Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Final efficacy analysis, interim safety analysis, and immunogenicity of a single dose of recombinant novel coronavirus vaccine (adenovirus type 5 vector) in adults 18 years and older: an international, multicentre, randomised, double-blinded, placebo-controlled phase 3 trial

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Summary

Background The Ad5-nCoV vaccine is a single-dose adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein that was well-tolerated and immunogenic in phase 1 and 2 studies. In this study, we report results on the final efficacy and interim safety analyses of the phase 3 trial.

Methods This double-blind, randomised, international, placebo-controlled, endpoint-case driven, phase 3, clinical trial enrolled adults aged 18 years older at study centres in Argentina, Chile, Mexico, Pakistan, and Russia. Participants were eligible for the study if they had no unstable or severe underlying medical or psychiatric conditions; had no history of a laboratory-confirmed SARS-CoV-2 infection; were not pregnant or breastfeeding; and had no previous receipt of an adenovirus-vectored, coronavirus, or SARS-CoV-2 vaccine. After informed consent was obtained, 25 mL of whole blood was withdrawn from all eligible participants who were randomised in a 1:1 ratio to receive a single intramuscular dose of 0·5 mL placebo or a 0·5 mL dose of 5×10^{10} viral particle (vp)/mL Ad5-nCoV vaccine; study staff and participants were blinded to treatment allocation. All participants were contacted weekly by email, telephone, or text message to self-report any symptoms of COVID-19 illness, and laboratory testing for SARS-CoV-2 was done for all participants with any symptoms. The primary efficacy objective evaluated Ad5-nCoV in preventing symptomatic, PCR-confirmed COVID-19 infection occurring at least 28 days after vaccination in all participants who were at least 28 days postvaccination on Jan 15, 2021. The primary safety objective evaluated the incidence of any serious adverse events or medically attended adverse events postvaccination in all participants who received a study injection. This trial is closed for enrolment and is registered with ClinicalTrials.gov (NCT04526990).

Findings Study enrolment began on Sept 22, 2020, in Pakistan, Nov 6, 2020, in Mexico, Dec 2, 2020, in Russia and Chile, and Dec 17, 2020, in Argentina; 150 endpoint cases were reached on Jan 15, 2021, triggering the final primary efficacy analysis. One dose of Ad5-nCoV showed a 57·5% (95% CI 39·7–70·0, p=0·0026) efficacy against symptomatic, PCR-confirmed, COVID-19 infection at 28 days or more postvaccination (21 250 participants; 45 days median duration of follow-up [IQR 36–58]). In the primary safety analysis undertaken at the time of the efficacy analysis (36 717 participants), there was no significant difference in the incidence of serious adverse events (14 [0·1%] of 18 363 Ad5-nCoV recipients and 10 [0·1%] of 18 354 placebo recipients, p=0·54) or medically attended adverse events (442 [2·4%] of 18 363 Ad5-nCoV recipients and 411 [2·2%] of 18 354 placebo recipients, p=0·30) between the Ad5-nCoV or placebo groups, or any serious adverse events considered related to the study product (none in both Ad5-nCoV and placebo recipients). In the extended safety cohort, 1004 (63·5%) of 1582 of Ad5-nCoV recipients and 729 (46·4%) of 1572 placebo recipients reported a solicited systemic adverse event (p<0·0001), of which headache was the most common (699 [44%] of Ad5-nCoV recipients and 481 [30·6%] of placebo recipients; p<0·0001). 971 (61·3%) of 1584 Ad5-nCoV recipients and 314 (20·0%) of 1573 placebo recipients reported an injection-site adverse event (p<0·0001), of which pain at the injection site was the most frequent; reported by 939 (59%) Ad5-nCoV recipients and 303 (19%) placebo recipients.

Interpretation One dose of Ad5-nCoV is efficacious and safe in healthy adults aged 18 years and older.

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See Online for appendix

Introduction

COVID-19, the disease caused by the SARS-CoV-2 virus, was declared a global pandemic on March 11, 2020, and has resulted in more than 267 million cases and 5·3 million deaths as of Dec 8, 202[1] Although there are 136 vaccines utilising various technologies in clinical development, only 12 have been listed by WHO for emergency use in countries around the world.[2,3] CanSino Biologics and the Beijing Institute of Biotechnology have developed an adenovirus vectored vaccine using the replication-deficient human adenovirus type 5 (Ad5-nCoV) as a vector, expressing the S protein of SARS-CoV-2. Among the first to initiate a phase 1, randomised clinical trial of their candidate COVID-19 vaccine in April, 2020, CanSino Biologics reported that one dose was well-tolerated and immunogenic in phase 1 and 2 studies.[4,5] In the phase 2 study, similar immunogenicity but higher rates of grade 3 (severe) solicited adverse events were found in the 1×10^{11} viral particle (vp) group (24 [9%] of 253 participants) than the 5×10^{10} vp group (1 [1%] of 129 participants) or the placebo group (none of 126).[5] Because the immunogenicity of the 5×10^{10} vp and the 1×10^{11} vp doses were very similar, but the 5×10^{10} vp dose showed a superior safety profile,[5] the 5×10^{10} vp dose was selected for further evaluation in the phase 3 trial. Here, we report the final primary efficacy outcome and interim primary safety outcome of a randomised, double-blinded, placebo-controlled, phase 3 trial of a single-dose Ad5-nCoV vaccine in adults 18 years and older.

Methods

Vaccine

The Ad5-nCoV vaccine (CanSino Biologics, Tianjin, China) uses the replication-defective, human adenovirus type 5 as a vector expressing the S protein of SARS-CoV-2 (ancestral strain; NC_045512.2) which is produced in HEK293SF-3F6 cells. Virus is harvested by chemical lysis of cells grown in bioreactors, followed by centrifugation, clarification, and ultrafiltration for impurity removal and

Research in context

Evidence before this study

At the time this study was designed (between July and August, 2020), the CanSino Ad5-nCoV vaccine was one of the first SARS-CoV-2 vaccines to be developed and, consequently, there were no published phase 3 clinical trials of SARS-CoV-2 vaccines. Many COVID-19 vaccines were under development; multiple phase 1 and phase 1/2 studies were underway, and results of several (Moderna's mRNA-1273, Pfizer BioNTech's BNT162b2 mRNA, AstraZeneca's ChaAdOx1 AZD1222, as well as this CanSino Ad5-nCoV vaccine) had been reported. Since then, randomised, placebo-controlled, phase 3 clinical trials have been published for the Moderna, Pfizer, and AstraZeneca vaccines as well as Johnson & Johnson's adenovirus-26-based vaccine, Gamaleya's Ad26/Ad5-based vaccine, Novavax's purified protein vaccine, Sinovac's inactivated whole-virion vaccine, and Sinopharm's inactivated vaccine. A literature search of PubMed on Dec 16, 2021, using the terms "SARS-CoV-2" or "COVID-19" and "vaccine" and "efficacy," with the filter of "randomised controlled trial," resulted in 17 peer-reviewed publications related to the efficacy of these eight vaccines against SARS-CoV-2. In general, the mRNA vaccines and protein vaccine have shown the highest efficacy (>90%) and the inactivated vaccines and adenoviral-vectored vaccines have shown efficacy in the range of 60–85%. All vaccines have been highly effective against severe COVID-19, preventing most cases requiring intensive care or resulting in death.

Added value of this study

This study provides evidence of the safety, immunogenicity, and efficacy of a single-dose, refrigerator-stable, adenovirus-vectored vaccine in a geographically and ethnically diverse population. The vaccine was 57·5% efficacious against symptomatic, PCR-confirmed, COVID-19 infection beginning 28 days postvaccination and 63·7% efficacious against symptomatic, PCR-confirmed, COVID-19 infection beginning 14 days postvaccination. Against severe disease, the Ad5-nCoV vaccine was 91·7% effective against severe disease beginning 28 days and 96·0% effective 14 days postvaccination. The vaccine was well-tolerated and immunogenic; serious adverse events were reported in 14 (0·1%) participants in the vaccine group and 10 (0·1%) participants in the placebo group. Medically attended adverse events assessed by blinded study investigators as related to the study product were reported by 40 (0·2%) Ad5-nCoV recipients and 43 (0·2%) placebo recipients. The data indicate that this Ad5-nCoV adenovirus-vectored vaccine can be added to the global armamentarium of effective COVID-19 vaccines. The vaccine has been given full authorisation in China, emergency use authorisation in ten countries (Argentina, Chile, China, Ecuador, Hungary, Indonesia, Malaysia, Mexico, Pakistan, Republic of Moldova), and is under review for emergency use listing by WHO.

Implications of all the available evidence

More than 7 billion doses of COVID-19 vaccines have been administered. Although effective COVID-19 vaccines are widely available in industrialised, wealthy countries and rates of vaccine coverage have reached 60–80%, availability of effective vaccines in lower-income and middle-income countries is lagging, with vaccine coverage only 5–30% in many countries and less than 5% in the poorest countries. The demonstration that a refrigerator-stable, single-dose vaccine is efficacious against symptomatic disease and highly efficacious against severe disease will further contribute to the goal of worldwide vaccine protection against COVID-19.

For more on **the countries in which the vaccine has been given emergency authorisation** see https://covid19.trackvaccines.org/vaccines/2/

two-step column chromatography for purification. After further ultrafiltration for buffer system replacement, preparation, and aseptic filtration, the bulk drug substance is obtained. Each 0·5 mL dose contains 5×10^{10} vp. Aside from the viral particles, the placebo contained identical excipients (mannitol, sucrose, sodium chloride, magnesium chloride, polysorbate 80, HEPES (Sigma-Aldrich, Missouri, USA), and glycerin) as the Ad5-nCoV vaccine. The vaccine is stored at 2–8°C.

Study design and participants

This double-blind, randomised, international, placebo-controlled, endpoint-case driven, phase 3 clinical trial investigated the efficacy, safety, and immunogenicity of one dose of 5×10^{10} vp/mL Ad5-nCoV vaccine in healthy adults. Participants were enrolled from 66 sites in Pakistan, Mexico, Russia, Chile, and Argentina, including 34 hospitals, 20 clinics, and 12 private practices.

Based on COVID-19 infection rates in the study countries, it was calculated that 30 000–54 000 participants would be needed to reach the efficacy-driven endpoint of 150 confirmed COVID-19 cases. Four cohorts were defined; all participants were enrolled in the main study cohort, the efficacy-safety cohort, which measured the efficacy of the Ad5-nCoV vaccine and the incidence of serious adverse events and medically attended adverse events. A subset of approximately 3000 participants, proportionately distributed among the enrolment countries, comprised three subcohorts: the extended safety cohort, which collected detailed solicited and unsolicited adverse events following immunisation; the immunogenicity cohort, a subset of the extended safety cohort (approximately 600 participants) in which antibody responses prevaccination and postvaccination were measured; and the extended immunogenicity cohort, a subset of the immunogenicity cohort (approximately 200 participants) in which cellular immunity was evaluated prevaccination and postvaccination (figure 1). The size of the subcohorts was based on regulatory guidance of size of the safety and immunogenicity database recommended for emergency use authorisation.

Recruitment was by invitation to people in the study centers' participant databases and through local advertisements. Participants were eligible to enrol in the study if they were 18 years or older; had no unstable or severe underlying medical or psychiatric conditions; had no history of a laboratory-confirmed SARS-CoV-2 infection; had no previous receipt of an adenovirus-vectored, coronavirus, or SARS-CoV-2 vaccine; and were able to understand the content of the informed consent form and provide written consent. Sex, gender, race, and ethnicity were determined by self-report. A negative pregnancy test was required for all women of childbearing potential before immunisation; women who were pregnant or breastfeeding were not eligible to participate, and all participants involved in heterosexual sexual activity had to agree to the use of approved contraceptive methods (see appendix pp 11–12. for the complete inclusion and exclusion criteria). This trial was designed and done in accordance with the Declaration of Helsinki, Good Clinical Practice, and the International Conference on Harmonisation regulations and guidelines. Ethics approval was obtained from the independent research ethics boards by the local investigators at each of the enrolment sites. The study was approved by the national regulatory authorities of each country before the start of the trial.

Randomisation and blinding

Using an interactive web response system, participants were randomised by centre in a 1:1 ratio to either the Ad5-nCoV group or the placebo control group. A subset of 3000 participants, proportionally balanced between countries of enrolment, comprised an extended safety and or immunogenicity cohort for additional monitoring. Participants were assigned a treatment identification number to ensure adequate blinding. Vaccine and an identical appearing placebo were provided in 0·5 mL prefilled syringes. Participants and study staff remained blinded to the participant's assigned group.

Procedures

After determining eligibility on day 0 and obtaining written informed consent, 25 mL of whole blood was withdrawn from all participants. Participants in the extended immunogenicity cohort provided an additional 30 mL of whole blood for cellular immune response analyses. A single 0·5 mL dose of either the Ad5-nCoV vaccine or placebo was administered to each participant in the deltoid muscle of the non-dominant arm. All participants were monitored at their study site for 30 mins following vaccination for any adverse events or serious adverse events.

To monitor for vaccine efficacy, all participants were contacted weekly by email, telephone, or text message to assess for any symptoms of COVID-19 illness (fever, cough, difficulty breathing, pneumonia, sore throat, congested or runny nose, persistent fatigue, myalgias, chills, headache, nausea, vomiting, diarrhoea, difficulty swallowing, loss of sense of taste or smell, or neurological complaints). The presence of any of these symptoms triggered laboratory testing for SARS-CoV-2 infection as well as collection of a blood sample at the time of illness during an in-person visit for symptom assessment and medical management and 4 weeks later for SARS-CoV-2 serology. Once every 4 weeks, participants were contacted by email, telephone, or text message to assess for any serious adverse events or medically attended adverse events. Any reported events were entered into the electronic data capture system (Dacima, Montreal, Canada).

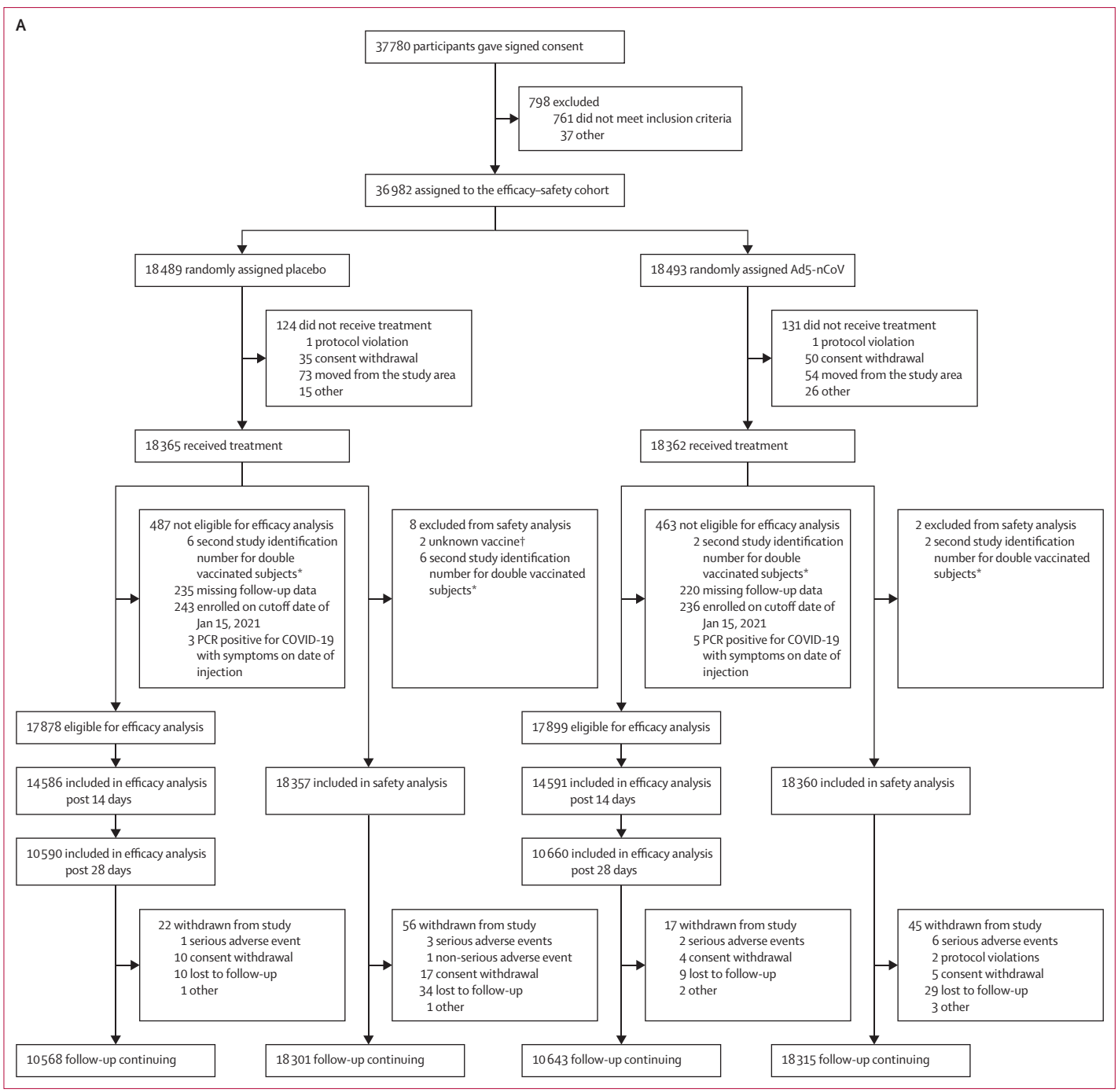
Participants in the extended safety, immunogenicity, and extended immunogenicity cohorts were instructed to record their temperature daily for 7 days after vaccination using a provided thermometer and to report any adverse

events in either an electronic or paper diary as provided. Data from paper diaries were entered into the electronic data capture system by study staff. All extended safety data were collected at day 28 postvaccination, at the participant's in-person study visit.

At day 28, 25 mL of whole blood for serological analysis was collected from participants in the immunogenicity and extended immunogenicity cohorts and an additional 30 mL was collected from participants in the extended immunogenicity cohort to evaluate cellular immune response using ELISpot.

Immunological assays

IgG antibodies to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein (ancestral strain) were measured by a validated enzyme-linked immunosorbent



(Figure 1 continues on next page)

assay (ELISA) at a CEPI global network laboratory (Nexelis Laboratories, Laval, Canada). Also at Nexelis Laboratories, neutralising antibodies against SARS-CoV-2 were measured with a validated pseudovirion neutralisation assay in which a vesicular stomatitis virus expressing the SARS-CoV-2 spike protein was used to show neutralisation capacity of antibodies in participants' serum.

Each laboratory-confirmed case of COVID-19 illness was reviewed by the blinded independent endpoint review committee according to predefined definitions of endpoint cases (appendix p 16), and an independent data monitoring committee reviewed all safety data and did the interim efficacy analysis according to the statistical analysis plan, allowing investigators and study staff to remain blinded.

Outcomes

The efficacy and safety outcomes were measured in all enrolled participants The primary safety objective was to evaluate the incidence of serious adverse events and medically attended adverse events after vaccination. The primary efficacy objective was the prevention of symptomatic, real-time PCR-confirmed COVID-19 infection occurring 28 days after vaccination. The secondary efficacy objectives were to evaluate the efficacy of Ad5-nCoV in preventing symptomatic, PCR-confirmed COVID-19 infection beginning 14 days postvaccination, to evaluate the efficacy of Ad5-nCoV in preventing severe COVID-19 disease (defined in the appendix p 13) beginning 14 and 28 days postvaccination, to evaluate the efficacy of Ad5-nCoV in different age groups (18 to <45 years, 45 to <60 years and ≥ 60 years) beginning 14 days and 28 days after vaccination, and to evaluate the efficacy of preventing serologically confirmed COVID-19 in those who reported symptoms.

Secondary safety objectives were measured in three subcohorts: the incidence of solicited local and systemic adverse events within 7 days of vaccination, and the incidence of unsolicited adverse events within seven to 28 days postvaccination. Immunogenicity objectives evaluated in participants in the immunogenicity and extended immunogenicity cohorts included seroconversion, geometric mean titres, and geometric mean increase of S-RBD IgG antibodies and pseudo-virus neutralising antibodies on day 28 postvaccination and the positive rate and concentration of interferon-γ (IFN-γ) via enzyme-linked immunosorbent spot (ELISpot) at 28 days following vaccination in the extended immunogenicity cohort. A full list of all study objectives is found in the appendix (pp 14–15).

Statistical analysis

Using WHO guidelines and with the assumption of a true vaccine efficacy of 60%, a total of 150 endpoint events was calculated to provide in excess of 90% power (adjusted for the interim analyses at 50 and 100 endpoint events) to show a minimum of 50% efficacy, with the lower limit of the CI to be more than 30%.[6] A modified intention-to-treat analysis was done for the primary safety and efficacy analysis which included all participants who received a study injection. A Cox proportional hazards model based on a time event analysis was used for primary and secondary efficacy hypotheses. Efficacy was calculated as one minus the hazard ratio for the Ad5-nCoV group relative to the placebo group. Assuming independent samples from Ad5-nCoV and placebo populations, and proportional hazards, the required number of events for testing the

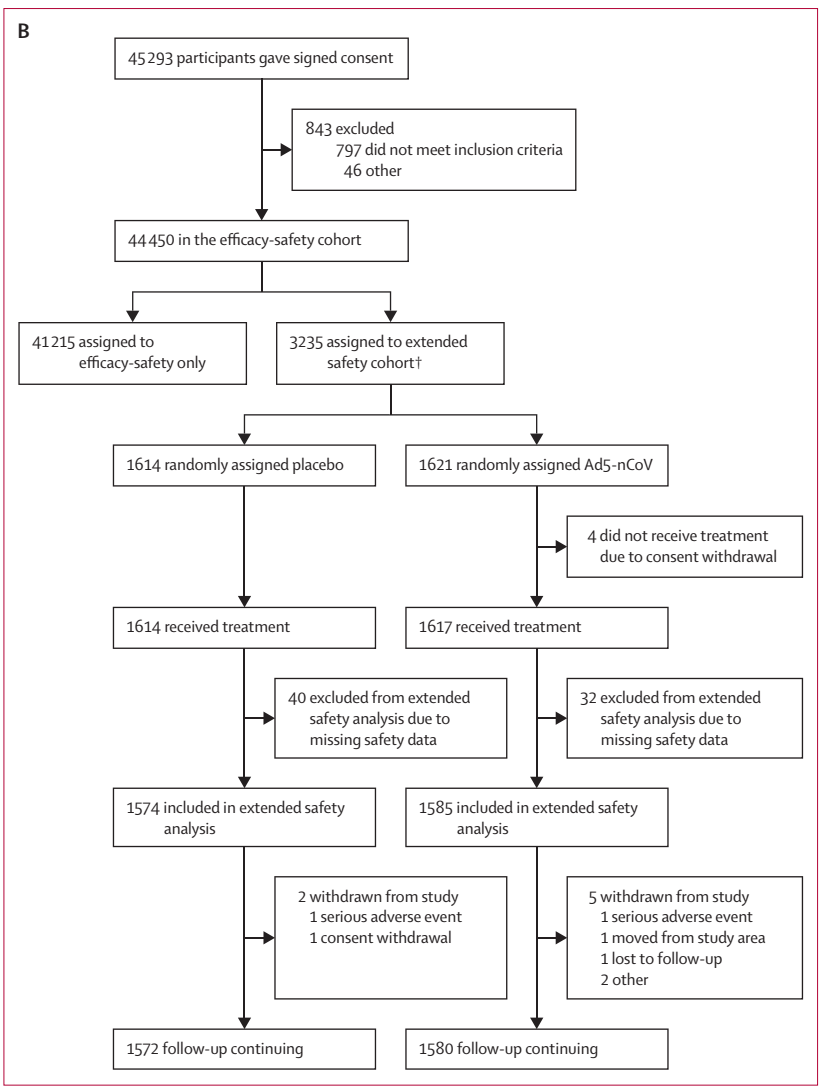


Figure 1: **Clinical trial profile**
Disposition of clinical trial participants for the efficacy analysis and safety analysis at the cutoff date of the efficacy analysis (Jan 15, 2021; A), and the extended safety and immunogenicity analyses at the cut off date for the extended safety and immunogenicity analyses (March 15, 2021; B). A subset (n=538) of participants in the extended safety and immunogenicity analyses were in the immunogenicity subcohort, allocated randomly to placebo (n=267) or Ad5-nCoV (n=271). All were included in the immunogenicity analysis. The extended immunogenicity results will be presented at a later date. *Second study identification number for double vaccinated participants are individuals who, unknown to study staff, enrolled in the study twice and were randomly assigned twice and received two study injections. In the intention-to-treat analysis, they were analysed according to the first randomisation allocation. †The unknown vaccine arose because two participants were randomised with the same dispensing code, and it is unclear which vaccine they received.

efficacy hypothesis followed Schoenfeld,[7] with an adjustment for interim monitoring using a result of Jennison and Turnbull.[8] Safety, demographic, and baseline data were listed and summarised using frequency counts and percentages, aggregated on the basis of categories and analysed using a two-sided, type 1 error rate of 5%. Endpoint safety data included incidence of serious adverse events and medically attended adverse events until the endpoint was reached on Jan 15, 2021, while extended safety endpoint data from the three subcohorts included diary recordings up to day 28 postvaccination. All proportions calculated from safety and supportive objective data were compared using binomial point estimates, binomial exact 95% CI, and Fisher's exact test to assess for differences between the vaccine and control groups.

For the immunogenicity analysis, geometric mean titres and geometric mean increase to S-RBD IgG antibodies and pseudo-virus neutralising antibodies and their two-sided 95% CIs were calculated for the vaccine and placebo groups at the previously specified timepoints. Analyses were done on the logarithmically (base 10) transformed values. Individual titres below the detection limit were set to half the limit. Rates were compared between groups using Fisher's exact tests, and geometric means were compared using t-tests. Statistical analysis was done using SAS software version 9. This trial is registered with ClinicalTrials.gov (NCT04526990).

Role of the funding source

The funders of the study were involved in the study design but not in trial procedures, data collection, or statistical analysis. They were involved in data interpretation, writing of the manuscript, and the decision to submit for publication. The funders were not involved in the data analysis.

Results

No changes were made to the analysis plan outlined in the study protocol except that only one interim analysis was done rather than the preplanned two interim analyses because of the rapid accrual of cases, which made the additional interim analysis unnecessary. However, despite only undertaking a single interim analysis, the predefined statistical adjustments for two interim analyses were applied as requested by the regulatory authorities. We report the final results of the primary and secondary efficacy analyses at the protocol-specified time points. Additional protocol-specified primary and secondary efficacy analyses and safety analyses planned at 24 and 52 weeks postvaccination, along with efficacy against serologically confirmed cases, extended immunogenicity, and supportive analyses will be reported at a later time (appendix pp 14–15).

Study enrolment and study injections commenced on Sept 22, 2020, in Pakistan, Nov 6, 2020, in Mexico, Dec 2, 2020, in Russia and Chile, and Dec 17, 2020, in Argentina. The prespecified outcome of 150 confirmed COVID-19 cases was reached by Jan 15, 2021, by which date 36 982 participants had been enrolled and randomised and 36 727 (99·3% randomised participants had received a study injection (18 365 [50·0%] received placebo and 18 362 [50·0%] received Ad5-nCoV; figure 1). The most frequent reason for not receiving an injection was moving from the study area and the withdrawal of consent. All but ten injected participants were included in the primary safety analysis (18 360 [99·99%] of 18 362 vaccine recipients and 18 357 [99·96%] of 18 365 of placebo recipients. Median follow-up of the safety cohort was 32 days (IQR 17–49). A total of 45 participants in the vaccine group and 56 participants in the placebo group withdrew early from the study; the most common reasons for withdrawal across both groups were withdrawal of consent and loss to follow-up. A serious adverse event led to early withdrawal in six Ad5-nCoV recipients and three placebo recipients. The cutoff date for the extended safety and immunogenicity analyses was set to be March 15, 2021, by which time 44 450 participants were randomised in total and 3235 (7.3%) participants were randomised in the extended safety cohort (1621 vaccine and 1614 placebo). 538 (1·2%) of 44 450 enrolled participants were randomised in the immunogenicity cohort (271 vaccine and 267 placebo), and 138 (0·3%) of 44 450 enrolled participants were randomised in the extended immunogenicity cohort (69 vaccine and 69 placebo). The results from the extended immunogenicity cohort will be presented at a later date.

There were 21 250 participants in the primary efficacy cohort (10 590 [49·8%] in the placebo group and 10 660 [50·2%] in the Ad5-nCoV group), which was defined as participants who were 28 days or more postvaccination on Jan 15, 2021. The median follow-up was 45 days (IQR 36–58). 3230 (30·5%) participants in the placebo group and 3238 (30·4%) participants in the Ad5-nCoV group had at least 8 weeks of follow-up. There were 29 177 participants in the secondary efficacy cohort (14 586 [50·0%] in the placebo group and 14 591 [50·0%] in the Ad5-nCoV group), defined as participants who were 14 days or more postvaccination on Jan 15, 2021. The median follow-up was 38 days (IQR 27–53). 3259 (22·3%) participants in the placebo group and 3261 (22·4%) participants in the Ad5-nCoV group had at least 8 weeks of follow-up. The characteristics of the participants in the primary efficacy cohort were similar in the vaccine and placebo groups and were similar to the safety cohort except for a higher proportion of Asian participants and a lower proportion of White and Hispanic participants than in the safety cohort (table 1; appendix pp 17–18). This discrepancy was accounted for by the earlier initiation of the study in Pakistan. The primary efficacy cohort comprised 12 479 (58·8%) participants from Pakistan, 7618 (35·8%) from Mexico, 781 (3·7%) from Russia, 362 (1·7%) from Chile, and 10 (0·1%) from Argentina. There were no differences between the characteristics of the Ad5-nCoV and placebo recipients in the cohort for

the secondary analysis of efficacy beginning 14 days postvaccination.

Of the 21250 participants in the primary efficacy cohort, there were 150 PCR-confirmed COVID-19 cases on Jan 15, 2021; 105 (1·0%) of 10590 participants in the placebo group and 45 (0·4%) of 10660 participants in the Ad5-nCoV group, resulting in a vaccine efficacy of 57·5% (95% CI 39·7 to 70·0; p=0·0026) beginning 28 days postvaccination (table 2). Vaccine efficacy was detectable approximately 12 days postvaccination and cases continued to accrue more quickly over time in the placebo group than in the Ad5-nCoV group (figure 2). Of the 29177 participants in the secondary efficacy cohort, there were 211 (1·4%) PCR-confirmed COVID-19 cases in the 14586 placebo recipients and 77 (0·5%) cases in the 14591 Ad5-nCoV recipients beginning 14 days post-vaccination, resulting in an efficacy of 63·7% (95% CI 52·9 to 72·1). Efficacy against severe disease was 91·7% (95% CI 36·1 to 99·0) beginning 28 days postvaccination and 96·0% (95% CI 70·5 to 99·5) beginning 14 days postvaccination. There were four COVID-19-related deaths in the placebo group and none in the Ad5-nCoV group; two deaths occurred between days 14 and 28 and two deaths occurred post-day 28. One additional death was reported in the Ad5-nCoV group that occurred four days postvaccination; this case was not a valid endpoint in either the 14-day or 28-day post-vaccination analysis.

Efficacy against severe disease in participants 60 years or older was similar to the overall study population beginning 14 days after immunisation (90·1%; 95% CI 22·3 to 98·7) but lower than the general study population with wide CIs beginning 28 days postvaccination, probably related to the smaller sample size (76·1%; 95% CI –114·3 to 97·3).

Vaccine efficacy by age was also calculated for prevention of COVID-19 of any severity; however, some analyses were not significant, possibly due to small sample sizes (table 2). Of the participants younger than 60 years, vaccine efficacy was similar beginning 28 days (60·9 to 62·2%) and 14 days (62·8 to 65·8%) postvaccination. Vaccine efficacy beginning 14 days postvaccination in participants 60 years and older was lower than it was in participants aged younger than 60 years, at 53·3% (95% CI 0·9 to 78·0), and vaccine efficacy beginning 28 days postvaccination was much lower in participants 60 years and older than in the participants aged younger than 60 years, with wide confidence intervals, at (17·5% [95% CI –127·6 to 70·1). A post-hoc analysis was done of vaccine efficacy by sex, body mass index (BMI), and country. Vaccine efficacy was higher in men (65·8%) than women (40·0%) beginning 28 days postvaccination; these differences were still observed but were less prominent in the cohort beginning 14 days postvaccination (68·5% in men and 55·7% in women; table 2). Analysis of vaccine efficacy by BMI and by country of enrolment are provided in the appendix (pp 19–20), although the precision of some estimates is affected by smaller sample sizes in these subanalyses. The assumption of proportional hazards was tested for the primary efficacy cohort using the method of Lin, Wei, and Ying.[9] The test was non-significant, with a p value of 0·22.

	Ad5-nCoV (n=10660*)	Placebo (n=10590†)
Mean age at consent (range, SD), years	37·8 (18·0–89·3, 13·8)	37·7 (18·0–93·5, 13·7)
Age distribution		
18–44 years	7623 (71·5%)	7579 (71·6%)
45–59 years	2198 (20·6%)	2171 (20·5%)
≥ 60 years	839 (7·9%)	840 (7·9%)
Sex‡		
Male	7452 (69·9%)	7578 (71·6%)
Female	3208 (30·1%)	3012 (28·4%)
Gender‡		
Male	7468 (70·1%)	7590 (71·7%)
Female	3192 (29·9%)	2998 (28·3%)
Transgender woman	0	1 (<0·1%)
Transgender man	0	1 (<0·1%)
Ethnicity‡		
Hispanic or Latino	4006 (37·6%)	3953 (37·3%)
Other	6654 (62·4%)	6637 (62·7%)
Race‡		
Data missing	18 (0·2%)	21 (0·2%)
Indigenous, Americas§	876 (8·2%)	875 (8·3%)
Asian	6230 (58·4%)	6216 (58·7%)
Black	3 (<0·1%)	4 (<0·1%)
White	1037 (9·7%)	1019 (9·6%)
Mixed race	2496 (23·4%)	2455 (23·2%)
Mean BMI (range, SD)	25·5 (11·2–77·1, 5.2)	25·6 (13·5–74·6, 5.3)
BMI category		
≥30·0	1863 (17·5%)	1850 (17·5%)
25·0–29·9	3569 (33·5%)	3588 (33·9%)
18·5–24·9	4529 (42·5%)	4389 (41·4%)
0 to <18·4	699 (6·6%)	763 (7·2%)

Data are n (%) unless otherwise stated. Ad5-nCoV=adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein. *Two participants who were randomly assigned to receive Ad5-nCoV and instead received placebo. †Two participants who were randomly assigned to receive placebo and instead received Ad5-nCoV. ‡Sex, gender, ethnicity, and race were determined by self-report. §This category includes individuals indigenous to the Americas (eg, Mayan, Diaguita, Mapuche, and Huilliche).

Table 1: **Characteristics of the study population (primary efficacy cohort)**

The demographic characteristics of the 36717 participants in the full safety cohort were similar in the vaccine and placebo groups. The mean age was 39·2 years (IQR 27–49) (10% of participants were aged ≥60 years) in the vaccine group and 39·1 (IQR 27–49) (10·1% were aged ≥60 years) in the placebo group. 6322 (34·4%) of 18363 participants in the vaccine group of the safety cohort were female and 6154 (33·5%) of 18354 participants in the placebo group were female (appendix pp 17–18). Participants were from Argentina (n=631 [1·7%]), Chile (n=1876 [5·1%]), Mexico (n=13559 [36·9%]), Pakistan (n=16950 [46·2%]), and Russia (n=3701 [10·1%]). Total medically attended adverse events were reported by 442 (2·4%) Ad5-nCoV recipients and 411 (2·2%) placebo recipients. Medically

	Ad5-nCoV group	Placebo group	Vaccine efficacy (95% CI)
Total number of COVID-19 cases			
Beginning 28 days postvaccination	45/10 660 (0·4%)	105/10 590 (1·0%)	57·5% (39·7 to 70·0)
Beginning 14 days postvaccination	77/14 591 (0·5%)	211/14 586 (1·4%)	63·7% (52·9 to 72·1)
Number of people with severe disease from COVID-19*			
Beginning 28 days postvaccination			
18–44 years	0/7623	3/7579 (<0·1%)	100%
45–59 years	0/2198	5/2171 (0·2%)	100%
≥ 60 years	1/839 (0·1%)	4/840 (0·5%)	76·1% (–114·3 to 97·3)
Beginning 14 days postvaccination			
18–44 years	0/10 102	8/10 114 (0·1%)	100%
45–59 years	0/3166	7/3125 (0·2%)	100%
≥ 60 years	1/1323 (0·1%)	10/1347 (0·7%)	90·1% (22·3 to 98·7)
Total number of COVID-19 cases by age and number of days postvaccination			
Beginning 28 days postvaccination			
18–44 years	27/7623 (0·4%)	69/7579 (0·9%)	60·9% (39·1 to 75·0)
45–59 years	11/2198 (0·5%)	28/2171 (1·3%)	62·2% (24·0 to 81·2)
≥ 60 years	7/839 (0·8%)	8/840 (1·0%)	17·5% (–127·6 to 70·1)
Beginning 14 days postvaccination			
18–44 years	49/10 102 (0·5%)	143/10 114 (1·4%)	65·8% (52·7, 75·3)
45–59 years	18/3166 (0·6%)	47/3125 (1·5%)	62·7% (35·8, 78·4)
≥ 60 years	10/1323 (0·8%)	21/1347 (1·6%)	53·3% (0·9, 78·0)
Total number of COVID-19 cases by sex and number of days postvaccination			
Beginning 28 days postvaccination			
Male	25/7452 (0·3%)	73/7578 (1·0%)	65·8% (46·1 to 78·3)
Female	20/3208 (0·6%)	32/3012 (1·1%)	40·0% (–4·9 to 65·7)
Beginning 14 days postvaccination			
Male	43/9797 (0·4%)	138/10 009 (1·4%)	68·5% (55·7 to 77·7)
Female	34/4794 (0·7%)	73/4577 (1·6%)	55·7% (33·5 to 70·5)

Ad5-nCoV=adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein. *Severe disease is defined as a minimum of one of any of the following: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 per min, heart rate ≥125 per min, SpO2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg); respiratory failure (defined as needing high- flow oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation); evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors); significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit.

Table 2: **Efficacy of Ad5-nCoV against COVID-19 with onset at least 28 days and at least 14 days after vaccination**

attended adverse events assessed by blinded study investigators as related to the study product were reported by 40 (0·2%) Ad5-nCoV recipients and 43 (0·2%) placebo recipients. Serious adverse events were reported in 14 (0·1%) participants in the vaccine group and ten (0·1%) participants in the placebo group (table 3). There were 17 non-COVID-19 related hospitalisations: nine (0·1%) in the placebo group and eight (0·04%) in the Ad5-nCoV group (p=0·814). There were 27 hospitalizations related to COVID-19 symptoms: 19 (0·1%) in the placebo group and eight (0·04%) in the Ad5-CoV group (p=0·036). There was a total of eight deaths among study participants; none of the deaths or other serious adverse events were assessed as related to the vaccine or placebo by study investigators. Angina or myocardial infarction was the most common serious adverse event, reported in five participants (two of whom died). Trauma, most often in relation to a motor vehicle accident, was reported by four participants (two of which were fatal). Appendicitis or bowel obstruction occurred in three individuals, one of whom died of sepsis. Other infections accounted for four serious adverse events. The remaining serious adverse events included a respiratory death from progression of sarcoidosis, a death associated with a central nervous system event and coma, a death of undetermined cause, a pregnancy that was ectopic, hypertriglyceridemia, syncope, exacerbated psoriasis, and attempted suicide. A list of serious adverse events and medically attended adverse events by sex and by country and a full list of serious adverse events can be found in the appendix (pp 21–24).

A total of 3235 participants were randomly assigned in the extended safety subcohort: 1621 (50·1%) received Ad5-nCoV and 1614 (49·9%) received placebo. Demographic characteristics of Ad5-nCoV and placebo recipients were similar in the extended safety cohort but differed from the overall safety cohort for several parameters including age, sex, ethnicity, and race (appendix pp 25–26). All participants randomly assigned to placebo and all but 4 (99·8%) randomly assigned to Ad5-nCoV received an injection. A total of 3159 injected participants reported safety data (either diary or unsolicited adverse event; 1585 [97·8%] vaccine recipients and 1574 [97·5%] placebo recipients) and were included in the analysis; 72 participants (32 [2·0%] vaccine recipients and 40 [2·5%] placebo recipients) were excluded due to missing data. Five (0·3%) Ad5-nCoV recipients and two (0·1%) placebo recipients withdrew early from the study; reasons included serious adverse events in two participants (one in the vaccine group and one in the placebo group), consent withdrawal not related to an adverse event in one participant in the placebo group, moved from the study area by one participant in the vaccine group, one participant lost to follow-up in the vaccine group, and other by two participants in the vaccine group.

Overall, 1004 (63·5%) 1582 of Ad5-nCoV recipients and 729 (46·4%) of 1572 placebo recipients reported a solicited systemic adverse event, and 971 (61·3%) of 1584 Ad5-nCoV recipients and 314 (20·0%) of 1573 placebo recipients reported an injection-site adverse event (p<0·0001; table 4; solicited adverse events by sex are in the appendix [pp 27–30]). Most adverse events were mild or moderate; 11·3% of Ad5-nCoV adverse events and 5·1% of placebo adverse events were categorised as grade 3 or higher (p<0·0001). Pain was the most frequent injection-site adverse event, reported by 939 (59%) Ad5-nCoV recipients and 303 (19%) placebo recipients. Redness and swelling at the injection site were

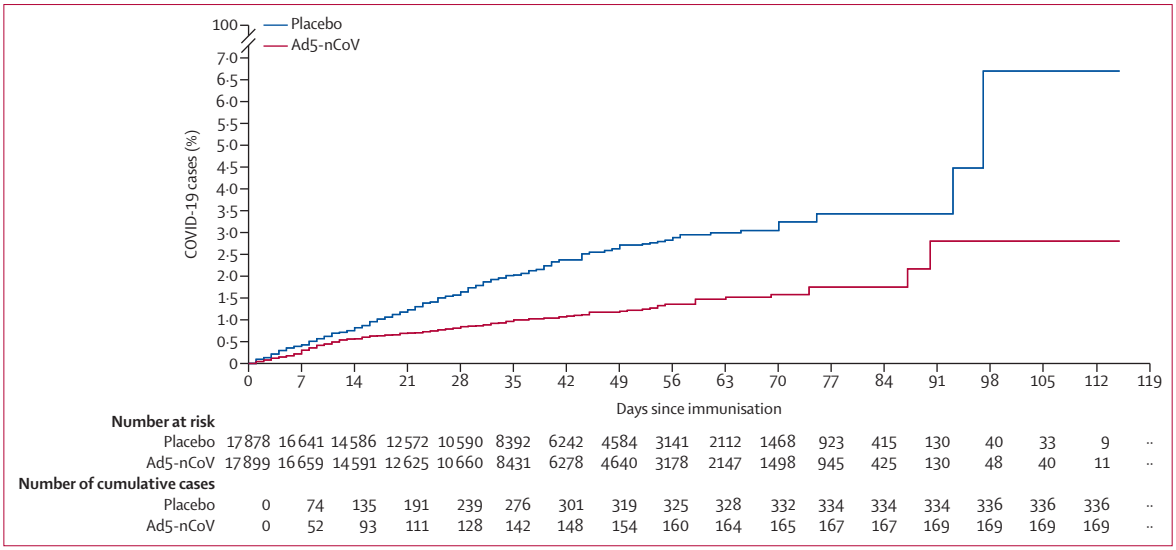


Figure 2: **Cumulative incidence of COVID-19 with onset at least 1-day postvaccination with either Ad5-nCoV or placebo**
Cases were all PCR-confirmed cases, adjudicated by the independent endpoint review committee. Ad5-nCoV=adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein.

reported in less than 10% of Ad5-nCoV recipients and less than 2% of placebo recipients. The most frequent systemic adverse events were headache (699 [44·2%] of Ad5-nCoV recipients and 481 [30·6%] of placebo recipients; p<0·0001), generalized muscle aches (651 [41·2%] and 306 [19·5%]; p<0·0001), and drowsiness (632 [40·0%] and 437 [27·8%]; p<0·0001). Fever was reported by 198 (12·5%) of Ad5-nCoV recipients and 25 (1·6%) of placebo recipients (p<0·0001); no differences were observed for vomiting or diarrhoea (table 4). Unsolicited adverse events were reported by 340 (21·4%) of 1585 Ad5-nCoV recipients and 309 (19·6%) of 1574 placebo recipients; these were categorised as grade 3 or higher by 48 (3·0%) Ad5-nCoV recipients and 33 (2·1%) placebo recipients (appendix p 31). There were no reports of thrombosis or thrombocytopenia in any study participants.

A total of 538 participants comprised the immunogenicity subcohort; 267 received placebo and 271 received Ad5-nCoV. Similar to the extended safety cohort, the demographic profile of participants in the immunogenicity cohort were slightly older, more balanced in terms of the ratio of men to women, and there were a higher proportion of Hispanic people and a lower proportion of Asian people than in the overall safety cohort (appendix pp 32–33). Ad5-nCoV elicited a substantive anti-spike antibody response (appendix p 34), with a geometric mean antibody titre increase of 32·0-fold from prevaccination to postvaccination in the Ad5-nCoV group compared with a 1·2-fold increase in the placebo group (p<0·0001). Seroconversion was shown in 236 (91·5%) of 258 Ad5-nCoV recipients compared with 6 (4·7%) of 247 placebo recipients (p<0·0001). Neutralising antibody response was also significantly higher in the Ad5-nCoV group than in the placebo group, with a geometric mean fold increase of 11·4 in Ad5-nCoV recipients compared with 1·2 in placebo recipients. Seroconversion of neutralising antibodies was shown in 195 (75·9%) of 257 Ad5-nCoV recipients and 8 (3·3%) of 246 placebo recipients.

Discussion

This multinational, phase 3, double-blinded, placebo-controlled trial showed the efficacy of a single dose of Ad5-nCoV vaccine in preventing symptomatic COVID-19 in adults 18 years of age or older. Along with previously completed phase 1 and 2 trials,[4,5] this study showed that Ad5-nCoV was well tolerated and produced high levels of anti-RBD antibodies as measured by ELISA and high levels of neutralising antibodies as measured by pseudovirion neutralization assay. Vaccine efficacy against severe disease was very high, exceeding 90% in the entire study population; there were no COVID-19 related deaths in vaccine recipients.

Efficacy calculated 14 days or longer after immunisation appeared higher than the efficacy calculated beginning at least 28 days postvaccination; however, these were point estimates and no formal statistical comparison was undertaken. Minimal efficacy was observed in the first 2 weeks postvaccination, suggesting that efficacy peaks early (2–4 weeks postvaccination) and then gradually diminishes. Most PCR-confirmed COVID-19 cases accrued in Mexico and Pakistan; throughout the study period for this analysis, the B.1.1.519 variant predominated throughout Mexico, and in Pakistan, in the last 4 weeks before reaching the study endpoint, nearly one-third of the sequenced isolates were the alpha variant, and the remainder were the ancestral strain. Presently, sequencing of the viral isolates from study participants is not available. Although vaccine efficacy might have been slightly lower

	Ad5-nCoV group (n=18 363)	Placebo group (n=18 354)	p value
Serious adverse events			
Total serious adverse events	14 (0·1%; 0·0–0·1)	10 (0·1%; 0·0–0·1)	0·54
Grade 1*	0 (0·0–0·0)	1 (<0·1%; 0·0–0·1)	0·50
Grade 2	0 (0·0–0·0)	3 (<0·1%; 0·0–0·1)	0·12
Grade 3	3 (<0·1%; 0·0–0·1)	6 (<0·1%; 0·0–0·1)	0·34
Grade 4	4 (<0·1%; 0·0–0·1)	0 (0·0–0·0)	0·12
Grade 5	7 (<0·1%; 0·0–0·1)	1 (<0·1%; 0·0–0·1)	0·07
Serious adverse events related to study product	0 (0·0–0·0)	0 (0·0–0·0)	NA
Medically attended adverse events			
Total medically attended adverse events	442 (2·4%; 2·2–2·6)	411 (2·2%; 2·0–2·5)	0·30
Grade 1	376 (2·0%; 1·9–2·3)	351 (1·9%; 1·7–2·1)	0·37
Grade 2	62 (0·3%; 0·3–0·4)	63 (0·3%; 0·3–0·4)	0·93
Grade 3	5 (<0·1%; 0·0–0·1)	10 (0·1%; 0·0–0·1)	0·21
Grade 4	3 (<0·1%; 0·0–0·1)	0 (0·0–0·0)	0·25
Grade 5	2 (<0·1%; 0·0–0·1)	1 (<0·1%; 0·0–0·1)	1·00
Total medically attended adverse events related to study product†	40 (0·2%; 0·2–0·3)	43 (0·2; 0·2–0·3)	0·74
Grade 1	35 (0·2%; 0·1–0·2)	33 (0·2; 0·1–0·3)	0·90
Grade 2	8 (<0·1%; 0·0–0·1)	10 (0·1%; 0·0–0·1)	0·65
Grade 3	0 (0·0, 0·02)	1 (<0·1%; 0·0–0·03)	0·50
Grade 4	0 (0·0, 0·02)	0 (0·0, 0·02)	NA
Grade 5	0 (0·0, 0·02)	0 (0·0, 0·02)	NA

Data are n (%; 95% CI) unless otherwise stated. Ad5-nCoV=adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein. NA=not applicable. *Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[6] †Related to study product as assessed by the local investigator.

Table 3: **Serious adverse events and medically attended adverse events following immunisation with Ad5-nCoV or placebo**

at 28 days postvaccination than efficacy at 14 days (57·5% *vs* 63·7%) for all participants, the difference between these two analysed time periods was more substantial in the older population (age ≥60 years) than in the younger age groups (18 to <45 years and 45 to <60 years). However, far fewer study participants were in the older age group than in the younger age groups (18 to <45 years and 45 to <60 years). Further postimplementation studies should be done to further substantiate the effectiveness of the vaccine in older individuals.

The single dose of 5×10^{10} vp/mL Ad5-nCoV vaccine exceeded target product profiles for efficacy calculated both 14 and 28 days postvaccination. The US Food and Drug Administration (FDA) and WHO consider licensure of a candidate vaccine with a minimum efficacy rate of 50%.[7,8] The FDA specifies that the lower limit of the appropriately used CI for COVID-19 vaccine efficacy should remain higher than 30%,[10] and WHO target profile for candidate vaccines states a vaccine efficacy greater than 70% is ideal.[11] The overall efficacy rate of one dose of Ad5-nCoV is aligned with these minimum efficacy targets at 28 days postvaccination, and most importantly, showed over 90% efficacy against severe disease and death.

Currently, one other single-dose adenoviral-vectored vaccine study has published the results of their phase 3 efficacy trial. Janssen's Ad26.COV2.S vaccine, given as a single dose, reported an efficacy of 66% at least 14 days postvaccination and at least 67% 28 days postvaccination in preventing moderate-to-severe cases of COVID-19, and 77% in preventing severe COVID-19 at least 14 days postvaccination and at least 85% 28 days postvaccination.[12] Two other two-dose adenoviral vectored vaccines have reported efficacy results: ChAdOx1 vaccine (AstraZeneca) showed an efficacy of 70·4% after two doses,[13,14] and Sputnik V vaccine (Gamaleya National Research Centre for Epidemiology and Microbiology, Russia) reported 92·0% efficacy in preventing COVID-19 after a two-dose schedule of their Ad26 followed by Ad5 vaccine.[15] A single dose of the Gamaleya Ad26 vaccine (Sputnik Light) was authorised for use in Russia on the basis of unpublished efficacy of 79·4% in an observational study of individuals who did not return for the second dose in the programme rollout.[16] Ad5-nCoV efficacy after a single dose is comparable to these other adenovirus-based COVID vaccines. Two mRNA vaccines to prevent COVID-19 also found very high efficacy rates after two doses of their vaccines: Moderna's lipid nanoparticle mRNA-1273 vaccine has a vaccine efficacy of 94·5%,[17] and Pfizer/BioNTech's BNT162b2 mRNA vaccine was found to be greater than 90% in preventing the disease.[18]

The Ad5-nCov vaccine was well-tolerated by participants and has a favourable safety profile. There were 14 serious adverse events in participants who received Ad5-nCoV and ten serious adverse events in those who received the placebo. None of the serious adverse events were assessed as vaccine-related. There were no reports of thrombotic events or vaccine-induced thrombotic thrombocytopenia, although the study was underpowered to detect an

	Ad5-nCoV	Placebo	p value
Total systemic adverse events	1004/1582 (63·5%; 61·0–65·8)	729/1572 (46·4%; 43·9–48·9)	<0·0001
Total systemic adverse events at grade 3 and above	160/1582 (10·1%; 8·7–11·7)	78/1572 (5·0%; 3·9–6·2)	<0·0001
Fever	198/1578 (12·5%; 11·0–14·3)	25/1570 (1·6%; 1·0–2·3)	<0·0001
Fever at grade 3 and above	27/1578 (1·7%; 1·1–2·5)	0/1570 (0%; 0–0·2)	<0·0001
Drowsiness	632/1581 (40·0%; 37·5–42·4)	437/1572 (27·8%; 25·6–30·1)	<0·0001
Drowsiness at grade 3 and above	66/1581 (4·2%; 3·2–5·3)	33/1572 (2·1%; 1·4–2·9)	00·0010
Headache	699/1582 (44·2%; 41·7–46·7)	481/1572 (30·6%; 28·3–32·9)	<0·0001
Headache at grade 3 and above	85/1582 (5·4%; 4·3–6·6)	30/1572 (1·9%; 1·3–2·7)	<0·0001
Nausea	192/1581 (12·1%; 10·6–13·9)	149/1571 (9·5%; 8·1–11·0)	0·019
Nausea at grade 3 and above	15/1581 (0·9%; 0·5–1·6)	6/1571 (0·4%; 0·1–0·8)	0·077
Diarrhoea	154/1581 (9·7%; 8·3–11·3)	127/1572 (8·1%; 6·8–9·5)	0·10
Diarrhoea at grade 3 and above	7/1581 (0·4%; 0·2–0·9)	6/1572 (0·4%; 0·1–0·8)	1·00
Vomiting	23/1581 (1·5%; 0·9–2·2)	21/1572 (1·3%; 0·8–2·0)	0·88
Vomiting at grade 3 and above	1/1581 (0·06%; 0·002–0·4)	3/1572 (0·2%; 0·04–0·6)	0·37
Generalised muscle aches	651/1581 (41·2%; 38·7–43·6)	306/1571 (19·5%; 17·5–21·5)	<0·0001
Generalised muscle aches at grade 3 and above	65/1581 (4·1%; 3·2–5·2)	16/1571 (1·0%; 0·6–1·6)	<0·0001
Total injection-site adverse events	971/1584 (61·3%; 58·9–63·7)	314/1573 (20·0%; 18·0–22·0)	<0·0001
Total injection-site adverse events at grade 3 and above	53/1584 (3·3%; 2·5–4·4)	10/1573 (0·6%; 0·3–1·2)	<0·0001
Redness	153/1581 (9·7%; 8·3–11·2)	19/1572 (1·2%; 0·7–1·9)	<0·0001
Redness at grade 3 and above	4/1581 (0·3%; 0·07–0·6)	1/1572 (0·06%; 0·002–0·4)	0·37
Swelling	112/1581 (7·1%; 5·9–8·5)	9/1572 (0·6%; 0·3–1·1)	<0·0001
Swelling at grade 3 and above	3/1581 (0·2%; 0·04–0·6)	0/1572 (0%; 0–0·2)	0·25
Pain	939/1584 (59·3%; 56·8–61·7)	303/1573 (19·3%; 17·3–21·3)	<0·0001
Pain at grade 3 and above	49/1584 (3·1%; 2·3–4·1)	9/1573 (0·6%; 0·3–1·1)	<0·0001
Total solicited adverse events	1180/1584 (74·5%; 72·3–76·6)	795/1573 (50·5%; 48·0–53·0)	<0·0001
Total solicited adverse events at grade 3 and above	179/1584 (11·3%; 9·8–13·0)	81/1573 (5·1%; 4·1–6·4)	<0·0001

Percentages were calculated among participants with data available. Ad5-nCoV=adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein.

Table 4: **Solicited systemic and injection-site adverse events from day 0 to day 7 postvaccination with Ad5-nCoV or placebo**

increase in this rare adverse event. In the subcohort in which detailed adverse events were collected by diary, as with the phase 1 and 2 trials, headache, drowsiness, and generalised muscle aches were the most frequently reported systemic adverse event, most described as mild or moderate in severity. As with the earlier trials with this vaccine, the most frequent adverse event reported by Ad5-nCoV recipients was mild to moderate injection-site pain, which mostly resolved in the first week postvaccination. These rates of adverse events were similar to other adenovirus vectored COVID-19 vaccines and less frequent than those reported following the mRNA vaccines.[12–20] The immunogenicity results from this study were also consistent with the results of phase 1 and 2 studies with Ad5-nCoV.[4,5] A robust neutralising antibody response was shown with a geometric mean antibody increase of over 10 fold and seroconversion in more than 75% of Ad5-nCoV recipients, a particularly important finding given the increasing evidence correlating neutralising antibody concentration and disease severity.[21]

This study had both strengths and limitations. This large study took place in multiple countries worldwide, including sites in Europe, south Asia, and South America, representing both low-income, middle-income, and high-income economies. Active case finding through weekly contact resulted in high participant retention rates; however, signs and symptoms were still self-reported (although confirmed through in-person study visits). The study population was relatively representative of the population in that people with stable chronic medical conditions were eligible to participate. However, people with immune compromising conditions, unstable medical conditions, people who were pregnant, and children were excluded from participation and women and older individuals were under-represented. The protocol-designated final efficacy analysis was done when 150 laboratory-confirmed COVID-19 cases had accrued; this resulted in a median participant follow-up of 38 days, 22·4% of participants having follow-up of 8 weeks, and a maximum participant follow-up of just under 4 months. Follow-up has continued since the final analysis cut-off with cases continuing to accrue. Additional efficacy analyses will provide data on the stability of the vaccine efficacy estimates over time and duration of protection and safety. Other secondary outcomes will also be analysed, including efficacy against variants of concern, efficacy against

asymptomatic infection, and efficacy against PCR-negative, seroconversion-positive cases.

Subsequent to the reporting of the interim efficacy results of the study, emergency use authorisation was received for Ad5-nCoV in a number of countries, including those where the clinical trial was occurring. This emergency authorisation led to widespread requests for unblinding so that placebo recipients could receive an approved active vaccine. In an effort to continue to generate useful safety, immunogenicity, and efficacy data and still provide benefit to participants, and to explore whether a second dose of Ad5-nCoV would enhance efficacy, all remaining study participants who still remain blinded have been offered a dose of Ad5-nCoV and will continue to be followed for safety and efficacy. This study extension will explore the relative efficacy of a single-dose versus a two-dose regimen of Ad5-nCoV and will be reported in due course.

In summary, in this international, placebo-controlled, randomised phase 3 clinical trial, we found that a single dose of the Ad5-nCoV vaccine protected against laboratory-confirmed, symptomatic COVID-19 and was highly effective against severe disease. As with all clinical trials, postimplementation monitoring for vaccine effectiveness and vaccine safety is necessary to further show efficacy in subpopulations that were under-represented in the study and to identify any rare adverse events that cannot be detected in the context of a clinical trial. This vaccine with its convenient refrigerator temperature storage requirements and long shelf life can play an important part in the public health response to COVID-19, particularly in resource-limited areas of the world.

Contributors

SAH, LL, and JG wrote the first draft of the study protocol and the other authors provided input and final approval. LY, BS, and DM-C were responsible for data management and statistical analysis. SAH, BS, DM-C, LY, and JG accessed and verified the underlying data. The first draft of the manuscript was completed by SAH and LL; all authors reviewed and provided comments on subsequent drafts and approved the final version; the writing group authors had final responsibility for the decision to submit for publication.

Declaration of interests

JG and TZ are employees of and own stock in CanSino Biologics, and LB is a senior scientific advisor to CanSino Biologics. All other authors received funding to their institutions to perform the clinical trial but did not receive any personal funding.

Data sharing

The clinical trial protocol can be found in the appendix (pp 40–167). De-identified individual participant data will be made available after 9 months and until 36 months following completion of the final study report, upon request to jinbo.gou@cansinotech.com. Proposals for use of the data for meta-analyses will be reviewed and approved by the study steering committee.

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