. Participant compensation varied by site and was approved prior to participant accrual by central and/or local IRBs and ECs, as required for each site.
Ethics oversight	Study protocol approval and ethical oversight was performed by a central Institutional Review Board (Advarra, Inc.).

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 ICMJEguidelines for publication of clinical research and a completedCONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04518410
Study protocol	The study protocol is provided as a supplement to this manuscript.
Data collection	Participants were enrolled and data was collected at multiple sites within in the United States. A full list of participating sites and investigators is included as a supplement to this manuscript. 94 participants were enrolled in the 7000mg cohort between August 2020 and October 2020, and 223 participants were enrolled in the 700mg cohort between October 2020 and November 2020. Respiratory sampling was performed up to 28 days after study entry. Blood draws for serological profiling were performed at study entry as well as 28 days and 12 weeks after study entry.

Outcomes	This paper is reporting on two of the trial's exploratory outcomes: to explore baseline and emergent viral resistance to the investigational agent and to explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents. These measures were assessed through targeted S gene next generation sequencing of patient respiratory samples to detect baseline and emergent drug resistance and relating these sequencing results to patient viral loads and symptom scores.