Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Material:

Title: Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa

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Author contributions

SAM & AJP conceived the trial, SAM is the national principal investigator. SAM, AI, CLC, GK, VB and AJP contributed to the protocol and design of the study. SAM, AI, CLC, GK, VB, ALK, CT were responsible for the design and conduct of the trial, database design and development, site selection and training, data collection, data cleaning and interpretation of results.

AI, MV conducted the statistical analysis.

SG designed the vaccine and reviewed manuscript.

SLB, QEB, CB, KD, LF, ALK and SDP are study site principal investigators and enrolled participants, collected data and contributed to manuscript preparation.

KA, SB, AEB, AE, MG, CH, EH, AJ, MM, MaM, MdM, KM, SO, FP, LR, CT, AT, SvE contributed to the implementation of the study at sites and/or data collection.

JNB, SH, SP, HR, HT, CKW, JG, TH, PK, LM, TM, YN and BO contributed to data generation and analysis. ML, JdP, SK, AM, SM, ML, JdP, NMD, EJK contributed to sample processing, data generation and analysis.

SAM, AI, CLC, VB, GK, PLM, AS, TdO, TLV, AP contributed to the preparation of the report.

All authors critically reviewed and approved the final version of the manuscript.

Ethics, regulatory and trial registration details

The trial was reviewed and approved by:

- South African Health Products Regulatory Authority (SAHPRA, ref 20200407),
- Human Research Ethics Committee of the University of the Witwatersrand (ref 200501),
- Human Research Ethics Committee of the University of Cape Town (ref 350/2020),
- Human Research Ethics Committee of the University Stellenbosch (ref M20/06/009_COVID-19)
- Oxford Tropical Research Ethics Committee (OxTREC, ref 35-20)

The trial was registered on

- Clinicaltrials.gov (NCT04444674)
- Pan African Clinical Trials registry (PACTR202006922165132).

1.1. Study inclusion and exclusion criteria:

Inclusion Criteria

The participants must satisfy all the following criteria to be eligible for the trial:

- Healthy adults aged 18-65 years.
- Documented result of not being infected with HIV (including screening by a rapid HIV antibody test) within two weeks of randomization into the study for Group-1 and Group-2 participants only.
- Able and willing (in the Investigator's opinion) to comply with all study requirements.
- Willing to allow investigators review available medical records, and review all medical and laboratory records if participant is admitted to hospital with respiratory tract infection suspected or confirmed to be COVID-19.
- For females only, willingness to practice continuous effective contraception (see below) during the study and a negative pregnancy test on the day(s) of screening (within 14 days of randomization) or vaccination.
- For Group-3 only (i.e. HIV-infected), need to have been on anti-retroviral treatment for at least three months and HIV-1 viral load is <1,000 copies/ml within two weeks of randomization.
- Agreement to refrain from blood donation during the course of the study.
- Provide written informed consent.

Exclusion Criteria

The participant may not enter the study if any of the following apply:

- Planned receipt of any vaccine other (licensed or investigational) than the study intervention within 30 days before and after each study vaccination.
- Use of any unproven registered and unregistered treatments for COVID-19.
- Evidence of current SARS-CoV-2 infection detected by molecular assay detection of SARS-CoV-2 done within 96 hours prior to randomization.
- Acute respiratory and/or non-respiratory illness consistent with potential COVID-19 (see Supplementary Table S1 for list of symptoms) concurrent or within 14 days prior to first study vaccination (medical history and/or physical examination) or documented temperature of > 38°C during this period. NOTE: This was a temporary exclusion for which the subject may be re-evaluated if they remain free from acute respiratory and/or non-respiratory illness consistent with potential COVID-19 after 14 days. Should a subject have a SARS-CoV-2 positive test, they may NOT be randomized.
- Prior receipt of an investigational or licensed vaccine likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines).
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate.
- HbSAg positivity on the screening sample, or any sample obtained within three months of randomization.
- Grade 2 or higher level of abnormality for FBC, U&E or LFT based on DAIDS Grading Criteria (Version 2.1, July 2017).

- History of allergic disease or reactions likely to be exacerbated by any component of the ChAdOx1 nCoV-19 vaccine.
- Any history of hereditary angioedema or idiopathic angioedema.
- Any history of anaphylaxis in relation to vaccination.
- Pregnancy, lactation or willingness/intention to become pregnant during the study.
- History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
- History of serious psychiatric condition likely to affect participation in the study.
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
- Any other serious chronic illness requiring hospital specialist supervision.
- Chronic respiratory diseases, including poorly controlled/ unstable asthma.
- Chronic disease inclusive of: a) hypertension if ≥Grade 2 based on DAIDS AE Grading Version 2.1-July 2017; b) congestive heart failure; c) chronic obstructive pulmonary disease by Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of ≥ 2; d) evidence of coronary artery disease as manifested by cardiac interventions or cardiac medications for control of symptoms; e) chronic type 2 diabetes (adult onset) requiring insulin; f) chronic kidney disease/renal insufficiency; g) chronic gastrointestinal and hepatic diseases; or h) chronic neurological diseases.
- Seriously overweight (BMI ≥ 40 Kg/m^2).
- Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week (% alcohol x volume (ml)/1000= number of units; e.g. Normal beer= 2 units, Glass of wine =3 units).
- Suspected or known injecting drug abuse in the 5 years preceding enrolment.
- Any clinically significant abnormal finding on screening urinalysis.
- Any other significant disease, disorder or finding which may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study or impair interpretation of the study data.
- History of laboratory confirmed COVID-19 illness or known close contact with a person that was infected with SARS-COV-2. Close contact refers to being in contact with someone in the same household, or for at least 15 minutes and in close proximity with an infected person in the absence of wearing of face masks.
- New onset of fever or a cough or shortness of breath in the 30 days preceding screening and/or enrolment.
- In addition to above, Group 1 & 2 participants need to fulfil the following exclusion criteria: Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; recurrent severe infections and chronic use (more than 14 days) immunosuppressant medication within the past 6 months (topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient state (except HIV infection for Group-3), asplenia, recurrent severe infections and chronic use (more than 14 days) immunosuppressant medication within the

past 6 months (topical steroids are allowed).

Note: Stable endocrine disorders that have a confirmed autoimmune etiology (eg, thyroid, pancreatic), including stable diabetes not requiring insulin are allowed.
Should participants develop COVID-19 prior to the booster dose of vaccine, or test positive for SARS-CoV-2 infection and be asymptomatic, the participants will remain eligible to receive a booster dose of assigned study-intervention. The booster dose of assigned study-drug will however be delayed for at least: i. 14 days in individuals that had asymptomatic SARS-CoV-2 infection, ii. 14 days after symptom resolution if mild illness; iii. 28 days after illness onset following moderate or severe illness, and is clinically stable based on the discretion of the investigator; iv. For cases requiring hospitalization for COVID-19, the 2nd dose should be delayed for at least 14 days post-discharge and participant needs to be clinically stable.

Re-vaccination exclusion criteria
The following AEs associated with any vaccine, or identified on or before the day of vaccination, constitute absolute contraindications to further administration of an IP to the participant in question. If any of these events occur during the study, the participant will continue follow-up in the study but will not receive any further study investigational vaccine: Anaphylactic reaction following administration of vaccine and Pregnancy.

1.2. ChaOx1 nCoV (AZD1222) vaccine supply for South African study

The vaccine used in the South Africa was manufactured and vialed by Advent (Pomezia, Italy), and additional batches produced by COBRA Biologics (Keele, UK) and vialed by Symbiosis (Sterling, UK). Both were manufactured according to Good Manufacturing Practice and approved by the UK Medicines and Healthcare products Regulatory Agency regulatory agency.[1,2] Inadvertently, 44 participants received a low dose ($2.2x10^{10}$vp) vaccine (21 as first and 23 as the booster dose) resulting from variability in the release assay characterization of concentration as detailed in the protocol (Appendix 1; pg 77-80).[1,2]

1.3. Safety and reactogenicity evaluation

Safety data for participants who received at least one dose of vaccine or placebo are included in this report. Participants were trained on how to complete a paper post-vaccination diary card, use a thermometer at enrolment and requested to complete the diary card for 7 days post each injection. Additionally, participants received a paper illness diary card, which was completed if they experienced any pre-specified Covid-19-related symptoms or if they tested positive for SARS-CoV-2 by nucleic acid amplification test (NAAT) anytime during the course of study participation. Participants attended trial clinic visits for any suspected Covid-19 illnesses, and informed trial staff of any adverse events or hospitalizations.

All adverse events were assessed by site PI-delegated clinician for relationship to vaccination, and protocol-specified safety group holding rules (for solicited local or systemic, unsolicited or laboratory adverse events; >25% of participants had grade 3; vaccination-related SAEs) and individual stopping rules (significant local reactions, grade 3 laboratory AEs or systemic solicited or unsolicited AEs, vaccination-related SAEs) were implemented. The Division of

AIDS (DAIDS) AE Grading Version 2.1-July 2017 was used for scoring of adverse event severity.

1.4. SARS-CoV-2 testing, whole genome sequencing and genome assembly

SARS-CoV-19 nucleic acid amplification test (NAAT) testing

All NAAT testing was done at one of two study-site laboratories, Vaccines and Infectious Diseases Analytics Research Unit (VIDA, Johannesburg) or University of Cape Town Lung Institute (Cape Town, South Africa). The same assay was employed at both sites as detailed.[3,4] Nasopharyngeal swabs taken for NAAT were tested for the presence of SARS-CoV-2 using Emergency Use Authorization assays developed by the Centres for Diseases Control and Prevention (CDC) which target two regions within the nucleocapsid gene and a third assay which detects the human RNase P gene.[3,4] Results were classified as positive for SARS-CoV-2 when both the N1 and N2 targets of the nucleocapsid gene were detected and cycle threshold (Ct) values were <40. Results were classified as inconclusive if only N1 or N2 was detected with Ct values <40. If a repeat swab test tested inconclusive, the participant considered to be infected with SARS-CoV-2. In order for negative results to be valid, the human RNase P assay needed to be detected with a cycle threshold <40.

Whole genome sequencing

Whole genome sequencing of samples from cases contributing to the primary endpoint were done either at VIDA or the KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP).

Superscript IV with random hexamers (Life Technologies, Carlsbad, CA) were used to generate cDNA from SARS-CoV-2 NAAT confirmed NP samples. The Swift Biosciences' Normalase Amplicon and SARS-CoV-2 amplicon panel were used to amplify, and index paired end libraries of genomic DNA according to manufacturers' instructions.[5] The resulting libraries were sequenced using a 300 cycle v2 iSeq 100 Reagent Kit on an illumina iSeq 100 instrument (Illumina, San Diego, CA, USA). The ARCTIC V3 protocol[6-8] and Illumina® Nextera Flex DNA Library Prep kits were also used to sequence, and index paired end libraries of genomic DNA according to manufacturers' instructions. These libraries were sequenced on a 500 cycle v2 MiSeq Reagent Kit on an Illumina MiSeq instrument (Illumina, San Diego, CA, USA).

Genome assembly

Genome Detective 1.126 (https://www.genomedetective.com) and the Coronavirus Typing Tool were used to generate paired-end fastq reads [9]. Low-quality mutations were filtered out of the initial assembly generated from Genome Detective using bcftools 1.7-2 mpileup method and all the sequences were deposited in GISAID (https://www.gisaid.org/), Supplementary Table S7.

Phylogenetic analysis methods

Prior to phylogenetic analysis, ten of the genomes were filtered out due to low genome coverage (77%-<90%); thus, we analyzed 30 South African whole genomes against the global reference dataset (N=2592) using a custom pipeline based on a local version of NextStrain. The pipeline contains several python scripts that manage the analysis workflow. It performs alignment of genotypes in MAFFT, phylogenetic tree inference in IQ-Tree20, tree dating and

ancestral state construction and annotation(https://github.com/nextstrain/ncov). For the new variant identified in South Africa in this study, we have assigned it the name 501Y.V2; the corresponding PANGO lineage classification is B.1.351 (lineages version 2021-01-06).[10]

1.5 Methods for pseudovirus and live virus neutralization assays

Validated pseudovirus neutralization assay

A lentivirus-based SARS-CoV-2 pseudovirus system generated expressing a non-B.1.351 Spike protein on the surface (Accession number: MN908947.3) was performed at a single laboratory, Monogram Biosciences, South San Francisco, USA. Briefly, neutralizing antibody activity is measured by assessing the inhibition of luciferase activity in HEK293 target cells expressing the ACE2 receptor, following preincubation of the pseudovirions with serial dilutions of the serum specimen. The expression of luciferase activity in target cells is inhibited in the presence of anti-SARS CoV-2 nAb. Titres are reported as the reciprocal of the serum dilution conferring 50% inhibition (ID50) of pseudovirus infection. To ensure that the measured nAb activity is SARS CoV-2 nAb specific, each test specimen is also assessed using a non-specific pseudovirus (specificity control) that expresses a nonreactive envelope protein of one or more unrelated viruses (eg, avian influenza virus). Method validation included accuracy, repeatability, intermediate precision, and linearity.

Lentiviral pseudovirus production and neutralization assay against B.1.351

293T/ACE2.MF[11] cells modified to overexpress human ACE2 were kindly provided by Dr Mike Farzan, Scripps Research. Cells were cultured in DMEM (Gibco BRL Life Technologies) containing 10% heat-inactivated FBS and 3 µg/mL puromycin at 37°C, 5% CO_2. Cell monolayers were disrupted at confluency by treatment with 0.25% trypsin in 1 mM EDTA (Gibco BRL Life Technologies). The SARS-CoV-2, Wuhan-1 spike, cloned into pCDNA3.1 was mutated using the QuikChange Lightning Site-Directed Mutagenesis Kit (Agilent Technologies) to include D614G (original) or K417N, E484K, N501Y, D614G (RBD only) or L18F, D80A, D215G, Δ242-244, K417N, E484K, N501Y, D614G, A701V (501Y.V2). Pseudoviruses were produced by co-transfection with a lentiviral backbone (HIV-1 pNL4.luc encoding the firefly luciferase gene) and either of the SARS-CoV-2 spike plasmids with PEIMAX (Polysicences). Culture supernatants were clarified of cells by 0.45µM filter and stored at -70°C. Plasma/serum samples were heat-inactivated and clarified by centrifugation. Pseudovirus and serially diluted plasma/sera were incubated for 1 hour at 37°C, 5% CO_2. Cells were added at $1x10^4$ cells per well after 72 hours incubation at 37°C, 5% CO_2, luminescence was measured using PerlinElmer Life Sciences Model Victor X luminometer. Neutralization was measured as described by a reduction in luciferase gene expression after single-round infection of 293T/ACE2.MF cells with spike-pseudotyped viruses. Titers were calculated as the reciprocal plasma dilution (ID50) causing 50% reduction of relative light units (RLU). Equivalency was established through participation in the SARS-CoV-2 Neutralizing Assay Concordance Survey (SNACS) Concordance Survey 1 (CS1) run by EQAPOL and VQU, Duke Human Vaccine Institute.

Live Virus Neutralization Assay against B.1.351

The B.1.351 (isolate 501Y.V2.HV001) and B.1.1 isolate (CoV.V003) were derived as previously described [12]. The LVNA tested a B1.1 D614G variant outgrown from a sample obtained during the first wave of the Covid-19 outbreak in South Africa; and a B.1.351 variant

with eight spike mutations including L18F, K417N, E484K, N501Y and the 242-244 deletion.[11,12]

For the focus forming assay to test neutralization, Vero E6 cells were plated in a 96 well plate (Eppendorf) at 30,000 cells per well 1 day pre-infection. Plasma was separated from EDTA-anticoagulated blood by centrifugation at 500 rcf for 10 minutes and stored at -80C. For experiments, plasma was serially diluted two-fold from 1:50 to 1:3200. Virus stocks were used at approximately 50 focus-forming units (FFU) per microwell ($2.5x10^4$ FFU/mL) and added to diluted plasma; antibody-virus mixtures were incubated for 1 hour at 37C, 5% CO_2. Cells were infected with 100µL of the virus-antibody mixtures, to allow adsorption of virus. Subsequently, 100µL of a 1x RPMI 1640 (Sigma-Aldrich R6504), 1.5% carboxymethylcellulose (Sigma-Aldrich C4888) overlay was added to the wells without removing the inoculum. Cells were fixed as follows: For 501Y.V2.HV001, due to the large focus size, infected cells were fixed at 18 hours post-infection using 4% paraformaldehyde (Sigma-Aldrich) for 20 minutes. For CoV.V003, fixation was at 24 hours. For staining of foci, a rabbit anti-Spike monoclonal antibody (mAb BS-R2B12, GenScript A02058) was used at 0.5µg/mL as the primary detection antibody. Antibody was resuspended in a permiabilization buffer containing 0.1% saponin (Sigma-Aldrich), 0.1% BSA (Sigma-Aldrich), and 0.05% tween (Sigma-Aldrich) in PBS. Plates were incubated with primary antibody overnight at 4C, then washed with wash buffer containing 0.05% tween in PBS. Secondary goat anti-rabbit horseradish peroxidase (Abcam ab205718) was added at 1 µg/mL and incubated for 2 hours at room temperature with shaking. The TrueBlue peroxidase substrate (SeraCare 5510-0030) was then added at 50µL per well and incubated for 20 minutes at room temperature. Plates were then dried for 2 hours and imaged using a Metamorph-controlled Nikon TiE motorized microscope with a 2x objective. Automated image analysis was performed using a Matlab2019b (Mathworks) custom script, where focus detection was automated and did not involve user curation. Image segmentation steps were stretching the image from minimum to maximum intensity, local Laplacian filtering, image complementation, thresholding and binarization.

To quantify neutralization, we fitted a sigmoidal function to the data and derived the reciprocal of the dilution at which 50% neutralization occurred (ID50).

1.6. Safety

Local and systemic elicited reactogenicity

Local and systemic reactogenicity data are presented in Supplementary Figures S3 and S4 and summarised in Supplementary Text 1.6. After the 1st injection, a higher proportion of vaccine-recipients experienced bruising, cough, feeling feverish, hardness, headache, joint pain, muscle pain, sweating tenderness and weakness at all severity levels compared to the placebo arm. Mild itching, mild cough and mild-moderate bruising were also reported amongst vaccine-recipients. Reactogenicity among vaccine-recipients was lower after the 2nd injection; with similar rates observed compared to after the 2nd injection in placebo participants; although a higher proportion of vaccine-recipients reported mild itching, joint and muscle pain and tenderness.

1.7. Pseudo-neutralization and live virus neutralization activity in full group of vaccine recipients

Testing on the PSVNA and LVNA, masked to study-arm assignment, was undertaken on sera from 25 (of 70 Group-1 participants) who were sero-negative for RBD IgG at randomization, but positive on RBD IgG 14 days post 2nd injection. Nineteen of the 25 were vaccine-recipients (including six who tested NAAT positive within 42 days of randomization), and six were placebo recipients (four who tested positive by NAAT) infected by SARS-CoV-2 between enrolment and Day 42. The high rate of infection among the Group-1 participants was likely due to enrolment coinciding with the peak of the first Covid-19 wave (Supplementary Figure 2).

Inclusive of the six vaccinees who had a reactive NAAT test between randomization and 42 days later, 47% (9/19) showed complete loss of neutralizing activity against the RDB-only mutant, with the remainder showing a 1 to >30-fold reduction in titer. Against B.1.351, 79% (15/19) showed complete loss of neutralizing activity, with the remaining five samples showing a 6-36 fold (average of 15-fold) reduction in activity (Figure 2a).

1.8 T-cell receptor variable beta chain sequencing

Immunosequencing of the CDR3 regions of human TCRβ chains was performed using the ImmunoSEQ® Assay (Adaptive Biotechnologies, Seattle, WA) in PBMCs isolated from 17 study participants from a Phase 2/3 study of ChAdOx1 nCoV19 in the UK (COV002). Extracted genomic DNA was amplified in a bias-controlled multiplex PCR, followed by high-throughput sequencing. Sequences were collapsed and filtered in order to identify and quantitate the absolute abundance of each unique TCRβ CDR3 region for further analysis as previously described.[13-15] The fraction of T cells was calculated by normalizing TCR-β template counts to the total amount of DNA usable for TCR sequencing, where the amount of usable DNA was determined by NAAT-amplification and sequencing of several reference genes that are expected to be present in all nucleated cells.

TCR sequences from the repertoire of patients receiving the ChAdOx1 nCoV19 vaccine were mapped against a set of TCR sequences that are known to react to SARS-CoV-2. Briefly, these sequences were first identified by Multiplex Identification of T-cell Receptor Antigen Specificity (MIRA).[16] TCRs that react were further screened for enrichment in COVID-19 positive repertoires collected as part of immuneCODE[17] compared to COVID-19 negative repertoires to remove TCRs that may be highly public or cross-reactive to common antigens. Individual response could be quantified by the number and/or frequency of SARS-CoV-2 TCRs seen post-vaccine. TCRs were further analyzed at the level specific ORF or position within ORF based on the MIRA antigens.

1.9. Phylogenetic analysis and comparison to known variants

Sequences of known variants were obtained from GISAID (www.gisaid.org) and aligned to known MIRA antigen locations. Antigens that contain any mutations in the B.1.1.7 (UK) or B.1.351 (SA) variants were labeled as potentially impacted.

Supplementary Table S1: Symptoms considered to be suggestive of Covid-19 which participants were requested to look out for and present for investigation for SARS-CoV-2 infection.

Respiratory	**Non-Respiratory**
New onset cough	Fever or feverishness (defined subjectively, or objective fever ≥ 37.8°C, regardless of use of anti-pyretic medications)
New onset rapid breathing	Myalgia (or muscle ache)
New onset shortness of breath (or breathlessness or difficulty breathing)	Chills
Sore throat	Loss of taste (or taste disturbance)
Loss of smell (or smell disturbance)	Headache
Nasal congestion	Diarrhea
Runny nose	Tiredness (or fatigue or weakness)
	Nausea or vomiting
	Loss of appetite

Abbreviations: Covid-19 = coronavirus disease 2019.

Participants were requested to present for an illness visit if they experienced any of the above symptoms. Participants were provided were a thermometer at time of randomization and trained on its use to record their own oral temperature.

Supplementary Table S2: Scoring algorithm for grading of Covid-19 severity score.

Covid-19 Severity	Endpoint Definitions
Mild	Any one of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough • ≥ 2 Covid-19 respiratory/non-respiratory symptoms in (Supplementary Table S1) **AND** • Does not meet criteria for moderate or severe
Moderate	≥ 1 of: • Fever (≥ 37.8°C) + any 2 Covid-19 symptoms in Supplementary Table S1 for ≥ 3 days (need not be contiguous days) • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) • Any evidence of significant LRTI: − Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (beyond baseline) − Tachypnea: 20 to 29 breaths per minute at rest − SpO_2: < 94% on room air − Abnormal chest x-ray/CT consistent with pneumonia or LRTI − Adventitious sounds on lung auscultation
Severe	≥ 1 of: • Tachypnea: ≥ 30 breaths per minute at rest • SpO_2: < 92% on room air or PAO_2/FiO_2 < 300 • High flow oxygen therapy, CPAP, or NIV (eg, CPAP/BiPAP) • Mechanical ventilation or ECMO • One or more major organ system failure[a] (eg, cardiac/circulatory, pulmonary, renal, hepatic to be defined by diagnostic testing/clinical syndrome/interventions)

Abbreviations: BiPAP = bi-level positive airway pressure; CPAP = continuous positive air pressure; CT = computed tomography; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; LRTI = lower respiratory tract infection; NIV = non-invasive ventilation; PAO_2 = partial pressure of oxygen in the alveolus; SpO_2 = oxygen saturation.

Evidence of major organ dysfunction or failure includes but is not limited to any of acute respiratory distress syndrome (ARDS), acute renal failure, acute hepatic failure, acute right or left heart failure, septic or cardiogenic shock, or requirement for vasopressors, systemic corticosteroids, or hemodialysis.

Supplementary Table S3: Adverse events reported throughout the study stratified by vaccine or placebo arms.

	Overall	Placebo	Vaccine
Total number of adverse events	2247	1167	1080
General disorders and administration site conditions	742 (36.7)	364 (36)	378 (37.4)
General system disorders NEC	651 (32.2)	334 (33.1)	317 (31.4)
Administration site reactions	72 (3.6)	21 (2.1)	51 (5)
Body temperature conditions	17 (0.8)	7 (0.7)	10 (1)
Complications associated with device	1 (<0.1)	1 (<0.1)	0 (<0.1)
Therapeutic and nontherapeutic effects (excl toxicity)	1 (<0.1)	1 (<0.1)	0 (<0.1)
Nervous system disorders	386 (19.1)	205 (20.3)	181 (17.9)
Headaches	309 (15.3)	166 (16.4)	143 (14.1)
Neurological disorders NEC	46 (2.3)	27 (2.7)	19 (1.9)
Cranial nerve disorders (excl neoplasms)	31 (1.5)	12 (1.2)	19 (1.9)
Respiratory, thoracic and mediastinal disorders	335 (16.6)	181 (17.9)	154 (15.2)
Respiratory disorders NEC	147 (7.3)	80 (7.9)	67 (6.6)
Respiratory tract signs and symptoms	139 (6.9)	72 (7.1)	67 (6.6)
Upper respiratory tract disorders (excl infections)	49 (2.4)	29 (2.9)	20 (2)
Infections and infestations	257 (12.7)	123 (12.2)	134 (13.3)
Infections - pathogen unspecified	209 (10.3)	100 (9.9)	109 (10.8)
Viral infectious disorders	33 (1.6)	15 (1.5)	18 (1.8)
Fungal infectious disorders	7 (0.3)	4 (0.4)	3 (0.3)
Bacterial infectious disorders	4 (0.2)	1 (<0.1)	3 (0.3)
Ectoparasitic disorders	2 (<0.1)	2 (0.2)	0 (<0.1)
Helminthic disorders	1 (<0.1)	1 (<0.1)	0 (<0.1)
Mycobacterial infectious disorders	1 (<0.1)	0 (<0.1)	1 (<0.1)
Gastrointestinal disorders	234 (11.6)	134 (13.3)	100 (9.9)
Gastrointestinal signs and symptoms	122 (6)	76 (7.5)	46 (4.6)
Gastrointestinal motility and defaecation conditions	94 (4.7)	51 (5)	43 (4.3)
Dental and gingival conditions	6 (0.3)	4 (0.4)	2 (0.2)
Oral soft tissue conditions	6 (0.3)	2 (0.2)	4 (0.4)
Exocrine pancreas conditions	2 (<0.1)	0 (<0.1)	2 (0.2)
Gastrointestinal vascular conditions	2 (<0.1)	1 (<0.1)	1 (<0.1)
Gastrointestinal stenosis and obstruction	1 (<0.1)	0 (<0.1)	1 (<0.1)
Gastrointestinal ulceration and perforation	1 (<0.1)	0 (<0.1)	1 (<0.1)
Musculoskeletal and connective tissue disorders	104 (5.1)	61 (6)	43 (4.3)
Muscle disorders	50 (2.5)	31 (3.1)	19 (1.9)
Musculoskeletal and connective tissue disorders NEC	28 (1.4)	13 (1.3)	15 (1.5)
Joint disorders	26 (1.3)	17 (1.7)	9 (0.9)
Skin and subcutaneous tissue disorders	53 (2.6)	37 (3.7)	16 (1.6)

Epidermal and dermal conditions	34 (1.7)	25 (2.5)	9 (0.9)
Skin appendage conditions	16 (0.8)	11 (1.1)	5 (0.5)
Angioedema and urticaria	3 (0.1)	1 (<0.1)	2 (0.2)
Investigations	41 (2)	12 (1.2)	29 (2.9)
Cardiac and vascular investigations (excl enzyme tests)	26 (1.3)	7 (0.7)	19 (1.9)
Physical examination and organ system status topics	6 (0.3)	1 (<0.1)	5 (0.5)
Microbiology and serology investigations	4 (0.2)	2 (0.2)	2 (0.2)
Water, electrolyte and mineral investigations	3 (0.1)	1 (<0.1)	2 (0.2)
Haematology investigations (incl blood groups)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Injury, poisoning and procedural complications	21 (1)	9 (0.9)	12 (1.2)
Injuries NEC	15 (0.7)	5 (0.5)	10 (1)
Bone and joint injuries	2 (<0.1)	1 (<0.1)	1 (<0.1)
Injuries by physical agents	2 (<0.1)	2 (0.2)	0 (<0.1)
Procedural related injuries and complications NEC	2 (<0.1)	1 (<0.1)	1 (<0.1)
Reproductive system and breast disorders	21 (1)	8 (0.8)	13 (1.3)
Menstrual cycle and uterine bleeding disorders	14 (0.7)	7 (0.7)	7 (0.7)
Sexual function and fertility disorders	4 (0.2)	0 (<0.1)	4 (0.4)
Vulvovaginal disorders (excl infections and inflammations)	2 (<0.1)	0 (<0.1)	2 (0.2)
Reproductive tract disorders NEC	1 (<0.1)	1 (<0.1)	0 (<0.1)
Eye disorders	16 (0.8)	11 (1.1)	5 (0.5)
Ocular infections, irritations and inflammations	16 (0.8)	11 (1.1)	5 (0.5)
Vascular disorders	11 (0.5)	6 (0.6)	5 (0.5)
Vascular hypertensive disorders	10 (0.5)	5 (0.5)	5 (0.5)
Embolism and thrombosis	1 (<0.1)	1 (<0.1)	0 (<0.1)
Metabolism and nutrition disorders	9 (0.4)	7 (0.7)	2 (0.2)
Appetite and general nutritional disorders	8 (0.4)	6 (0.6)	2 (0.2)
Purine and pyrimidine metabolism disorders	1 (<0.1)	1 (<0.1)	0 (<0.1)
Ear and labyrinth disorders	4 (0.2)	2 (0.2)	2 (0.2)
Aural disorders NEC	3 (0.1)	2 (0.2)	1 (<0.1)
External ear disorders (excl congenital)	1 (<0.1)	0 (<0.1)	1 (<0.1)
Immune system disorders	4 (0.2)	3 (0.3)	1 (<0.1)
Allergic conditions	4 (0.2)	3 (0.3)	1 (<0.1)
Renal and urinary disorders	4 (0.2)	1 (<0.1)	3 (0.3)
Urinary tract signs and symptoms	3 (0.1)	0 (<0.1)	3 (0.3)
Urolithiases	1 (<0.1)	1 (<0.1)	0 (<0.1)
Blood and lymphatic system disorders	2 (<0.1)	2 (0.2)	0 (<0.1)
Spleen, lymphatic and reticuloendothelial system disorders	2 (<0.1)	2 (0.2)	0 (<0.1)
Psychiatric disorders	2 (<0.1)	1 (<0.1)	1 (<0.1)

Anxiety disorders and symptoms	1 (<0.1)	1 (<0.1)	0 (<0.1)
Schizophrenia and other psychotic disorders	1 (<0.1)	0 (<0.1)	1 (<0.1)
Cardiac disorders	1 (<0.1)	0 (<0.1)	1 (<0.1)
Cardiac disorders, signs and symptoms NE	1 (<0.1)	0 (<0.1)	1 (<0.1)

NEC- Not elsewhere classified

Supplementary Table S4: Listing of serious adverse events.

	Overall (N = 27)	Placebo (N=13)	Vaccine (N=14)
Gastrointestinal disorders	6 (0.3)	2 (0.2)	4 (0.4)
Exocrine pancreas conditions	2 (<0.1)	0 (<0.1)	2 (0.2)
Gastrointestinal motility and defaecation conditions	2 (<0.1)	1 (<0.1)	1 (<0.1)
Gastrointestinal inflammatory conditions	1 (<0.1)	1 (<0.1)	0 (<0.1)
Gastrointestinal stenosis and obstruction	1 (<0.1)	0 (<0.1)	1 (<0.1)
Social circumstances	1 (<0.1)	1 (<0.1)	0 (<0.1)
Legal issues	1 (<0.1)	1 (<0.1)	0 (<0.1)
Injury, poisoning and procedural complications	6 (0.3)	2 (0.2)	4 (0.4)
Injuries NEC	4 (0.2)	1 (<0.1)	3 (0.3)
Bone and joint injuries	2 (<0.1)	1 (<0.1)	1 (<0.1)
Infections and infestations	4 (0.2)	2 (0.2)	2 (0.2)
Infections - pathogen unspecified	3 (0.1)	2 (0.2)	1 (<0.1)
Mycobacterial infectious disorders	1 (<0.1)	0 (<0.1)	1 (<0.1)
Psychiatric disorders	4 (0.2)	2 (0.2)	2 (0.2)
Schizophrenia and other psychotic disorders	2 (<0.1)	1 (<0.1)	1 (<0.1)
Psychiatric disorders NEC	1 (<0.1)	0 (<0.1)	1 (<0.1)
Suicidal and self-injurious behaviours NEC	1 (<0.1)	1 (<0.1)	0 (<0.1)
Pregnancy, puerperium and perinatal conditions	2 (<0.1)	1 (<0.1)	1 (<0.1)
Abortions and stillbirth	2 (<0.1)	1 (<0.1)	1 (<0.1)
Cardiac disorders	1 (<0.1)	1 (<0.1)	0 (<0.1)
Coronary artery disorders	1 (<0.1)	1 (<0.1)	0 (<0.1)
General disorders and administration site conditions	1 (<0.1)	0 (<0.1)	1 (<0.1)
Febrile disorders	1 (<0.1)	0 (<0.1)	1 (<0.1)[a]
Hepatobiliary disorders	1 (<0.1)	1 (<0.1)	0 (<0.1)
Hepatic and hepatobiliary disorders	1 (<0.1)	1 (<0.1)	0 (<0.1)
Reproductive system and breast disorders	1 (<0.1)	1 (<0.1)	0 (<0.1)
Uterine, pelvic and broad ligament disorders	1 (<0.1)	1 (<0.1)	0 (<0.1)

[a]All SAEs were graded as not related or unlikely related to the vaccine with the exception of the Febrile disorder. NEC- Not elsewhere classified.

Supplementary Table S5: Summary statistics of pseudoneutralizing Antibody responses for seronegative SDSD AZD1222 treated study participants from the UK, Brazil, and South Africa

Country	N	Baseline Median Titer [IQR]	N	Post Dose 1 Median Titer [IQR]	N	Post Dose 2 Median Titer [IQR]
United Kingdom	326	[20, 20]	290	41.35 ;[20-135.44]	307	200.44 ; [108.39-393.39]
Brazil	226	[20, 20]	205	46.69; [20-144.62]	192	154.40 ; [70.72-307.71]
South Africa	107	[20, 20]	82	131.57 ; [20-403.72]	99	276.61 ; [123.96-525.46]

IQR: Interquartile range

Supplementary Table S6: Secondary and exploratory objectives of ChadOx-1 nCoV19 vaccine efficacy against Covid-19.

Baseline serology[a]	Total number of cases	Placebo n/N (%)	IR[b] per 1000 person-years (person-days)	Vaccine n/N (%)	IR per 1000 person-years (person-days)	Vaccine efficacy (95%Confidence Interval)
Secondary endpoints[c]: Mild-moderate[d] Covid-19 clinical disease >14 days post-prime[e]						
Overall	62	37/938 (3.9)	95.9 (140774)	25/944 (2.6)	63.7 (143140)	33.5% (-13.4 to 61.7)
Negative	53	32/776 (4.1)	99.1 (117879)	21/804 (2.6)	61.9 (123852)	37.5% (-11.7 to 65.8)
Positive	7	4/153 (2.6)	67.5 (21623)	3/135 (2.2)	59.1 (18516)	12.4% (-417.7 to 87.2)
Exploratory analysis: Mild-moderate Covid-19 clinical disease >21 days post-prime and <=14 days post-boost						
Overall	11	9/913 (1)	81.8 (40162)	2/916 (0.2)	18 (40458)	77.9% (-6.6 to 97.7)
Negative	7	6/755 (0.8)	65.8 (33275)	1/778 (0.1)	10.6 (34393)	83.9% (-32.9 to 99.6)
Positive	3	2/149 (1.3)	111.9 (6524)	1/134 (0.7)	61.9 (5894)	44.7% (-963.1 to 99.1)
Secondary endpoint: Any NAAT confirmed infection >14 days post-boost						
Overall	64	35/865 (4)	119.5 (106898)	29/884 (3.3)	96.5 (109659)	19.2% (-36 to 52.4)
Negative	57	32/717 (4.5)	130.2 (89714)	25/750 (3.3)	96.2 (94881)	26.1% (-28.7 to 58)
Positive	6	3/141 (2.1)	67.1 (16310)	3/130 (2.3)	76.7 (14278)	-14.2% (-752.9 to 84.7)
Secondary endpoint Any NAAT confirmed infection outcomes >14 days post-primary[e]						
Overall	101	59/938 (6.3)	153 (140774)	42/944 (4.4)	107.1 (143140)	30% (-5.8 to 54)
Negative	85	50/776 (6.4)	154.8 (117879)	35/804 (4.4)	103.1 (123852)	33.4% (-4.7 to 58)
Positive	14	8/153 (5.2)	135 (21623)	6/135 (4.4)	118.3 (18516)	12.4% (-187.9 to 75)
Exploratory: Any NAAT confirmed infection outcomes >21 days post-prime and <=14 days post-boost						
Overall	28	19/913 (2.1)	172.7 (40162)	9/916 (1)	81.2 (40458)	53% (-9.1 to 81.3)
Negative	20	14/755 (1.9)	153.6 (33275)	6/778 (0.8)	63.7 (34393)	58.5% (-14.9 to 86.9)
Positive	7	4/149 (2.7)	223.8 (6524)	3/134 (2.2)	185.8 (5894)	17% (-390.7 to 87.8)
Secondary Objective: Moderate Covid-19 clinical disease 14 days post-boost						
Overall	12	6/865 (0.7)	20.5 (106898)	6/884 (0.7)	20 (109659)	2.5% (-264.6 to 73.9)
Negative	10	6/717 (0.8)	24.4 (89714)	4/750 (0.5)	15.4 (94881)	37% (-165.8 to 86.9)
Positive	1	0/141 (0)	0 (16310)	1/130 (0.8)	25.6 (14278)	NE[f]
Secondary Objective: Moderate Covid-19 clinical disease >14 days post-prime[e]						

Overall	19	12/938 (1.3)	31.1 (140774)	7/944 (0.7)	17.8 (143140)	42.6% (-58 to 80.9)
Negative	16	12/776 (1.5)	37.2 (117879)	4/804 (0.5)	11.8 (123852)	68.3% (-4.7 to 92.5)
Positive	2	0/153 (0)	0 (21623)	2/135 (1.5)	39.4 (18516)	NE
Exploratory endpoint: Moderate Covid-19 clinical disease >21 days post prime and <=14 days post-boost						
Overall	6	5/913 (0.5)	45.4 (40162)	1/916 (0.1)	9 (40458)	80.1% (-77.4 to 99.6)
Negative	5	5/755 (0.7)	54.8 (33275)	0/778 (0)	0 (34393)	100% (-5.6 to 100)
Positive	1	0/149 (0)	0 (6524)	1/134 (0.7)	61.9 (5894)	NE
Secondary Objective: Analysis using Oxford Covid-19 definition[g] >14 days post-boost						
Overall	41	22/865 (2.5)	75.1 (106898)	19/884 (2.1%)	63.2 (109659)	15.8% (-63 to 56.9)
Negative	38	21/717 (2.9)	85.4 (89714)	17/750 (2.)	65.4 (94881)	23.5% (-52.3 to 62.1)
Positive	2	1/141 (0.7)	22.4 (16310)	1/130 (0.8)	25.6 (14278)	-14.2% (-8866.8 to 98.5)
Secondary Objective: Analysis using Oxford definition >14 days post-prime[e]						
Overall	55	33/938 (3.5)	85.6 (140774)	22/944 (2.3)	56.1 (143140)	34.4% (-15.9 to 63.6)
Negative	47	28/776 (3.6)	86.7 (117879)	19/804 (2.4)	56 (123852)	35.4% (-19.8 to 65.9)
Positive	6	4/153 (2.6)	67.5 (21623)	2/135 (1.5)	39.4 (18516)	41.6% (-307.4 to 94.7)
Secondary objective: Analysis using Oxford definition >21 and <=14 days post-prime						
Overall	9	7/913 (0.8)	63.6 (40162)	2/916 (0.2)	18 (40458)	71.6% (-49 to 97.1)
Negative	5	4/755 (0.5)	43.9 (33275)	1/778 (0.1)	10.6 (34393)	75.8% (-144.4 to 99.5)
Positive	3	2/149 (1.3)	111.9 (6524)	1/134 (0.7)	61.9 (5894)	44.7% (-963.1 to 99.1)

[a] Sero-status evaluated using an assay to detect IgG to SARS-CoV-2 Nucleoprotein on serum obtained on day of 1st injection. Overall includes participants who did not have a serology result at baseline.
[b]IR= Incidence risk.
[c]Vaccine efficacy against endpoints included in the secondary objectives are reported here along with confidence intervals which are not adjusted for multiplicity.
[d]The pre-specified primary endpoint was all-severity which includes mild, moderate and severe NAAT-confirmed Covid-19 disease. As there were no participants in the study who had severe Covid-19, the wording “mild-moderate” is used.
[e]Vaccine efficacy estimates endpoint cases occurring at >7 or >21 days were similar to observation when analysed with >14 days threshold.
[f]NE = Not evaluable.
[g]Refers to definition used in the United Kingdom and Brazil pooled efficacy analysis[1].

Supplementary Table S7: GISAID submission of sequences from primary endpoint cases

Strain	Collection date	Coverage length	Age	Lineage	Country	gisaid_epi_isl	Submission Date	Region of exposure	CT_score
hCoV-19/SouthAfrica/VIDA-KRISP-K008026/2020	Dec 2020	98.30%	50-59	501Y.V2	South Africa	EPI_ISL_940880	05 Feb 21	Gauteng	34.41
hCoV-19/SouthAfrica/VIDA-KRISP-K008074/2021	Jan 2021	86.85%	40-49	501Y.V2	South Africa	EPI_ISL_940875	05 Feb 21	Gauteng	29.62
hCoV-19/SouthAfrica/VIDA-KRISP-V001020/2020	Dec 2020	99.19%	30-39	501Y.V2	South Africa	EPI_ISL_940861	05 Feb 21	Gauteng	15.84
hCoV-19/SouthAfrica/VIDA-KRISP-K008058/2021	Jan 2021	80.30%	50-59	501Y.V2	South Africa	EPI_ISL_940869	05 Feb 21	Gauteng	28.52
hCoV-19/SouthAfrica/VIDA-KRISP-K008019/2021	Jan 2021	77.30%	20-29	501Y.V2	South Africa	EPI_ISL_940867	05 Feb 21	Gauteng	12.95
hCoV-19/SouthAfrica/VIDA-KRISP-K008085/2020	Sep 2020	95.20%	20-29	20B	South Africa	EPI_ISL_940851	05 Feb 21	Gauteng	36.47
hCoV-19/SouthAfrica/VIDA-KRISP-K008076/2021	Jan 2021	99.83%	30-39	501Y.V2	South Africa	EPI_ISL_940891	05 Feb 21	Gauteng	32.33
hCoV-19/SouthAfrica/VIDA-KRISP-K008044/2021	Jan 2021	81.60%	20-29	501Y.V2	South Africa	EPI_ISL_940870	05 Feb 21	Gauteng	37.27
hCoV-19/SouthAfrica/VIDA-KRISP-K008107/2021	Jan 2021	99.95%	30-39	501Y.V2	South Africa	EPI_ISL_940889	05 Feb 21	Gauteng	33.82
hCoV-19/SouthAfrica/VIDA-KRISP-K008079/2021	Jan 2021	99.71%	10-19	501Y.V2	South Africa	EPI_ISL_940890	05 Feb 21	Gauteng	30.33
hCoV-19/SouthAfrica/VIDA-KRISP-V001014/2021	Jan 2021	98.03%	30-39	501Y.V2	South Africa	EPI_ISL_940856	05 Feb 21	Gauteng	16.78
hCoV-19/SouthAfrica/VIDA-KRISP-K008022/2021	Jan 2021	82.00%	20-29	501Y.V2	South Africa	EPI_ISL_940871	05 Feb 21	Gauteng	14.85
hCoV-19/SouthAfrica/VIDA-KRISP-V001003/2021	Jan 2021	100.00%	40-49	501Y.V2	South Africa	EPI_ISL_940886	05 Feb 21	Gauteng	25.73
hCoV-19/SouthAfrica/VIDA-KRISP-K008063/2021	Jan 2021	87.38%	20-29	501Y.V2	South Africa	EPI_ISL_940876	05 Feb 21	Gauteng	35.66
hCoV-19/SouthAfrica/VIDA-KRISP-K008043/2021	Jan 2021	96.20%	20-29	501Y.V2	South Africa	EPI_ISL_940852	05 Feb 21	Gauteng	30.60
hCoV-19/SouthAfrica/VIDA-KRISP-V001016/2020	Dec 2020	98.89%	40-49	501Y.V2	South Africa	EPI_ISL_940885	05 Feb 21	Gauteng	15.54
hCoV-19/SouthAfrica/VIDA-KRISP-V001008/2020	Dec 2020	97.42%	30-39	501Y.V2	South Africa	EPI_ISL_940853	05 Feb 21	Gauteng	21.17
hCoV-19/SouthAfrica/VIDA-KRISP-K008064/2021	Jan 2021	99.08%	40-49	501Y.V2	South Africa	EPI_ISL_940888	05 Feb 21	Gauteng	37.95
hCoV-19/SouthAfrica/VIDA-KRISP-V001012/2020	Dec 2020	99.08%	30-39	501Y.V2	South Africa	EPI_ISL_940882	05 Feb 21	Gauteng	18.13
hCoV-19/SouthAfrica/VIDA-KRISP-V001011/2020	Dec 2020	98.77%	20-29	501Y.V2	South Africa	EPI_ISL_940858	05 Feb 21	Gauteng	18.22

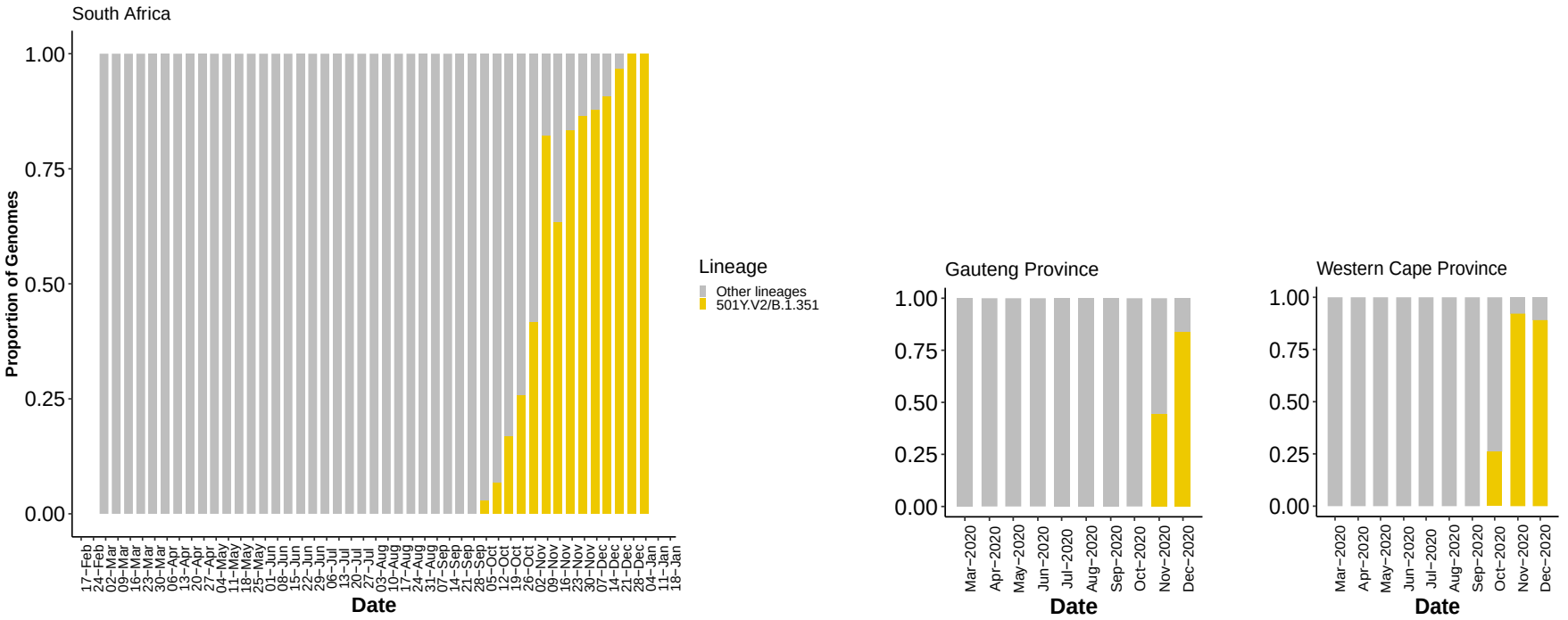
hCoV-19/SouthAfrica/VIDA-KRISP-V001004/2020	**Nov 2020**	**98.06%**	30-39	**501Y.V2**	**South Africa**	**EPI_ISL_940855**	**05 Feb 21**	**Gauteng**	**24.57**
hCoV-19/SouthAfrica/VIDA-KRISP-V001013/2020	**Dec 2020**	**98.83%**	50-59	**501Y.V2**	**South Africa**	**EPI_ISL_940859**	**05 Feb 21**	**Gauteng**	**16.91**
hCoV-19/SouthAfrica/VIDA-KRISP-V001001/2021	**Jan 2021**	**93.26%**	30-39	**20B**	**South Africa**	**EPI_ISL_940866**	**05 Feb 21**	**Gauteng**	**30.66**
hCoV-19/SouthAfrica/VIDA-KRISP-K008023/2021	**Jan 2021**	**93.40%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940865**	**05 Feb 21**	**Gauteng**	**22.08**
hCoV-19/SouthAfrica/VIDA-KRISP-K008057/2021	**Jan 2021**	**98.30%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940862**	**05 Feb 21**	**Gauteng**	**32.88**
hCoV-19/SouthAfrica/VIDA-KRISP-K008029/2021	**Jan 2021**	**85.40%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940874**	**05 Feb 21**	**Gauteng**	**16.03**
hCoV-19/SouthAfrica/VIDA-KRISP-K008036/2021	**Jan 2021**	**78.20%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940868**	**05 Feb 21**	**Gauteng**	**34.16**
hCoV-19/SouthAfrica/VIDA-KRISP-V001010/2020	**Dec 2020**	**99.07%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940863**	**05 Feb 21**	**Gauteng**	**20.60**
hCoV-19/SouthAfrica/VIDA-KRISP-V001007/2020	**Dec 2020**	**95.29%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940854**	**05 Feb 21**	**Gauteng**	**23.01**
hCoV-19/SouthAfrica/VIDA-KRISP-V001009/2020	**Dec 2020**	**98.96%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940881**	**05 Feb 21**	**Gauteng**	**20.48**
hCoV-19/SouthAfrica/VIDA-KRISP-V001006/2020	**Dec 2020**	**95.29%**	30-39	**501Y.V2**	**South Africa**	**EPI_ISL_940850**	**05 Feb 21**	**Gauteng**	**23.01**
hCoV-19/SouthAfrica/VIDA-KRISP-V001017/2021	**Jan 2021**	**98.96%**	30-39	**501Y.V2**	**South Africa**	**EPI_ISL_940887**	**05 Feb 21**	**Gauteng**	**14.52**
hCoV-19/SouthAfrica/VIDA-KRISP-V001018/2020	**Dec 2020**	**99.22%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940878**	**05 Feb 21**	**Gauteng**	**14.70**
hCoV-19/SouthAfrica/VIDA-KRISP-V001002/2020	**Dec 2020**	**98.16%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940884**	**05 Feb 21**	**Gauteng**	**26.31**
hCoV-19/SouthAfrica/VIDA-KRISP-V001015/2020	**Dec 2020**	**99.28%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940879**	**05 Feb 21**	**Gauteng**	**16.09**
hCoV-19/SouthAfrica/VIDA-KRISP-V001019/2020	**Nov 2020**	**99.99%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940877**	**05 Feb 21**	**Gauteng**	**13.95**
hCoV-19/SouthAfrica/VIDA-KRISP-V001005/2021	**Jan 2021**	**99.80%**	30-39	**501Y.V2**	**South Africa**	**EPI_ISL_940864**	**05 Feb 21**	**Western Cape**	**23.75**
hCoV-19/SouthAfrica/VIDA-KRISP-K008050/2020	**Dec 2020**	**85.40%**	20-29	**501Y.V2**	**South Africa**	**EPI_ISL_940873**	**05 Feb 21**	**Western Cape**	**26.82**
hCoV-19/SouthAfrica/VIDA-KRISP-K008056/2020	**Dec 2020**	**97.20%**	40-49	**501Y.V2**	**South Africa**	**EPI_ISL_940857**	**05 Feb 21**	**Western Cape**	**28.15**
hCoV-19/SouthAfrica/VIDA-KRISP-K008052/2020	**Dec 2020**	**98.30%**	60-69	**501Y.V2**	**South Africa**	**EPI_ISL_940883**	**05 Feb 21**	**Western Cape**	**23.58**
hCoV-19/SouthAfrica/VIDA-KRISP-K008053/2020	**Nov 2020**	**83.90%**	40-49	**501Y.V2**	**South Africa**	**EPI_ISL_940872**	**05 Feb 21**	**Western Cape**	**22.67**

Supplementary Table S8: Vaccine efficacy against Covid-19 greater than 14 days following the primary dose and censored through to 31 October 2020 (i.e. proxy for non-B1.135 variant).

Baseline serology[a]	Total number of cases	Placebo n/N (%)	IR[b] per 1000 person-years (person-days)	Vaccine n/N (%)	IR per 1000 person-years (person-days)	Vaccine efficacy (95%Confidence Interval)
Mild-moderate[c] Covid-19 disease (all were mild or moderate illness[d]						
Overall	15	12/938 (1.3)	31.1 (140774)	3/944 (0.3)	7.6 (143140)	75.4% (8.9 to 95.5)
Negative	9	7/776 (0.9)	21.7 (117879)	2/804 (0.2)	5.9 (123852)	72.8% (-42.8 to 97.2)
Positive	5	4/153 (2.6)	67.5 (21623)	1/135 (0.7)	19.7 (18516)	70.8% (-195 to 99.4)
Moderate Covid-19 disease only						
Any	5	4/938 (0.4)	10.4 (140774)	1/944 (0.1)	2.5 (143140)	75.4% (-148.5 to 99.5)
Negative	5	4/776 (0.5)	12.4 (117879)	1/804 (0.1)	2.9 (123852)	76.2% (-140.4 to 99.5)
Covid-19 outcomes fulfilling definition used in the United Kingdom and Brazil pooled VE analysis[e]						
Any	13	11/938 (1.2)	28.5 (140774)	2/944 (0.2)	5.1 (143140)	82.1% (18.1 to 98.1)
Negative	8	6/776 (0.8)	18.6 (117879)	2/804 (0.2)	5.9 (123852)	68.3% (-77.4 to 96.9)
Positive	4	4/153 (2.6)	67.5 (21623)	0/135 (0)	0 (18516)	100% (-76.9 to 100)
Any SARS-CoV-19 NAAT confirmed illness (inclusive of asymptomatic cases and any symptomatic Covid-19)						
Any	37	24/938 (2.6)	62.2 (140774)	13/944 (1.4)	33.1 (143140)	46.7% (-8.9 to 75.1)
Negative	24	15/776 (1.9)	46.4 (117879)	9/804 (1.1)	26.5 (123852)	42.9% (-39.3 to 78)
Positive	12	8/153 (5.2)	135 (21623)	4/135 (3)	78.9 (18516)	41.6% (-118 to 87.1)

[a] Sero-status evaluated using an assay to detect IgG to SARS-CoV-2 Nucleoprotein on serum obtained on day of 1st injection.
[b]IR= Incidence risk.
[c] The pre-specified primary endpoint was all-severity which includes mild, moderate and severe NAAT-confirmed Covid-19 disease. As there were no participants in the study who had severe Covid-19, the wording “mild-moderate” is used.
[d]Vaccine efficacy against endpoints included as a post-hoc analysis are reported here along with confidence intervals which are not adjusted for multiplicity.
[e]Refers to definition used in the United Kingdom and Brazil pooled efficacy analysis[1]

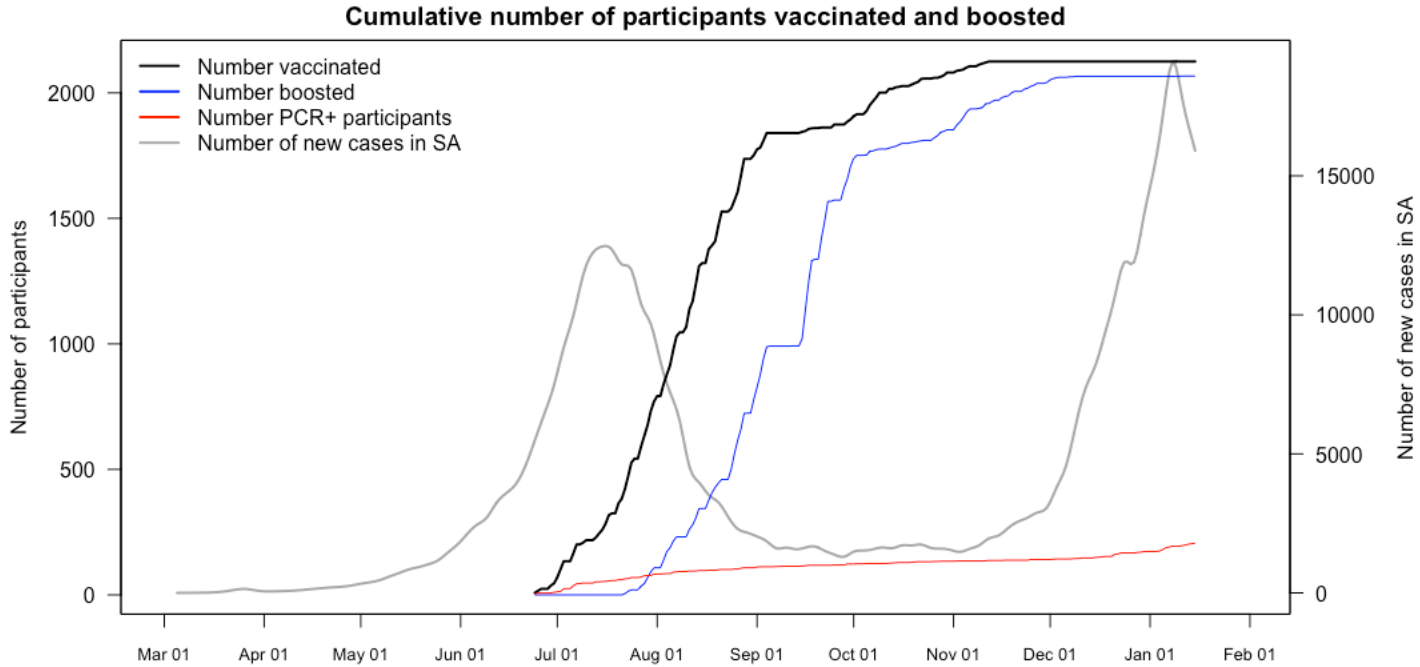
Supplementary Figure S1: Temporal evolution of the B.1351 variant in South Africa, including in two Provinces where the study sites were based.



In Cape Metro, the first sequenced case of the B.1.351 variant was identified during the week of 23rd November, and the spread of the variant to Gauteng Province followed on from spread in Western Cape.

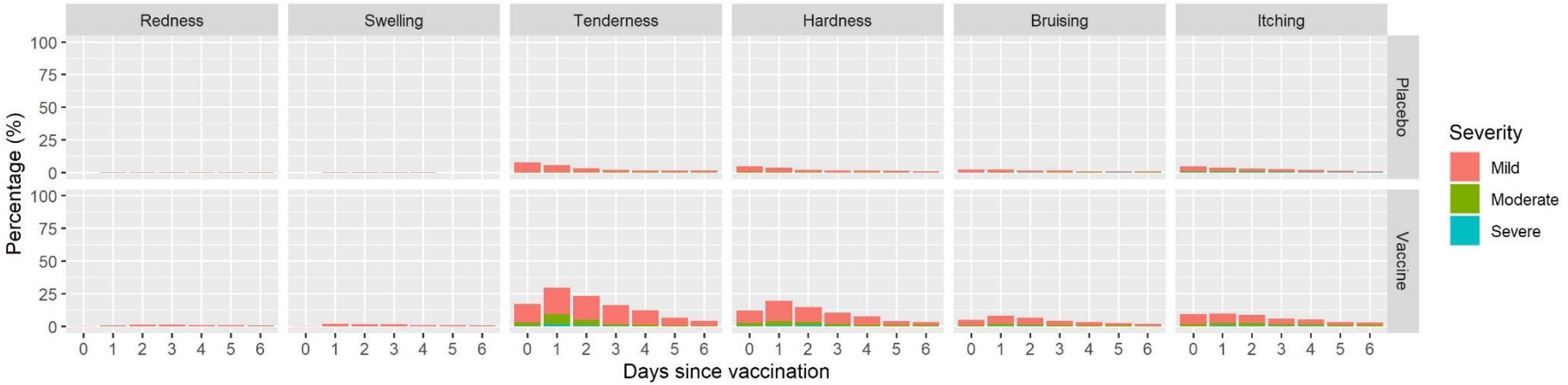
Source: GISAID + NICD report (Dominance of the SARS-CoV-2 B.1351 lineage in Gauteng- 28 Jan 2021)[18]

Supplementary Figure S2: Temporal association of Covid-19 cases (data from Our World in Data Covid-19, South Africa)[19] and receipt of first or booster dose of study vaccine in randomized participants.

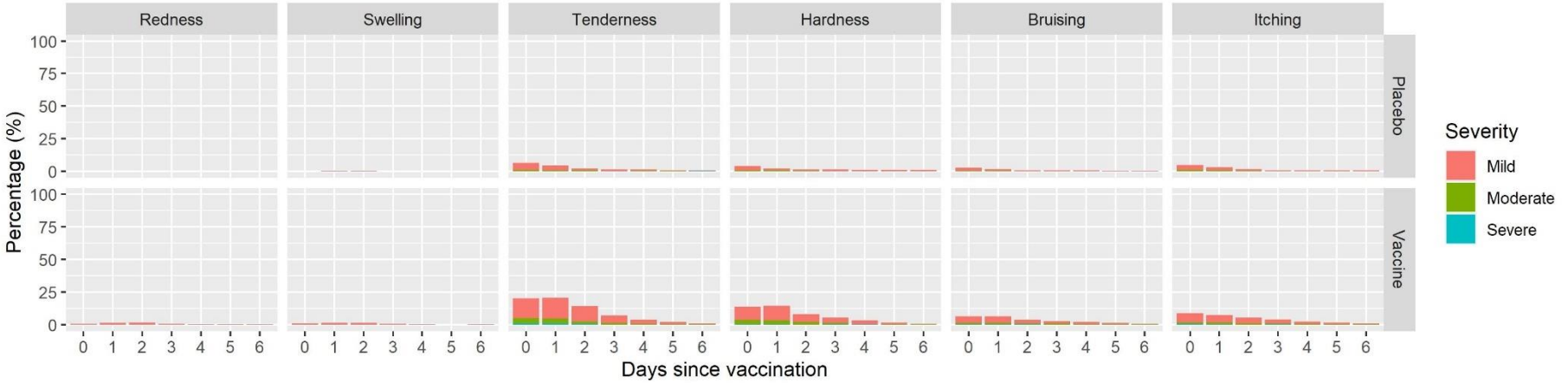


Supplementary Figure S3: Solicited local reactogenicity following the first and booster doses of assigned injection.

Post-first dose

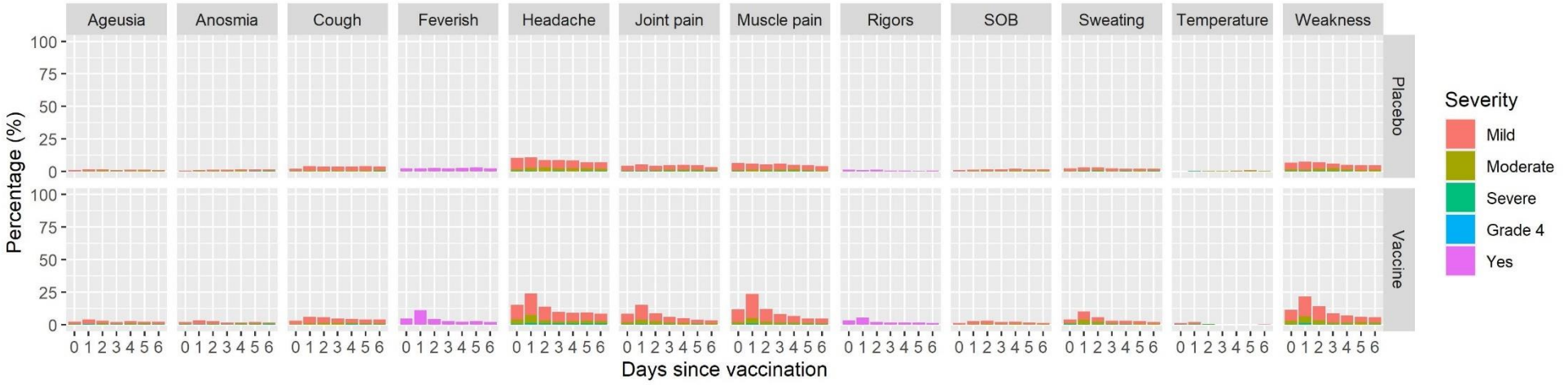


Post booster study injection

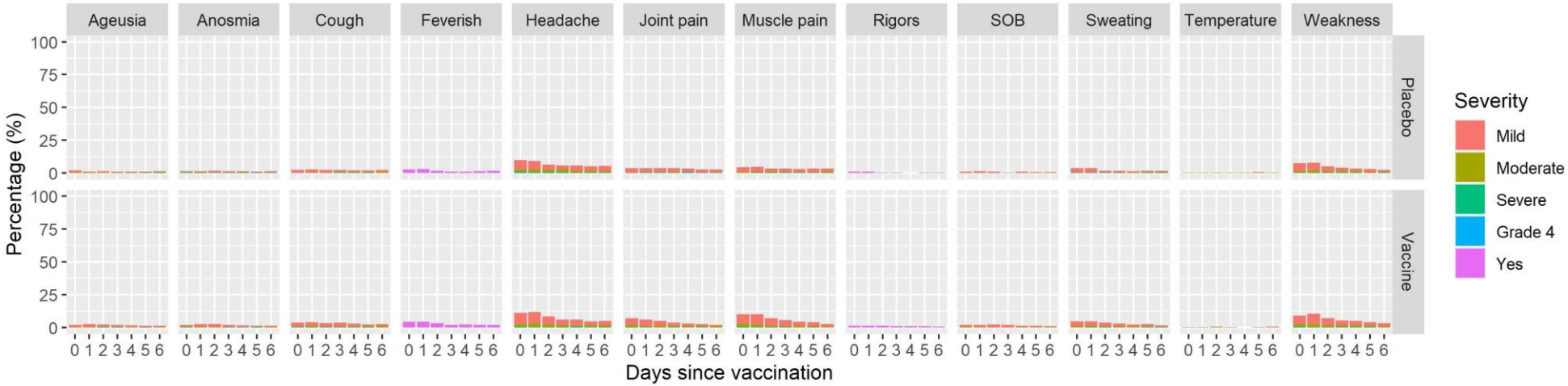


Supplementary Figure S4: Solicited systemic reactogenicity following the first and booster doses of assigned injections.

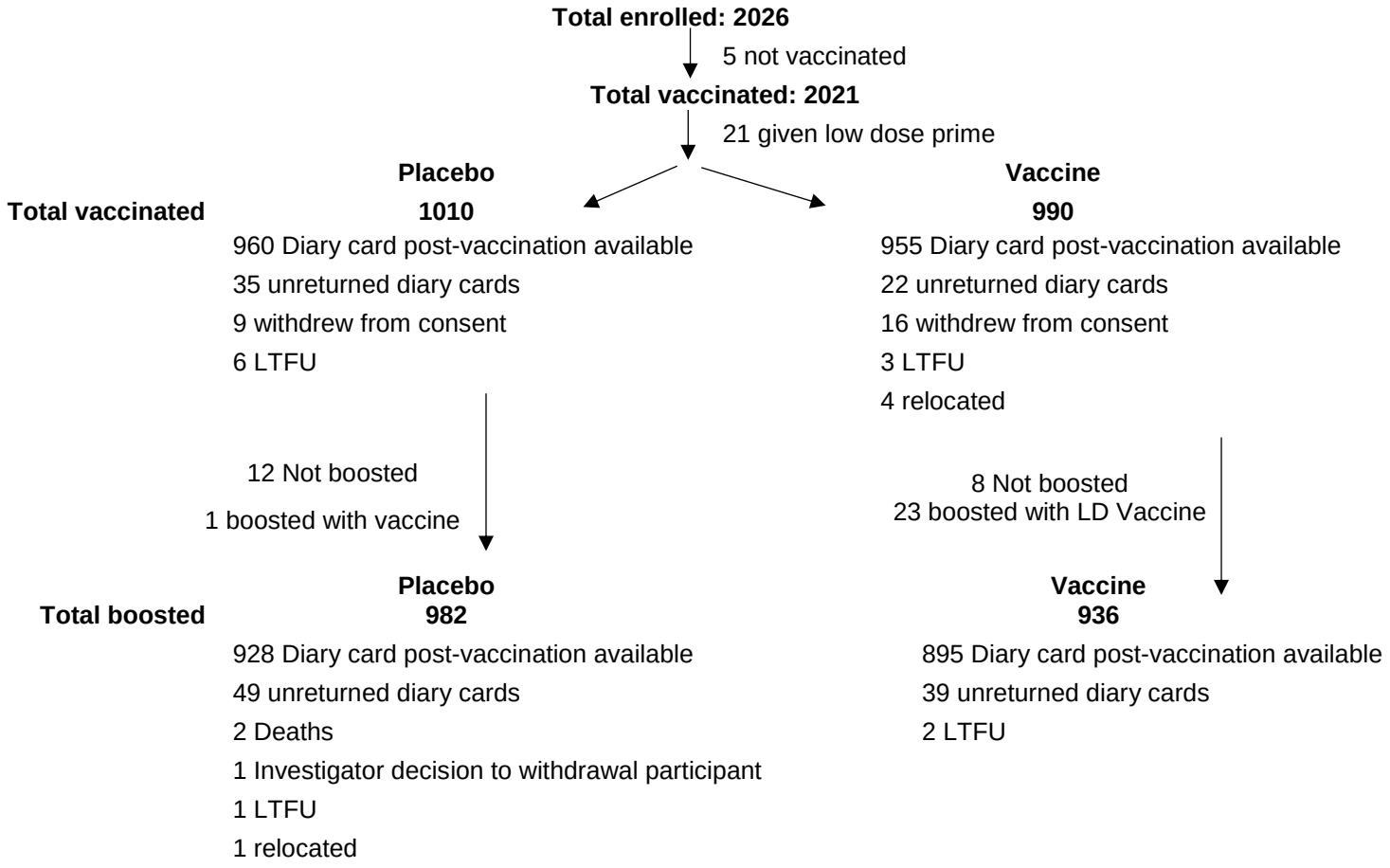
Post first dose

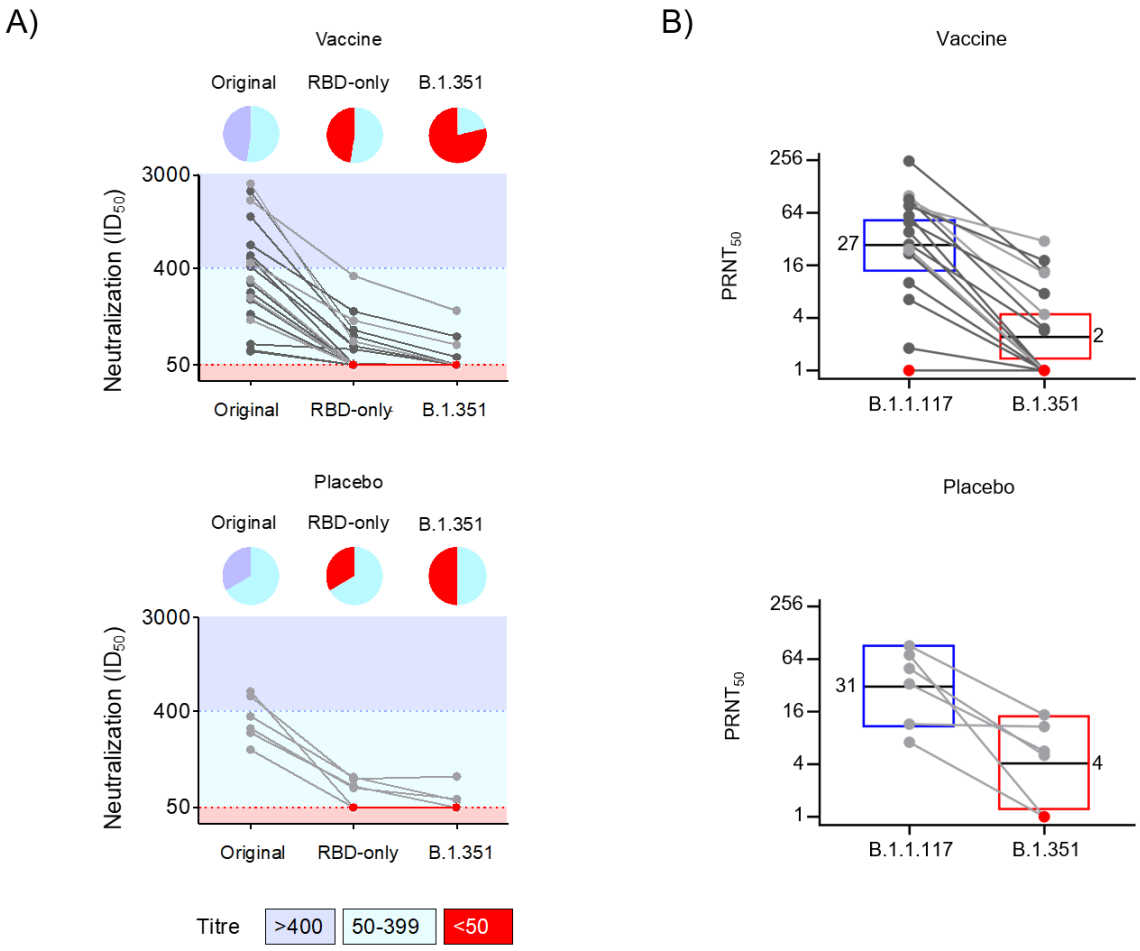


Post booster



Supplementary Figure S5: Consort diagram for safety analysis





Supplementary Figure S6: A) Pseudovirus and B) live virus neutralization assay against SARS-CoV-2 original D614G virus, receptor binding domain triple mutant and B.1.351 virus construct.

Legend Figure S6: A) All ChAdOx1-nCoV19 vaccine recipients, six of whom had confirmed SARS-CoV-2 infection between time of first vaccine dose and Day 42 (14 days post-booster dose) when PSVNA was done (light grey lines). PSVNA against the original SARS-CoV-2 D614G lineage (left), an RBD-only chimeric virus containing the K417N, E484K, and N501Y substitutions (middle) and the B1.351 lineage virus (right). Colored background indicates dilutional titre, where titers greater than 1:400 are colored dark blue, 25-400 in light blue, and titers <1:50 are colored red. Pie charts above each line graph summarize the proportion of viruses by dilutional titer. B) Live virus neutralization assay (LVNA). Neutralization by plasma of vaccinated participants (n=13, top panel, including with NAAT confirmed illness (n=6)) and placebo recipients who had natural-infection induced antibody (n=6, bottom panel) of B.1.1.117and B.1.351 variants. Participants were as for the PSVNA assay. Neutralization is represented by the 50% plaque reduction neutralization titer ($PRNT_{50}$), the reciprocal

of the 50% inhibitory dilution per participant. Participants with NAAT confirmed illness are shaded in grey and participants with no detectable neutralization (defined as $PRNT_{50}$<1) shaded in red. Bars and associated numbers represent geometric means (using the limit of detection of $PRNT_{50}$ = 1 for undetectable participants) and boxes 95% confidence intervals.

Supplementary Figure S7: Frequencies of T cells from isolated PBMCs at D56 following vaccination with ChAdOx1 nCoV19

Fig S7a

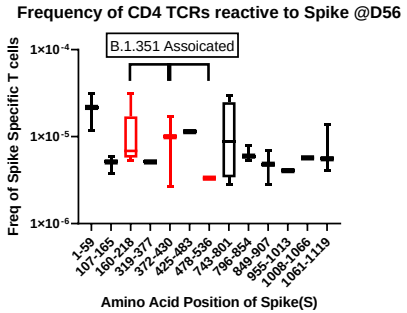


Fig. S7b		1-59	107-165	160-218	319-377	372-430	425-483	478-536	743-801	796-854	849-907	955-1013	1008-1066	1061-1119
Count		2	3	13	1	3	1	1	6	3	2	1	1	3
Median		2.2e5-	5.1e-6	6.9e-6	5.1e-6	1e-5	1.1e-5	3.3e-6	6e-6	6e-6	4.8e-6	4.1e-6	5.7e-6	5.6e-6

Fig. S7c

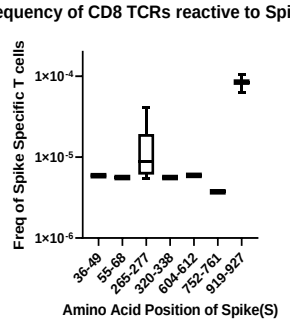
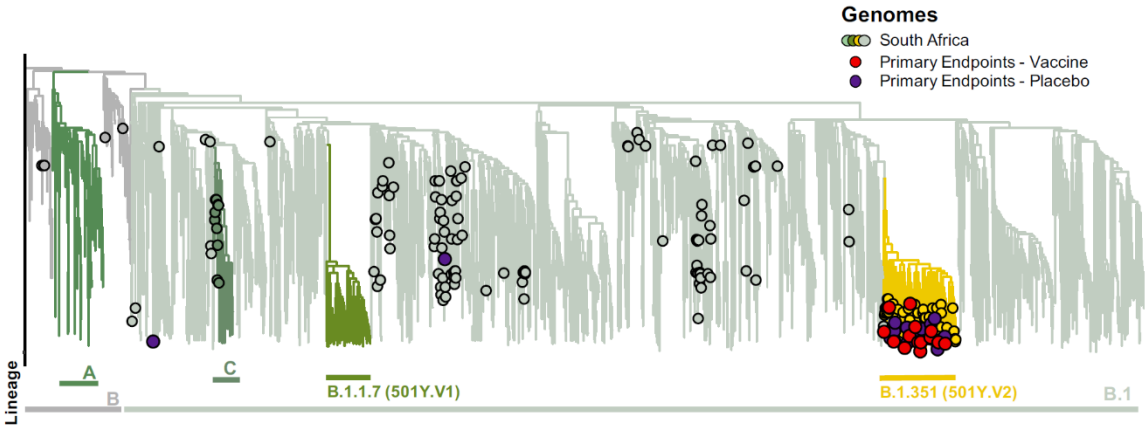


Fig. S7d		36-49	55-68	265-277	320-338	604-612	752-761	919-927
Count		1	1	8	1	1	1	2
Median		5.9e-6	5.6e-6	8.9e-6	5.6e-6	6e-6	3.7e-6	8.4e-5

Legend Figure S7a-d: Shown are the frequencies of T cells from isolated PBMCs at D56 following vaccination with ChAdOx1 nCoV19 using TCRβ sequencing and alignment with known SARS-COV2 epitopes from MIRA®(Adaptive Biotechnologies, Seattle, WA). CD4 responses (Panel S7a) and CD8 responses (Panel S7c) to Spike protein regions are shown from 17 patients. The regions affected by the South African variant are highlighted in Panel A. Summary statistics including frequency of study participants with SARS-CoV2 specific expansion in identified Spike regions and median frequency of CD4(Panel S7b) and CD8(Panel S7d).



Supplementary Figure S8 - The maximum clade credibility phylogeny of 30 SARS-CoV-2 sequences of participants included in the primary efficacy analysis.

The South African variant B.1.351 is highlighted in yellow, the phylogeny of the NAAT-confirmed post-booster dose participants are indicated by the red dots and the placebo recipients are indicated by the purple dots.

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