Background document on the CanSinoBIO Ad5-nCoV-S [recombinant] vaccine (Convidecia™) against COVID-19

Background document to the WHO Interim recommendations for use of the CanSinoBIO Ad5-nCoV-S vaccine (Convidecia™) against COVID-19

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World Health Organization

Note. This background document was developed to inform the initial recommendation-making process. It will not be updated on a regular basis. The latest Grade and ETR tables can be obtained here: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Ad5-nCoV-Convidecia-annexes

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Background

This background document was prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines to inform the discussions of SAGE for CanSinoBIO's COVID-19 vaccine (Ad5-nCoV-S [recombinant]) at its meeting on 5 April 2022, which resulted in the issuance of the interim recommendations *(1)* and evidence to recommendation tables (annexes) *(2)*. These are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

This document refers to the COVID-19 vaccine developed by CanSino Biologics Inc (Ad5-nCoV-S recombinant) which is authorized under the emergency use listing (EUL) procedure by WHO. It is based on the Ad5-nCoV-S recombinant core non-clinical and clinical data for regulatory evaluation. Ad5-nCoV-S recombinant will be marketed as Convidecia™. In the subsequent text, the vaccine will be referred to as Ad5-nCoV.

Context

Ad5-nCoV is a single dose recombinant replication-defective human Ad5 vector-based vaccine expressing spike S protein from SARS-CoV-2 (ancestral strain; NC_045512.2, which is produced in HEK293SF-3F6 cells) *(3)*. The vaccine presents the spike S protein of SARS-CoV-2 virus to stimulate the human immune system to generate antibodies and cellular immune responses against the virus and prevent COVID-19.

As of 31 December 2021, Ad5-nCoV has been used to vaccinate over 58 million people in China and internationally (Argentina, Chile, Malaysia, Mexico, Pakistan and Russia), including in clinical studies and in approved emergency use vaccination programmes. It demonstrates a favourable safety profile in people across different age groups (adults, older people, children and adolescents) and can elicit strong humoral immune responses with both binding antibodies and neutralizing antibodies, as well as cellular immune responses.

Characteristics of Ad5-nCoV (COVID-19) vaccine

Composition

One dose of Ad5-nCoV contains 5×10^{10} viral particles (vp) of human type 5 adenovirus encoding SARS-CoV-2 Spike (S) glycoprotein.

Ad5-nCoV includes the following excipients: mannitol, sucrose, sodium chloride, magnesium chloride, polysorbate 80, glycerin, N-(2-Hydroxyethyl) piperazine-N'-(2-ethanesulfonic acid) (HEPES) and Water for Injection (as solvent).

No preservatives or antibiotics are used in this vaccine. No animal derived components are used in the manufacturing of the Ad5-nCoV vaccine.

Dosing regimen

Ad5-nCoV is administered intramuscularly as a single intramuscular injection (0.5 ml per dose). It can be used in the primary series vaccination or as a booster dose.

Stability and shelf-life

A shelf-life of 12 months is proposed for unopened single-dose or three-dose vials. The vaccine is provided as single-dose glass vials or multidose glass vials containing 3 doses per vial (0.5 ml per dose). The vaccine should be stored and transported at 2–8 °C.

In the multidose vials, after the first dose has been withdrawn, the vial may be held at 2–8 °C for up to 6 hours. The vial should be discarded if the vaccine is not used within this time.

Drug product description

Ad5-nCoV is a colourless or slightly white solution for injection, free from visible particles, with a pH of 7.0–8.0 and does not require reconstitution.

Container

The vaccine is provided in single-dose (0.5 ml) and multidose glass vials (3 doses; 3×0.5 ml).

Each single dose vial contains a target fill volume of 0.6 ml to allow for an extractable volume of 0.5 ml. Each multidose vial contains a target fill volume of 1.8 ml to allow for an extractable volume of 1.5 ml, as 3 extractions of 0.5 ml.

Developmental and reproductive toxicity

The developmental and reproductive toxicity (DART) study was performed in male and female Sprague Dawley (SD) rats, in the pre-mating stage, mating stage, and gestational stage to lactation stage. There were no adverse findings for fertility, pregnancy, lactation, growth, development of the embryo, foetus and offspring through to postnatal day 21.

Preclinical studies

Immunogenicity and efficacy

Immunogenicity of Ad5-nCoV was evaluated in multiple animal models including in mice, rats, guinea pigs, ferrets and cynomolgus monkeys. The results demonstrated that Ad5-nCoV is immunogenic, can effectively express coronavirus S protein antigen and can induce strong humoral and cellular immune responses in animal models. The dose–response effect has been observed in animal models including mice, guinea pigs, SD rats, and cynomolgus monkeys. Animal models of hACE2 transgenic mice, Balb/c mice, ferrets *(4)* and rhesus monkeys, demonstrated that immunization with Ad5-nCoV provided good protection against challenges with live virus SARS-CoV-2 and reduced viral infection. No antibody-dependent enhancement (ADE) was observed during these challenge tests.

Biodistribution

The viral adsorption, biodistribution and shedding study of Ad5-nCoV was carried out in cynomolgus monkeys with two repeated intramuscular injections once every 2 weeks one dose (5×10^{10}vp/0.5ml/monkey) for the low-dose group and three doses (1.5×10^{11} vp/0.5ml/monkey) for the high-dose group on day 1 and day 15 respectively. The viral contents in whole blood decreased with time. In the distribution study, the highest adenoviral vector content was found in local injected muscle, followed by non-injection muscle and whole blood. For other tissues, the virus content was low. At the end of the recovery period (day 29), most of the adenovirus vector content had decreased, and the adenovirus vector content in some tissues decreased below the standard curve of detection.

Toxicology

Toxicity testing of Ad5-nCoV included a single intramuscular injection (a single human dose) in SD rats and repeated dose toxicity studies (one human dose administered singly, or three human doses administered with 2 weeks between each dose) in cynomolgus monkeys and rats. Single human dose (5×10^{10} viral particles, vp) or three human doses (1.5×10^{11}vp) were administered into SD rats or monkeys in the repeated dose toxicity studies.

In the single dose toxicity study in SD rats, the maximum tolerated dose of SD rats is equal to or greater than one dose (5×10^{10} vp/dose) as there was no toxicity reaction when vaccinated with a single intramuscular injection of Ad5-nCoV vaccine.

In the repeated dose toxicity study in cynomolgus monkeys, one dose (5×10^{10} vp/0.5 ml/monkey) or three doses (15×10^{10} vp/1.5 ml/monkey) of Ad5-nCoV were injected intramuscularly by two injections with an interval of 2 weeks. There were no toxicity reactions in all groups of animals. The No Observed Adverse Effect Level (NOAEL) of Ad5-nCoV is three doses (15×10^{10} vp). During the study, no immune-toxicity reactions were found.

In the repeated dose toxicity study in SD rats, one dose (5×10^{10} vp/rat) or three doses (15×10^{10} vp/rat) of Ad5-nCoV were injected intramuscularly with three injections with an interval of 2 weeks. No systemic toxicity reactions in any of the groups were observed. The NOAEL was 3 doses/rat (5×10^{10} vp/dose; 15×10^{10} vp in total).

The results demonstrated that Ad5-nCoV had a good safety profile in the animal models studied.

Clinical studies

The pivotal data relating to safety, efficacy, and immunogenicity of Ad5-nCoV and which informed registration of the vaccine are derived from the following studies:

- **NCT04313127**. This is a dose-escalation, single-centre, open-label, non-randomized, (phase 1, first-in-human) study of Ad5-nCoV in Wuhan, China. The study included adults aged 18–60 years who were sequentially enrolled and allocated to one of three Ad5-nCoV vaccine dose groups (5×10^{10} vp, 1×10^{11} vp, or 1.5×10^{11} vp) *(5)*.
- **NCT04341389**. This is a randomized, double-blind, placebo-controlled phase 2 clinical trial in people aged 18 years and older in a single centre in Wuhan, China. Healthy adults aged 18 years or older, who were HIV-negative and free from previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, were eligible to participate and were randomly assigned to receive the vaccine at a dose of 1×10^{11} vp, or 5×10^{10} vp, or placebo *(6)*.
- **NCT04526990.** This is a randomized, double-blind, placebo-controlled, multicentre phase 3 efficacy clinical trial in people aged 18 years and older in Argentina, Chile, Mexico, Pakistan and Russia. Those elegible to participate were healthy adults aged 18 years or older, who had no unstable or severe underlying medical or psychiatric conditions, 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. Subjects were randomized in a 1:1 ratio to receive either placebo or a 0.5 ml per dose of 5×10^{10} vp Ad5-nCoV vaccine *(3)*.
- **NCT04566770**. This is a randomized, double-blind and placebo-controlled, phase 2b single-centre clinical trial in healthy participants aged 6 years and older (enrolled in an age-sequential manner, into a younger adults cohort, aged 18–55 years (middle: MID cohort); an older adults cohort, aged 56 years and older (old: OLD cohort); and a children and adolescents cohort, aged 6–17 years (minor: MIN cohort) *(7)*.
- **NCT04568811**. This is a single-centre, open-label, phase 1 clinical trial of a booster vaccination of Ad5-nCoV in healthy adults aged 18–60 years.
- **NCT04892459.** This is a single-centre, randomized, observer-blinded, parallel-controlled, phase 4 clinical study on heterologous vaccination to evaluate the safety and immunogenicity of heterologous vaccination with inactivated novel coronavirus vaccine (Vero cell) and Ad5-nCoV in healthy adults aged 18–59 years *(8)***.**
- **NCT04916886**. This is a single-centre, randomized, double-blind bridging clinical trial and was initiated to bridge the immunogenicity among different age groups (i.e. the 6–17 years age groups and the 18–59 years age group). The trial also aimed to bridge the different commercial production scales and demonstrate the lot-to-lot consistency for Ad5-nCoV.

The Ad5-nCoV vaccine has also been developed using another immunization route – aerosol inhalation. The vaccine for inhalation (abbreviated as Ad5-nCoV-IH) has the same manufacturing process, analytical methods and specifications as the intramuscular (IM) use Ad5-nCoV vaccine. Several clinical trials have been initiated for Ad5-nCoV-IH, however administration via inhalation (IH) has not yet received EUL.

- **NCT04552366**. This is a randomized, single-centre, open-label, phase 1 trial conducted in Zhongnan Hospital (Wuhan, China), to evaluate the safety and immunogenicity of the Ad5-nCoV vaccine by aerosol inhalation in adults (aged 18 years and older) seronegative for SARS-CoV-2 *(9)*.
- **NCT04840992**. This is a phase 1/2 randomized, double-blind, placebo-controlled study, with 120 people for phase 1 divided into 5 groups (low-dose group, medium-dose group, high-dose group, mixed group and single-dose group) with 24 patients in each group. The ratio of trial vaccine to placebo was 3:1. The total sample size for the phase 2 study was 720, divided into two age groups: 18–59 years, and 60 years and older, with 6 groups in each age group (low-dose group, medium-dose group, high-dose group, mixed group (IM+IH with interval of 56 days), single-dose intramuscular injection group, single-dose group) and 60 participants in each group. The ratio of trial vaccine to placebo was 5:1.
- **NCT05043259**. This is a randomized, open-label, parallel-controlled trial to evaluate the safety and immunogenicity of heterologous boost immunization with an aerosolized adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) after two-dose priming with an inactivated SARS-CoV-2 vaccine CoronaVac in adults aged 18 years and older (*pre-print, not peer-reviewed*) *(10)*.

Immunogenicity studies in humans

The phase 1 trial (NCT04313127), conducted in China, included 108 volunteers, aged 18–60 years, vaccinated with Ad5-nCoV, who were given the low dose (5×10^{10} vp/dose), medium dose (1×10^{11} vp/dose), or high dose (1.5×10^{11} vp/dose); there were 36 subjects in each dose group. Subjects vaccinated with the three different dosages of Ad5-nCoV all showed acceptable safety profile and immunogenicity profiles *(5)*.

The phase 2 trial (NCT04341389) included 508 healthy adults aged 18 years and older, who were randomly assigned to the 1×10^{11} vp/dose group, the 5×10^{10} vp/dose group or the placebo group at a 2:1:1 ratio. Both groups who received Ad5-nCoV vaccine showed strong immune responses; the immunogenicity levels of the two groups within 28 days were roughly equivalent between the low-dose group and medium-dose group and were superior to immunogenicity levels of subjects in the placebo group *(6)*.

During the phase 1 and 2 studies, the binding anti-spike protein receptor-binding domain (S-RBD) antibody at day 28 after vaccination was found in at least 94% of study participants; the neutralizing antibody was found in at least 75% of study participants. Besides the humoral immunity, the cellular response[1] was found in at least 91% of study participants, demonstrating the good immunogenicity profile of Ad5-nCoV.

In the phase 3 trial (NCT04526990), immunoglobulin G (IgG) antibodies to the RBD of the SARS-CoV-2 spike protein were measured by a validated enzyme-linked immunosorbent assay (ELISA) at a CEPI global network laboratory (Nexelis Laboratories, Laval, Canada). Neutralizing antibodies against SARS-CoV-2 were measured with a validated pseudovirus neutralization assay where a vesicular stomatitis virus expressing the SARS-CoV-2 spike protein was used to demonstrate neutralization capacity of antibodies in participant serum (Nexelis Laboratories, Laval, Canada). In the Ad5-nCoV group, the vaccine elicited an antibody response with a geometric mean antibody titre (GMT) increase of 32.0-fold from pre-vaccination to post-vaccination compared to a 1.2-fold increase in the placebo group ($p<0.0001$). Seroconversion of S-RBD IgG antibody was demonstrated in 92% of Ad5-nCoV recipients compared to 5% of placebo recipients ($p<0.0001$). Neutralizing antibody response was also significantly higher in the Ad5-nCoV group with a GMT rising from 7.7 to 89.6 pre-vaccination to post-vaccination, compared to 7.5 to 8.4 in placebo recipients (geometric mean fold increase of 11.4 in Ad5-nCoV recipients compared to 1.1 in placebo recipients). Seroconversion of neutralizing antibodies was demonstrated in 76% of Ad5-nCoV and 3% of placebo recipients respectively. The results are summarized in Table 1 (3); Tables 2–4 provide additional analyses with age, country, and gender (*unpublished*, from data on file).

Table 1. Neutralizing antibody titres for one-dose schedule on days 0/28 for Ad5-nCoV from the phase 3 trial*

Days since first dose	Metric	Subjects with a valid assay[a]	
		Ad5-nCoV (*n*=269)	Placebo (*n*=266)
Day 0 (baseline)	GMT	7.7	7.5
	95% CI	6.7–8.9	6.3–8.6
Day 28	GMT	89.6	8.4
	95% CI	72.3–111.1	7.2–9.8

**Source*: Halperin et al. 2022 *(3)*.
[a] Immunogenicity data are based on the immunogenicity cohort subset where the subjects had a valid assay (PNA, SARS-CoV-2 antibody measured by pseudovirion neutralization assay).

Table 2. Neutralizing antibody titres by age group for one-dose schedule on days 0/28 for Ad5-nCoV from the phase 3 trial*

Days since first dose	Metric	18–59 years (n=526)		≥60 years (n=53)	
		Ad5-nCoV (*n*=263)	Placebo (*n*=263)	Ad5-nCoV (*n*=29)	Placebo (*n*=24)
Day 0 (baseline)	GMT	7.93	7.72	5.75	6.02
	95% CI	6.89–9.12	6.70–8.89	4.32–7.67	4.44–8.16
Day 28	GMT	93.91	9.21	46.49	5.79
	95% CI	75.96–116.10	7.81–10.87	23.59–91.61	4.28–7.82

**Source*: from data on file.

[1] The cytokine INF-γ was used as a main factor to evaluate the cellular response after the vaccination. In addition, the expression of TNF-α and IL-2 were also evaluated. Ad5-nCoV was capable of eliciting cellular responses and the cytokines peaked on day 14 post-vaccination.

Table 3. Neutralizing antibody titres by countries for one-dose schedule on days 0/28 for Ad5-nCoV from the phase 3 trial*

Days since first dose	Metric	Subjects with a valid assay[a]	
Pakistan (*n*=103)		**Ad5-nCoV (*n*=53)**	**Placebo (*n*=50)**
Day 0 (Baseline)	GMT	15.38	14.49
	95% CI	9.76–24.23	8.95–23.45
Day 28	GMT	174.75	21.49
	95% CI	98.48–310.10	12.79–36.11
Mexico (*n*=233)		**Ad5-nCoV (*n*=118)**	**Placebo (*n*=115)**
Day 0 (Baseline)	GMT	6.76	8.03
	95% CI	5.68–8.05	6.46–9.98
Day 28	GMT	95.68	8.21
	95% CI	70.54–129.77	6.59–10.24
Russia (*n*=49)		**Ad5-nCoV (*n*=25)**	**Placebo (*n*=24)**
Day 0 (Baseline)	GMT	12.01	7.67
	95% CI	6.67–21.61	4.74–12.41
Day 28	GMT	115.08	15.37
	95% CI	48.21–274.72	6.67–35.42
Chile (*n*=47)		**Ad5-nCoV (*n*=24)**	**Placebo (*n*=23)**
Day 0 (Baseline)	GMT	5.92	5.00
	95% CI	4.17–8.41	NE
Day 28	GMT	86.12	5.00
	95% CI	42.88–172.93	NE
Argentina (*n*=147)		**Ad5-nCoV (*n*=72)**	**Placebo (*n*=75)**
Day 0 (Baseline)	GMT	5.31	5.05
	95% CI	4.87–5.80	4.95–5.14
Day 28	GMT	41.67	5.51
	95% CI	31.00–56.01	4.95–6.13

**Source*: from data on file.

NE: not evaluable.

[a] Immunogenicity data are based on the immunogenicity cohort subset where the subjects had a valid assay (PNA, SARS-CoV-2 antibody measured by pseudovirion neutralization assay).

Table 4. Neutralizing antibody titres by sex for one-dose schedule on days 0/28 for Ad5-nCoV from the phase 3 trial*

Days since first dose	Metric	Subjects with a valid assay[a]			
		Male (*n*=317)		Female (*n*=262)	
		Ad5-nCoV (*n*=170)	Placebo (*n*=147)	Ad5-nCoV (*n*=122)	Placebo (*n*=140)
Day 0 (Baseline)	GMT	7.95	8.73	7.32	6.50
	95% CI	6.66 – 9.50	7.04 – 10.81	6.06 – 8.83	5.61 – 7.53
Day 28	GMT	98.28	9.82	74.58	7.95
	95% CI	74.18 – 130.21	7.74 – 12.47	55.90 – 99.49	6.55 – 9.65

**Source*: from data on file.

[a] Immunogenicity data are based on the immunogenicity cohort subset where the subjects had a valid assay (PNA, SARS-CoV-2 antibody measured by pseudovirion neutralization assay).

Immunogenicity for variants of concern

The neutralizing antibody titre of human serum immunized with Ad5-nCoV was tested against different strains by using the microdose cytopathogenic effect assay. The serum samples were collected from a phase 2b clinical trial (NCT04566770). As summarized in Table 5, 10 strains were used for testing.

Table 5. Number and description of virus strains*

No.	Serial number	Description
1	HB01	Early epidemic strain, genotype is L-type
2	HB02	Early epidemic strain, genotype is L-type
3	CQ01	Early epidemic strain, genotype is L-type
4	QD01	Early epidemic strain, genotype is L-type
5	BJ01	D614G, originated from Europe
6	DL01	D614G, originated from Europe
7	XT01	Representative strains in Russia
8	SJZ01	Representative strains in Russia
9	BJ2021	British isolated strain
10	GDPCC	Representative strains in South Africa

**Source*: from data on file.

The analysis of results of neutralizing antibody titres of sera from 20 subjects vaccinated with Ad5-nCoV are shown in Table 6. The immune serum of Ad5-nCoV recipients produced neutralizing antibodies against 10 virus strains, except for the Delta variant which showed a lower neutralizing antibody titre.

Table 6. Results of the test against variant strains for Ad5-nCoV*

Serial number of virus strain	Range of titres	GMT	Lower limit of 95%CI	Upper limit of 95%CI
CQ01	8–64	28.35	21.18	37.87
HB02	8–32	14.55	11.23	18.80
BJ01	6–24	11.65	8.73	15.50
GDPCC	2–12	4.05	2.91	5.63
HB01	8–48	20.17	16.28	24.91
QD01	12–96	26.61	20.66	34.19
DL01	8–64	15.28	11.30	20.61
XT01	8–32	18.02	14.36	22.54
SJZ01	8–32	17.20	13.61	21.70
BJ2021	6–24	12.38	10.32	14.79

**Source*: from data on file.

A study collected serum samples from individuals who had received different vaccines, including Ad5-nCoV, 28 days after completion of a standard vaccination procedure (1 dose at 0 days; 300µl/dose). In the study, 18 serum samples were used for Ad5-nCoV. Comparison was made with the D614G reference strain, and with three B.1.617 variants (B.1.617.1-H/L, B.1.617.2-H/L (Delta variant), and B.1.617.3-H/L). The neutralization activities of Ad5-nCoV-immunized sera were reduced by 1.2–1.7-fold, 0.9–1.4-fold, and 1.4–1.7-fold respectively for the three B.1.617 variants. Notably, the low-frequency variants with more mutations consistently reduced the neutralization abilities to a greater extent, compared with the high-frequency variants. Single-mutation analyses indicated that E484Q was the main source of neutralization resistance, whereas the L452R and T478K mutations showed weaker effects. Furthermore, E484Q induced neutralization resistance to an extent comparable with the resistance induced by E484K (*pre-print, not peer-reviewed*) *(11)*.

A study measured the binding, blocking and neutralizing activities of serum specimens post-vaccination of different vaccines; samples were obtained from 30 recipients of one dose of Ad5-nCoV (1 month after vaccine receipt). The binding antibody titres (coated antigen was wild type RBD or Omicron RBD detected by ELISA assay) were lower for the Omicron variant than for the prototype strain. All the specimens lost the blocking activity against the Omicron variant (hACE2-blocking antibody titres were detected by ELISA using wild-type or Omicron spike protein, which binds to human ACE2), whereas nearly all the specimens exhibited positive blocking activity against the prototype strain. Pseudovirus-based neutralization assays demonstrated that the geometric mean NT_{50} titres against the Omicron variant were 6-fold lower than those against the prototype strain, suggesting a lower immune response against Omicron (*pre-print, not peer-reviewed*) *(12)*.

Efficacy studies

The following discussion relates to the phase 3 study conducted in Argentina, Chile, Mexico, Pakistan and Russia (NCT04526990) *(3)*.

Case definitions

Case definitions for probable, confirmed and endpoint cases (including severe disease) are given in Box 1. Study endpoints are described in Box 2.

Box 1. Case definitions for probable, confirmed and endpoint cases (including severe disease) in the phase phase 3 study (NCT04526990) (3)

Suspected case
Subject with any of the following symptoms (or signs) is reported as a suspected case:
Fever, cough, dyspnoea and difficulty breathing, anosmia/ageusia, chills, myalgia, sore throat, prolonged fatigue, diarrhoea, nausea, vomiting, headache, congested/runny nose, pneumonia, difficulty swallowing, loss of sense of smell and taste, and neurological events.

Probable case
1. A suspected case for whom testing for the COVID-19 virus is inconclusive; OR
2. A suspected case for whom testing could not be performed for any reason.

Confirmed case
A suspected case with laboratory confirmation of COVID-19 infection (including PCR positive result, OR a 4-fold or greater increase of anti N IgG at convalescence phase as compared to acute phase).

Endpoint case
Confirmed cases are categorized into primary endpoint cases and secondary endpoint cases according to the time of onset after vaccination.

Primary endpoint case: the clinical symptom(s) of the participant occurred not less than 28 days post-vaccination and the PCR test is positive.

Secondary endpoint case: the clinical symptom(s) of the participant occurred not less than 14 days post-vaccination and the PCR test is positive; or a 4-fold or greater increase of anti N IgG is detected after the occurrence of the clinical symptom(s).

Both primary and secondary endpoint cases need to be reported to the Endpoint Review Committee (ERC) for final review.

Severe disease was defined as any of the following:

- clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 per minute; heart rate ≥125 per minute; SpO2 ≤93% on room air at sea level; or PaO2/FiO2 <300 mm Hg);
- respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or extra corporeal membrane oxygenation [ECMO]);
- 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.

Box 2. Primary and secondary efficacy, safety and immunogenicity endpoints in the phase 3 study (NCT04526990) *(3)*

Primary efficacy endpoint

The primary efficacy endpoint is the efficacy of Ad5-nCoV in preventing virologically-confirmed (PCR positive) COVID-19 disease occurring 28 days to 52 weeks after vaccination, regardless of severity.

Main secondary efficacy endpoints

- The number of virologically-confirmed (PCR positive) COVID-19 cases occurring from day 14 to week 52 after vaccination, regardless of severity, in the Ad5-nCoV group compared to the placebo group.
- The number of virologically-confirmed (PCR positive) severe COVID-19 cases caused by SARS-CoV-2 infection occurring from day 28 to weeks 24 and 52 after vaccination, in the Ad5-nCoV group compared to the placebo group.
- The number of virologically-confirmed (PCR positive) severe COVID-19 cases caused by SARS-CoV-2 infection from day 14 to weeks 24 and 52 after vaccination, in the Ad5-nCoV group compared to the placebo group.
- The number of virologically-confirmed (PCR positive) SARS-CoV-19 cases in different age groups from day 28 to weeks 24 and 52 after vaccination in the Ad5-nCoV group compared to the placebo group.
- The number of virologically-confirmed (PCR positive) SARS-CoV-19 cases in different age groups from day 14 to weeks 24 and 52 after vaccination in the Ad5-nCoV group compared to the placebo group.

Primary safety endpoint

The number of serious adverse events (SAEs) and medically attended adverse events (MAEs) within 52 weeks after vaccination in all participants reported in the Ad5-nCoV group compared to the placebo group.

The efficacy-safety cohorts will be used to assess the primary safety endpoint.

Main secondary safety endpoints

- The incidence of solicited adverse reactions within 7 days after vaccination (in a safety subset of about 3000 participants only; approximately 7–10% of total).
- The incidence of unsolicited adverse events within 28 days after vaccination (in a safety subset of about 3000 participants only; approximately 7–10% of total).

The efficacy-extended safety; efficacy-extended safety-immunogenicity; and efficacy-extended safety-extended immunogenicity cohorts will be used to assess the secondary safety endpoints.

Immunogenicity endpoints

The main immunogenicity endpoints include:

- Seroconversion rate, GMT and geometric mean increase (GMI) of S-RBD IgG antibody on day 28, weeks 24 and 52 after vaccination by ELISA.
- Seroconversion rate, GMT and GMI of pseudo-virus neutralizing antibody on day 28, weeks 24 and 52 after vaccination.
- Positive rate and level of IFN-γ by peptide pool of S protein on day 28, weeks 24 and 52 after vaccination, measured by ELISpot.
- Positive rate and level of IL-2, IL-4, IL-13, and IFN-γ stimulated by peptide pool of S protein on day 28, and weeks 24 and 52 after vaccination, measured by intracellular cytokine staining (ICS).

Participant characteristics

Study enrollment for the phase 3 trial (NCT04526990) commenced on 15 September 2020; the first study injection was administered on 22 September 2020. The pre-specified outcome of 150 confirmed COVID-19 cases was reached on 15 January 2021. Table 7 provides the distribution across the country cohorts; Table 8 and Table 9 (3) provide the demographic characteristics of the study participants.

Table 7. Sample size at each country in the phase 3 study (NCT04526990)*

Cohort	Total sample size	Pakistan	Mexico	Chile	Argentina	Russia
Efficacy-safety cohort	40 939	16 742	13 478	3068	2906	4745
Efficacy-extended safety cohort	2698	500	801	300	475	622
Efficacy- extended safety-immunogenicity cohort	400	50	150	50	100	50
Efficacy-extended safety-extended immunogenicity cohort	210	60	100	0	50	0
Total	**44 247**	**17 352**	**14 529**	**3418**	**3531**	**5417**

**Source*: from data on file.

Table 8. Demographic characteristics of participants in the phase 3 study – safety cohort (NCT04526990)*

		Administered Group				
		Ad5-nCoV		Placebo		
Characteristics		N	%	N	%	p value
Randomized group	Placebo	6[a]	0.0	18 351	100.0	–
	Ad5-nCoV	18 357	100.0	3*	0.0	–
Age at consent	N	18 363	–	18 354	–	0.802
	Mean (range)	39.2 (18.0–91.5)	–	39.1 (18–93.5)	–	–
Age distribution	18 to <45 years	12 398	67.5	12 385	67.5	0.955
	45 to <60 years	4121	22.4	4109	22.4	–
	≥60 years	1844	10.0	1860	10.1	–
Sex[b]	Male	12 041	65.6	12 200	66.5	0.069
	Female	6322	34.4	6154	33.5	–
Gender[b]	Male	12 070	65.7	12 213	66.5	0.376
	Female	6287	34.2	6136	33.4	–
	Transgender – male to female	1	0.0	0	0.0	–
	Transgender – female to male	1	0.0	2	0.0	–
	Neither male nor female	1	0.0	2	0.0	–
	Prefer not to identify	3	0.0	1	0.0	–
Ethnicity[b]	Hispanic or Latino	7967	43.4	7995	43.6	0.737
	Not Hispanic or Latino	10 396	56.6	10 359	56.4	–
Race[b]	Missing	30	0.2	38	0.2	0.914
	Indigenous, Americas	1257	6.8	1261	6.9	–
	Asian	8524	46.4	8495	46.3	–
	Black	4	0.0	6	0.0	–
	Native Hawaiian or other Pacific Islander	0	0.0	1	0.0	–
	White	4021	21.9	4037	22	–
	Mixed race	4527	24.7	4516	24.6	–
BMI	N	18363	–	18 354	–	0.889
	Median (range)	25.4 (11.2–77.1)	–	25.4 (13.1–74.6)	–	–
BMI Category	≥30	3475	18.9	3451	18.8	0.404
	25 to <30	6341	34.5	6369	34.7	–
	18.5 to <25	7560	41.2	7478	40.7	–
	0 to <18.5	987	5.4	1056	5.8	–

**Source*: Halperin et al. 2022 *(3)*.

[a] Participants randomized to receive Ad5-nCoV who received placebo, or who were randomized to placebo and administered Ad5-nCoV; [b] Sex, gender, ethnicity, and race were determined by self-report.

Table 9. Demographic characteristics of participants in the phase 3 study – full analysis set (NCT04526990)*

	Ad5-nCoV (*n*=10660[a])	Placebo (*n*=10590[b])
Mean age at consent (range, standard deviation (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[c]		
Male	7452 (69.9%)	7578 (71.6%)
Female	3208 (30.1%)	3012 (28.4%)
Gender[c]		
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[c]		
Hispanic or Latino	4006 (37.6%)	3953 (37.3%)
Other	6654 (62.4%)	6637 (62.7%)
Race[c]		
Data missing	18 (0.2%)	21 (0.2%)
Indigenous, Americas[d]	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%)

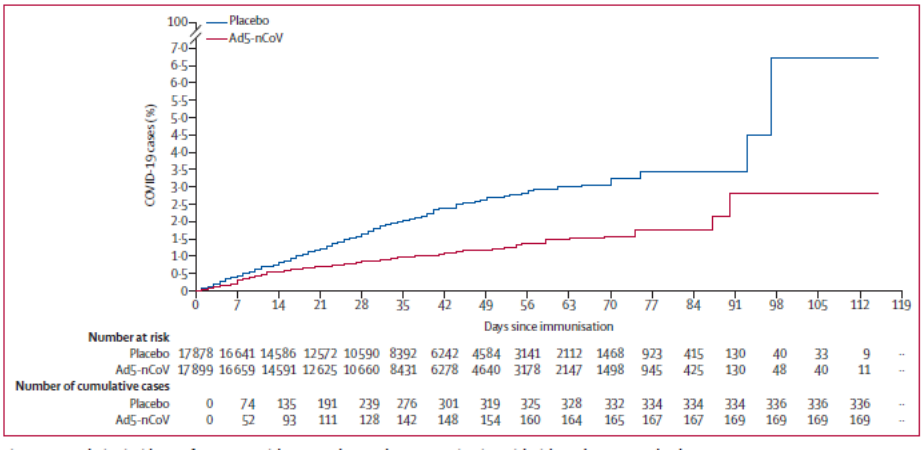
**Source*: Halperin et al. 2022 *(3)*. Data are n (%) unless otherwise stated. Ad5-nCoV=adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein.
[a]Two participants who were randomly assigned to receive Ad5-nCoV and instead received placebo. [b]Two participants who were randomly assigned to receive placebo and instead received Ad5-nCoV. [c]Sex, gender, ethnicity, and race were determined by self-report. [d]This category includes individuals indigenous to the Americas (e.g. Mayan, Diaguita, Mapuche, and Huilliche).

Summary of results

There were 21 250 participants in the primary efficacy cohort, which was defined as participants who were 28 days or more post-vaccination on 15 January 2021. The median follow-up was 45 days, interquartile range (IQR) 36-58 (6468 [30.4%] participants had at least 8 weeks of follow-up). The longer term (up to 6 months) follow-up results are expected to be available after July 2022. There were 29 177 participants in the secondary efficacy cohort, defined as participants who were 14 days or more post-vaccination on 15 January 2021. The median follow-up was 38 days, IQR 27-53 (6520 [22.4%] participants had at least 8 weeks of follow-up). The characteristics of the 21 250 participants in the primary efficacy cohort were similar in the vaccine and placebo groups (Table 8) (from data on file and *(3)*).

Of the 21 250 participants in the primary efficacy cohort, there were 150 cases of symptomatic COVID-19 on 15 January 2021: 105 cases in the placebo group and 45 in the Ad5-nCoV group, for an efficacy of 58% (95% CI: 40–70) beginning 28 days post-vaccination. Vaccine efficacy was detectable approximately 12 days post-vaccination; cases continued to accrue more quickly over time in the placebo group. Among the 29 177 participants in the secondary efficacy cohort, there were 211 cases of symptomatic COVID-19 in placebo recipients and 77 cases in the Ad5-nCoV recipients, for an efficacy of 64% (95% CI: 53–72), see Figure 1 *(3)*.

Figure 1. Cumulative incidence of COVID-19 with onset at least 1-day post-vaccination with either Ad5-nCoV or placebo in the phase 3 study (NCT04526990)*



* Cases were all PCR-confirmed, adjudicated by the independent endpoint review committee. Ad5-nCoV=adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein (3).

Efficacy against severe disease

Efficacy against severe disease was 92% (95% CI: 36–99) beginning 28 days post-vaccination and 96% (95% CI: 71–99) beginning 14 days post-vaccination. There were four COVID-19-related deaths in the placebo group and none in the Ad5-nCoV group. Efficacy against severe disease in participants aged 60 years or older was similar to the overall study population beginning 14 days after vaccination (90%; 95% CI: 22–99) but lower with wide confidence intervals beginning 28 days post-vaccination, which is likely related to the smaller sample size (76%; 95% CI: -114–97) *(3)*.

Efficacy by age

Among participants aged less than 60 years, vaccine efficacy was similar beginning 28 days (95% CI: 61–62.2) or 14 days (95% CI: 62.8–65.8) post-vaccination. In participants aged 60 years or older, vaccine efficacy beginning 14 days post-vaccination was lower at 53% (95% CI: 1–78), and much lower with wide confidence intervals beginning 28 days post-vaccination (18%; 95% CI: -128–70) *(3)*.

Efficacy by sex

Vaccine efficacy was also higher in males (66%, 95% CI: 46–78) than in females (40%, 95% CI: -5–66) beginning 28 days post-vaccination. These differences continued to be observed but were less prominent in the cohort beginning 14 days post-vaccination, with 69%, (95% CI: 56–78) in males versus 56% (95% CI: 34–71) in females *(3)*.

Efficacy for people with comorbidities

Efficacy is calculated in the subgroup with any comorbidities[1] (6182 subjects in total). No significant difference was seen in vaccine efficacy against comorbidities (61%, 95% CI: 36–76), compared to the overall population efficacy of 64% (95% CI: 53–72) 14 days post-vaccination (from data on file). The VE for people with any comorbidities (3753 subjects in total) was 49% (95% CI 0, 74) beginning 28 days post-vaccination.

Vaccine efficacy for the obesity subgroup (184 people in the vaccine group versus 161 people in the placebo group) was 61% (95% CI: 37– 76), while it was 55% (95% CI: -16–83) for the diabetes subgroup (495 people in the vaccine group versus 488 people in the placebo group), and 67% (95% CI: 30–85) for the hypertension subgroup (1016 people in the vaccine group and 1010 people in the placebo group) (from data on file).

[1] Cormobidities were mainly hypertension, diabetes mellitus, type 2 diabetes mellitus, obesity (defined as obese according to the comorbidity data in the electronic data capture database and as diagnosed by site investigators), drug hypersensitivity, depression and anxiety.

Efficacy for people with pre-existing immunity associated with Ad5

There were no differences seen in the pre-existing immunity associated with Ad5 across the five countries in the phase 3 study (p=0.32, assayed from approximately 100 pre-immunization sera samples randomly selected from each country). The stratified comparison with a cutoff value of Ad5 antibody 200 showed that the percentage of pre-existing Ad5 antibody ≤ 200 ranged from 65.4%-67.7% in these five countries, while those > 200 ranged from 32.4%-34.6%. Once again there were no differences seen between the countries (p=0.10). Results stratified by pre-existing Ad5 immunity will be available after the end of 2022.

Table 10 and Table 11 summarize the vaccine efficacy results from the phase 3 clinical trial after 14 and 28 days respectively.

Table 10. Vaccine efficacy as per full analysis set, 14 days post-vaccination in the phase 3 study (NCT04526990)*

	Ad5-nCoV		Placebo			
Group/subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	**Vaccine efficacy (%) (95% CI)**	**Notes**
All	14 591	77	14 586	211	64 (53–72)	Medium follow-up time at datalock: 39 days. Datalock time: 15 January 2021.
Sex						
Male	9797	43	10 009	138	69 (56–78)	–
Female	4794	34	4577	73	56 (34–71)	–
Age group (yrs) and vaccine efficacy against confirmed symptomatic COVID-19 disease of any severity						
All ages	14 591	77	14 586	211	64 (53–72)	–
18 to <45	10 102	49	10 114	143	66 (53–75)	–
45 to <60	3166	18	3125	47	63 (36–78)	–
18 to <60	13 268	67	13 239	190	65 (54–74)	–
≥60	1323	10	1347	21	53 (1–78)	–
Age group (yrs) and vaccine efficacy against severe/critical confirmed COVID-19 disease						
All ages	14 591	1	14 586	25	96 (71–100)	–
≥60	1323	1	1347	10	90 (22–99)	–
Age group (yrs) and vaccine efficacy against hospitalization with confirmed COVID-19 disease						
All ages	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Hospitalization is not tracked in this study per protocol design.
18 to 59	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	
≥60	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	
Region and vaccine efficacy against confirmed symptomatic COVID-19 disease						
Pakistan	7509	28	7510	90	69 (53–80)	–
Mexico	5587	46	5579	109	58 (41–70)	–

	Ad5-nCoV		Placebo			
Group/subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	**Vaccine efficacy (%) (95% CI)**	**Notes**
Russia	982	2	982	5	60 (-104–92)	–
Chile	461	1	461	7	86 (-15–98)	–
Argentina	52	0	54	0	–	
Region and vaccine efficacy against severe/critical confirmed symptomatic COVID-19 disease						
Pakistan	7509	0	7510	6	100 (-0–100)	–
Mexico	5587	1	5579	18	95 (59–99)	–
Russia	982	0	982	1	100 (-0–100)	–
Chile	461	0	461	0	–	–
Argentina	52	0	54	0	–	–
Race and vaccine efficacy against confirmed symptomatic COVID-19 disease						
American Indian or Alaska Native	1080	10	1078	11	–	–
Asian	7510	28	7506	90	69 (53–80)	–
Black	3	0	4	0	–	–
Native Hawaiian or Other Pacific Islander	0	0	1	0	–	–
White	2214	10	2226	32	69 (37–85)	–
Other	3765	29	3744	78	63 (44–76)	–
Missing	19	0	27	0	–	–
Comorbidity, presence						
Yes	3123	23	3059	56	61 (36–76)	–
Age group and comorbidity present and vaccine efficacy against confirmed symptomatic COVID-19 disease of any severity						
18 to 59, yes	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
≥60, yes	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Age group and comorbidity present and vaccine efficacy against severe/critical COVID-19 disease						
18 to 59, yes	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
≥60, yes	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
BMI and vaccine efficacy against confirmed symptomatic COVID-19 disease						
<18.5	848	2	918	10	78 (-0–95)	–
18.5 to <25	6048	22	5956	67	68 (49–80)	–
25 to <30	4988	30	5031	75	60 (39–74)	–
≥30	2707	23	2681	59	61 (37–76)	–
Comorbidity, type						
HIV infection	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–

	Ad5-nCoV		Placebo			
Group/subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	**Vaccine efficacy (%) (95% CI)**	**Notes**
Baseline SARS-CoV-2 Status and vaccine efficacy against confirmed symptomatic COVID-19 disease of any severity						
Regardless of baseline SARS- CoV-2 status	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Positive SARS- CoV-2	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Negative SARS- CoV-2	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Vaccine efficacy against asymptomatic infection						
All participants	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Vaccine efficacy against hospitalization with onset at least 14 days after vaccination						
All participants	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–

**Source*: Halperin et al. 2022 *(3)*; and from data on file.

Table 11. Vaccine efficacy as per full analysis set, 28 days post vaccination in the phase 3 study (NCT04526990)*

	Ad5-nCoV		Placebo			
Group/subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	**Vaccine efficacy (%) (95% CI)**	**Notes**
All	10 660	45	10 590	105	58 (40–70)	Medium follow-up time at datalock: 46 days. Datalock time: 15 January 2021.
Sex						
Male	7452	25	7578	73	66 (46–78)	–
Female	3208	20	3012	32	40 (-5–66)	–
Age group (yrs) and vaccine efficacy against confirmed symptomatic COVID-19 disease of any severity						
All ages	10 660	45	10 590	105	58 (40–70)	–
18 to <45	7623	27	7579	69	61 (39–75)	–
45 to <60	2198	11	2171	28	62 (24–81)	–
18 to <60	9821	38	9750	97	61 (43–73)	–
≥60	839	7	840	8	18 (-128–70)	–
Age group (yrs) and vaccine efficacy against severe/critical confirmed COVID-19 disease						
All ages	10 660	1	10 590	12	92 (36–99)	–
≥60	839	1	840	4	76 (-114–97)	–
Age group (yrs) and vaccine efficacy against hospitalization with confirmed COVID-19 disease						
All ages	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Hospitalization is not tracked in this study per protocol design.
18 to 59	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	
≥60	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	

	Ad5-nCoV		Placebo			
Group/subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	**Vaccine efficacy (%) (95% CI)**	**Notes**
Region and vaccine efficacy against confirmed symptomatic COVID-19 disease						
Pakistan	6244	19	6235	57	67 (45–80)	–
Mexico	3834	26	3784	47	45 (11–66)	–
Russia	394	0	387	1	100 (-1–100)	–
Chile	184	0	178	0	–	–
Argentina	4	0	6	0	–	–
Region and vaccine efficacy against severe/critical confirmed symptomatic COVID-19 disease						
Pakistan	6244	0	6235	4	100 (-1–100)	–
Mexico	3834	1	3784	8	88 (0–98)	–
Russia	394	0	387	0	–	–
Chile	184	0	178	0	–	–
Argentina	4	0	6	0	–	–
Race and vaccine efficacy against confirmed symptomatic COVID-19 disease						
American Indian or Alaska Native	878	4	876	3	–	–
Asian	6230	19	6216	57	67 (44–81)	–
Black	3	0	4	0	–	–
White	1035	3	1019	8	63 (-44–90)	–
Other	2499	19	2455	37	49 (11–71)	–
Missing	15	0	20	0	–	–
Comorbidity, presence						
Yes	1893	13	1860	24	49 (0–74)	–
Age group and comorbidity present and vaccine efficacy against confirmed symptomatic COVID-19 disease of any severity						
18 to 59, yes	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
≥60, yes	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Age group and comorbidity present and vaccine efficacy against severe/critical COVID-19 disease						
18 to 59, yes	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
≥60, yes	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
BMI and vaccine efficacy against confirmed symptomatic COVID-19 disease						
<18.5	699	2	763	4	45 (-200–89)	–
18.5 to <25	4529	10	4389	33	71 (41–86)	–

	Ad5-nCoV		Placebo			
Group/subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	**Vaccine efficacy (%) (95% CI)**	**Notes**
25 to <30	3569	20	3588	31	35 (-13–63)	–
≥30	1863	13	1850	37	65 (34–81)	–
Comorbidity, type						
HIV infection	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Baseline SARS-CoV-2 status and vaccine efficacy against confirmed symptomatic COVID-19 disease of any severity						
Regardless of baseline SARS- CoV-2 status	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Positive SARS- CoV-2	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Negative SARS- CoV-2	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Vaccine efficacy against asymptomatic infection						
All participants	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–
Vaccine efficacy against hospitalization with onset at least 14 days After vaccination						
All participants	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	–

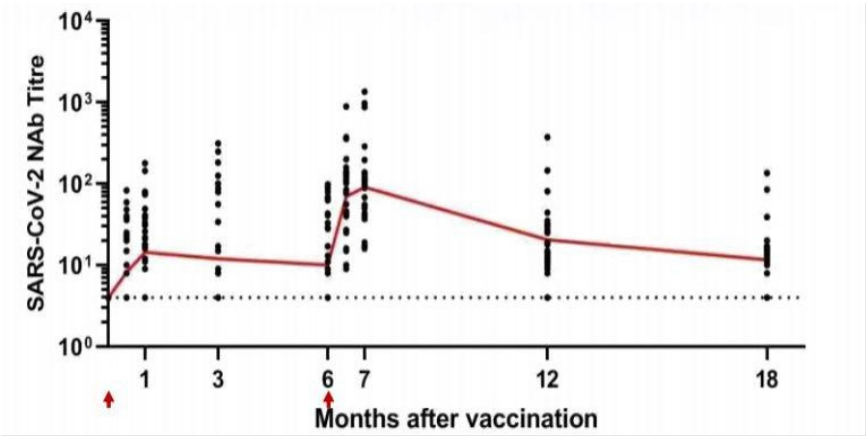
**Source*: Halperin et al. 2022 *(3)*; and from data on file.

Booster dose studies

To evaluate the safety, immunogenicity and immuno-persistency of one booster dose of Ad5-nCoV, a clinical trial was conducted of a homologous booster dose (5×10^{10} vp/dose) administered 6 months after previous vaccination with Ad5-nCoV. A total of 89 healthy adults aged 18–60 years, previously vaccinated at low dose, medium dose or high dose of Ad5-nCoV vaccine in the phase 1 clinical trial (NCT04313127) were enrolled in the booster trial (NCT04568811). Immunogenicity at 28 days, 6 months and 12 months after the homologous booster dose was laboratory tested.

The solicited incidence of adverse reactions within 14 days post the booster vaccination was 82.1%; most were grade 1 of pain at the injection site, and grade 1 of fatigue. No adverse reactions or adverse events of grade 3 or above occurred within 0–14 days after receipt of the booster dose. The neutralizing antibody against live virus was reduced by 28.9% after the first vaccination, from 14.2 at 28 days to 10.1 at 6 months. The GMT of neutralizing antibody was elevated after the booster dose to 74.4 at 14 days to 101.8 at 28 days. The GMT at 28 days after the booster dose was increased about 10 times compared with before the booster dose, and more than 7 times compared with 28 days after the first vaccination. At 6 months after the booster dose, the GMT of neutralizing antibody was 16.1, still approximately 1.2 times the level at 28 days after the first vaccination. At 12 months after the booster dose, the GMT of neutralizing antibody was 11.6, still 82% of the level at 28 days after the first vaccination. The level of cellular immune response-IFN-γ (by Elispot) after the booster dose, was 41.6, around the level at 14 days after the first vaccination (52.4), see Figure 2 (from data on file).

Figure 2. Neutralizing antibody of booster vaccination of phase 1 trial



**Source*: from data on file.

In the phase 3 clinical trial (NCT04526990), 44 247 participants were vaccinated with Ad5-nCoV or placebo. To keep the blind status of the trial and meet the vaccination request of participants, the protocol was updated to version 2.0 where participants were enrolled in a relative efficacy trial receiving either two booster doses or one booster dose 6–8 months after the primary series vaccination. At present, approximately 21 000 participants have received either their first or their second booster dose of vaccine. The safety and efficacy data of the booster vaccination will be available soon.

A study (*unpublished*) looking at the vaccine effectiveness of different COVID-19 vaccines used in Chile, showed that the single dose effectiveness against the COVID-19 cases for Ad5-nCoV was 52% (the efficacy trial result at 28 days post-vaccination in phase 3 trial was 58%, similar to that of the inactivated vaccine from Sinovac which was 54%).

Safety

Phase 3 safety findings

At total of 3235 participants were randomized in the extended safety subcohort; 1621 received Ad5-nCoV and 1614 received placebo. All participants randomized to placebo, and all but 4 (99.8%) randomized to Ad5-nCoV, received an injection. A total of 3159 injected participants (1585 vaccine and 1574 placebo) were included in the analysis. Median follow-up of the safety cohort was 32 days (IQR 17–49), with a total of 45 participants in the vaccine group and 56 participants in the placebo group withdrawing early from the study. All unsolicited adverse events were reviewed by the site investigators, often in consultation with the global principal investigator.

The most common reasons for withdrawal across both groups were (i) withdrawal of consent and (ii) loss to follow-up. A serious adverse event led to early withdrawal in 6 Ad5-nCoV recipients and 3 placebo recipients *(3)*.

Overall, 63.5% and 61.3% of Ad5-nCoV recipients and 46.4% and 20.0% of placebo recipients reported a solicited systemic or injection-site adverse event, respectively ($p<0.001$). Most adverse events were mild or moderate; 11.3% of Ad5-nCoV adverse events and 5.1% of placebo adverse events were categorized as grade 3 or higher ($p<0.001$). Pain at the injection site was the most frequent adverse event, reported by 59% of Ad5-nCoV recipients and 19% of placebo recipients. Redness and swelling at the injection site were reported in less than 10% of Ad5-nCoV recipients and less than 2% of placebo recipients. The most frequent systemic adverse events were headache (44.2% of Ad5-nCoV and 30.6% of placebo recipients; $p<0.001$), generalized muscle aches (41.2% and 19.5%; $p<0.001$), and drowsiness (40.0% and 27.8%; $p<0.001$). Fever was reported by 12.5% of Ad5-nCoV and 1.6% of placebo recipients ($p<0.001$); no differences were observed for vomiting or diarrhoea. Unsolicited adverse events were reported by 21.4% of Ad5-nCoV and 19.6% of placebo recipients; these were categorized as grade 3 or greater by 3.0% of Ad5-nCoV and 2.1% of placebo recipients. There were no reports of thrombosis or thrombocytopenia in any study participants ((3) or from data on file).

The incidence rate of unsolicited adverse events in the trial was lower than 1% and there were no serious adverse events related to Ad5-nCoV, as considered by investigators in this analysis. There were four cases of thrombosis (not classified as thrombosis with thrombocytopenia syndrome, TTS); details are available in

Table 16 (from data on file).

There was one case of Guillain-Barré syndrome (GBS male; 18–59 year age group) that the investigator assessed as being related to the vaccine product as there was no other plausible explanation (this case was also reviewed by the global principal investigator and the data and safety monitoring board). The individual continues in a rehabilitation programme and is regaining motor functions (now walking without support, although he continues to have paresthesia in the lower limbs) (from data on file).

Table 12. Adverse events reported 0/28 days after vaccination, by age group in the phase 3 study (NCT04526990)*

	Total		
Adverse event	**Ad5-nCoV N (%)**	**Placebo N (%)**	**p-value**
All ages			
Overall adverse events	1209 (76.3)	868 (55.2)	<.0001
Adverse events unrelated to vaccination	Not available	Not available	Not available
Adverse events related to vaccination	1115 (70.4)	610 (38.8)	<.0001
Solicited adverse events	1112 (70.2)	599 (38.1)	<.0001
Unsolicited adverse events	Not available	Not available	Not available
Systemic adverse events	Not available	Not available	Not available
Local adverse events	Not available	Not available	Not available
Within 30 minutes	61 (3.9)	36 (2.3)	0.0110
Within 7 days	1190 (75.1)	819 (52.1)	<.0001
18–59 years			
Overall solicited adverse events	1054 (77.2)	716 (52.2)	<.0001
Adverse events unrelated to vaccination	Not available	Not available	Not available
Adverse events related to vaccination	Not available	Not available	Not available
Related solicited adverse events	1002/ 1366 (73.6)	539/ 1372 (39.3)	<.0001
Unsolicited adverse events	Not available	Not available	Not available
Solicited general adverse events	908 (66.6)	658 (48.0)	<.0001

Adverse event	Total		
	Ad5-nCoV N (%)	Placebo N (%)	p-value
Solicited local adverse event	883 (64.6)	286 (20.9)	<.0001
Within 30 minutes	Not available	Not available	Not available
Within 7 days	Not available	Not available	Not available
≥60 years			
Overall solicited adverse events	126 (57.8)	79 (39.3)	0.0002
Adverse events unrelated to vaccination	Not available	Not available	Not available
Adverse events related to vaccination	Not available	Not available	Not available
Related solicited adverse events	110 (50.5)	60 (29.9)	<.0001
Unsolicited adverse events	Not available	Not available	Not available
Solicited general adverse events	96 (44.0)	71 (35.3)	0.0688
Solicited local adverse events	88 (40.4)	28 (13.9)	<.0001
Within 30 minutes	Not available	Not available	Not available
Within 7 days	Not available	Not available	Not available

Source: Halperin et al. 2022 *(3)*; and from data on file. The safety data are taken from the phase 3 efficacy trial for Ad5-nCoV (single dose). The total population enrolled in this trial is 44 247 subjects; the safety cohort (vaccine and placebo) has 3157 subjects. The solicited and unsolicited adverse events datalock date is 12 April 2021.

Table 13. Solicited adverse events 0–7 days after vaccination, by age in the phase 3 study (NCT04526990)*

Adverse event	Total		
	Ad5-nCoV N (%)	Placebo N (%)	p-value
All ages			
Any local (All grades)	971 (61.3)	314 (20.0)	<.0001
Grade 3	53 (3.4)	10 (0.6)	<.0001
Pain	939 (59.3)	303 (19.3)	<.0001
Grade 3	49 (3.1)	9 (0.6)	<.0001
Redness	153 (9.7)	19 (1.2)	<.0001
Grade 3	4 (0.3)	1 (0.1)	0.3746
Swelling	112 (7.1)	9 (0.6)	<.0001
Grade 3	3 (0.20)	0	0.2498
Any general	1004 (63.5)	729 (46.4)	<.0001
Grade 3	158 (10.0)	78 (5.0)	Unavailable
Drowsiness	632 (40.0)	437 (27.8)	<.0001
Grade 3	66 (4.2)	33 (2.1)	0.0008
Fever	197 (12.5)	25 (1.6)	<.0001
Grade 3	25 (1.6)	0	Unavailable
Headache	699 (44.2)	481 (30.6)	<.0001
Grade 3	85 (5.4)	30 (1.9)	<.0001
Nausea	192 (12.1)	149 (9.5)	0.0162
Grade 3	15 (1.0)	6 (0.4)	0.0505
Diarrhoea	154 (9.7)	127 (8.1)	0.1005
Grade 3	7 (0.4)	6 (0.4)	0.7890
Vomiting	23 (1.5)	21 (1.3)	0.7760
Grade 3	1 (0.1)	3 (0.2)	0.3733
Generalized muscle aches	651 (41.2)	306 (19.5)	<.0001
Grade 3	65 (4.1)	16 (1.1)	<.0001
18–59 years			
Any local (All grades)	883 (64.6)	286 (20.9)	<.0001
Grade 3	51 (3.7)	8 (0.6)	<.0001

	Total		
Adverse event	**Ad5-nCoV N (%)**	**Placebo N (%)**	**p-value**
Pain	856 (62.7)	275 (20.0)	<.0001
Grade 3	47 (3.4)	7 (0.5)	<.0001
Redness	135 (9.9)	19 (1.4)	<.0001
Grade 3	4 (0.3)	1 (0.1)	0.2170
Swelling	102 (7.5)	8 (0.6)	<.0001
Grade 3	3 (0.2)	0	0.1238
Any general	908 (66.6)	658 (48.0)	<.0001
Grade 3	153 (11.2)	71 (5.2)	Unavailable
Drowsiness	582 (42.7)	392 (28.6)	<.0001
Grade 3	65 (4.8)	29 (2.1)	0.0001
Fever	189 (13.9)	24 (1.8)	<.0001
Grade 3	25 (1.8)	0	Unavailable
Headache	638 (46.8)	448 (32.9)	<.0001
Grade 3	83 (6.1)	29 (2.1)	<.0001
Nausea	180 (13.2)	138 (10.1)	0.0106
Grade 3	15 (1.1)	6 (0.4)	0.0473
Diarrhoea	142 (10.4)	109 (8.0)	0.0255
Grade 3	6 (0.4)	4 (0.3)	0.5470
Vomiting	22 (1.6)	21 (1.5)	0.8626
Grade 3	1 (0.1)	3 (0.2)	0.6247
Generalized muscle aches	601 (44.1)	274 (20.0)	<.0001
Grade 3	61 (4.5)	15(1.1)	<.0001
≥60 years			
Any local (All grades)	88 (40.4)	28 (13.9)	<.0001
Grade 3	2 (0.9)	2 (1.0)	>.9999
Pain	83 (38.1)	28 (13.9)	<.0001
Grade 3	2 (0.9)	2 (1.0)	>.9999

	Total		
Adverse event	**Ad5-nCoV N (%)**	**Placebo N (%)**	**p-value**
Redness	18 (8.3)	0	<.0001
Grade 3	0	0	Unavailable
Swelling	10 (4.6)	1 (0.5)	0.0089
Grade 3	0	0	Unavailable
Any general	96 (44.0)	71 (35.3)	0.0688
Grade 3	5 (2.3)	7 (3.5)	Unavailable
Drowsiness	50 (22.9)	45 (22.4)	0.8936
Grade 3	1 (0.5)	4 (2.0)	0.1990
Fever	8 (3.7)	1 (0.5)	0.0386
Grade 3	0	0	Unavailable
Headache	61 (28.0)	33 (16.4)	0.0046
Grade 3	2 (0.9)	1 (0.5)	>.9999
Nausea	12 (5.5)	11 (5.5)	0.9886
Grade 3	0	0	Unavailable
Diarrhoea	12 (5.5)	18 (9.0)	0.1711
Grade 3	1 (0.5)	2 (1.0)	0.6094
Vomiting	1 (0.5)	0	>.9999
Grade 3	0	0	Unavailable
Generalized muscle aches	50 (22.9)	32 (15.9)	0.0706
Grade 3	4 (1.8)	1 (0.5)	0.3741

**Source*: from data on file.

Table 14. Serious adverse events occurring within 28 days following vaccination in the phase 3 study (NCT04526990)*

	All ages		18–59 years		≥60 years	
	No. of events	**No. of subjects**	**Ad5-nCoV N (%)**	**Placebo N (%)**	**Ad5-nCoV N (%)**	**Placebo N (%)**
Any serious adverse event						
Appendicitis	1	1	0	1	0	0
Hypertriglyceridaemia	1	1	0	0	1	0
Intestinal obstruction	2	2	0	1	0	1
Diaphragmatic hernia	1	1	0	1	0	0
Electrolyte imbalance	1	1	0	1	0	0
Pneumonia	2	2	0	1	0	1
Sepsis	1	1	0	1	0	0
Ruptured ectopic pregnancy	1	1	1	0	0	0
Asthma	1	1	1	0	0	0
Craniocerebral injury	1	1	0	1	0	0
Spinal cord compression	1	1	0	1	0	0
Acute myocardial infarction	1	1	0	0	0	1
Gastroenteritis	1	1	0	1	0	0
Coronary artery disease	1	1	0	0	1	0
Myocardial infarction	1	1	0	0	1	0
Suicide attempt	1	1	1	0	0	0
Orchitis	1	1	1	0	0	0
Cellulitis	1	1	1	0	0	0

**Source*: from data on file.

Table 15. Deaths among trial participants in the phase 3 study (NCT04526990)*

Vaccine/placebo group	Age	Cause of death	If cause of death was COVID-19, list comorbidities	Vaccination date	Onset date	End date
Vaccine	35	Sudden heart attack	NA	2020/11/11	2021/1/3	2021/1/3
Vaccine	34	Coma	NA	2020/11/25	2021/1/28	2021/2/23
Vaccine	34	Road traffic accident	NA	2020/12/01	2021/1/4	2021/1/4
Vaccine	72	Sarcoidosis	NA	2020/12/24	2021/4/1	2021/4/3
Vaccine	23	Unknown cause of death. The subject had asthma diagnosed about one year prior to death.	NA	2020/12/10	2020/12/28	2020/12/28
Vaccine	43	Road traffic accident	NA	2020/11/30	2020/12/3	2020/12/3
Vaccine	60	Cardiac arrest	NA	2020/10/20	2021/1/3	2021/1/3
Placebo	54	Intestinal occlusion	NA	2020/12/11	2020/12/3	2021/1/7

**Source*: from data on file.
NA: Not applicable

Table 16. Serious adverse event associated with thrombosis*

Subjects	Adverse event	Preferred term	Vaccination date	Start date	End date	Outcome
Subject 01	Acute thrombosis	Thrombosis	2020/12/28	2021/03/13	2021/03/13	Recovered
Subject 02	Deep venous thrombosis	Deep vein thrombosis	2021/2/4	2021/2/24	2021/03/11	Recovered
Subject 03	Left leg deep venous thrombosis	Deep vein thrombosis	2020/10/30	2021/07/10	2021/07/13	Recovered
Subject 04	Right lung segmental artery A5 thromboembolism	Pulmonary artery thrombosis	2021/1/13	2021/06/11	2021/11/27	Recovered

**Source*: from data on file.

Special considerations

Pregnancy

A total of 92 pregnancies have been recorded in the phase 3 trial to date; none of the outcomes of special interest were significantly different between the vaccine group and the placebo group (Table 17).

Table 17. Safety data for pregnancy in the phase 3 study*

Outcome	Ad5-nCoV			Placebo			*P*
	N	Incidence (%)	95% CI (%)	N	Incidence (%)	95% CI (%)	
Outcome of special interest							
Birth defect	1	1.85	0.05–9.89	0	0.00	0.00–9.25	>0.999
Miscarriage (unknown reason/manner)	1	1.85	0.05–9.89	3	7.89	1.66–21.38	0.303
Spontaneous abortion/miscarriage	2	3.70	0.45–12.75	1	2.63	0.07–13.81	>0.999
Stillbirth	1	1.85	0.05–9.89	0	0.00	0.00–9.25	>0.999
Premature live birth	6	11.11	4.19–22.63	4	10.53	2.94–24.80	0.929
Nominal and Other							
Full term live birth	2	3.70	0.45–12.75	2	5.26	0.64–17.75	>0.999
Neonatal health/normal	11	20.37	10.63–33.53	13	34.21	19.63–51.35	0.137
Induced/elective abortion	3	5.56	1.16–15.39	5	13.16	4.412–8.09	0.203
Outcome pending	8	14.81	6.62–27.12	2	5.26	0.64–17.75	0.147
Lost to follow-up	2	3.70	0.45–12.75	0	0.00	0.00–9.25	0.510
Unknown	16	29.63	17.98–43.61	8	21.05	9.55–37.32	0.356
Other	1	1.85	0.05–9.89	0	0.00	0.00–9.25	>0.999
Total	54	——	——	38	——	——	——

**Source*: from data on file.

During the post-marketing passive monitoring, 44 reports of exposure to pregnancy were identified until 28 February 2022, where 2 selective abortion cases were noted. No additional safety risk was found in the pregnant population.

Paediatric population

A randomized, double-blinded, placebo-controlled phase 2b trial (NCT04566770) with an expanded study population and a 56-day two-dose vaccination regimen was carried out in children and adolescents aged 6–17 years (MIN group: 150 subjects). Subjects received 0.3 ml as 3×10^{10} vp for this specific "children and adolescents" group. The ratio of Ad5-nCoV vaccine and placebo recipients was 2:1. Vaccination was carried out at an interval of 56 days between the two doses. All the subjects will be followed up for 6 months after the second dose. The level of neutralizing antibody of the children and adolescents was about 2 times that observed in the adult group, both for the first dose and the second dose *(7)*.

Another randomized, double-blind bridging trial (NCT04916886) was initiated to bridge immunogenicity among the age groups 6–17 years and 18–59 years. The safety analysis showed comparable safety profiles across the age groups (Table 18). Through the non-inferiority comparison of the GMT levels of RBD antibody in the adolescent group and the adult group, it is apparent that the GMT level of RBD antibody in the 6–17 age group, the 6–12 age group and the 13–17 age group is not inferior to that in 18–59 age group (from data on file) (Table 19).

Table 18. Analysis of safety results of day 28 after vaccination in the bridging study (NCT04916886)*

Safety category	Items	6–17 years N (%)	18–59 years N (%)
Adverse events (AEs)	**Total adverse events**	**818**	**979**
	Total number of subjects	415 (41.21%)	446 (44.3%)
	Experienced AEs within 30 minutes after vaccination	56 (5.56%)	51 (5.1%)
	Experienced AEs within 0–7 days after vaccination	401 (39.82%)	426 (42.7%)
	Experienced AEs within 0–28 days after vaccination	415 (41.21%)	444 (44.1%)
Adverse reactions (ARs)	**Total adverse reactions**	**785**	**902**
	Total number of subjects	399 (39.62%)	414 (41.1%)
	Experienced ARs within 30 minutes after vaccination	55 (5.46%)	51 (5.1%)
	Experienced ARs within 0–7 days after vaccination	399 (39.62%)	414 (41.1%)
	Experienced ARs within 0–28 days after vaccination	399 (39.62%)	414 (41.1%)
Solicited adverse events (AEs)	**Total solicited adverse events**	**771**	**886**
	Total number of subjects	396 (39.32%)	415 (41.2%)
	Experienced solicited AEs within 30 minutes after vaccination	51 (5.06%)	49 (4.9%)
	Experienced solicited AEs within 0–7 days after vaccination	394 (39.13%)	410 (40.7%)
	Experienced solicited AEs within 0–28 days after vaccination	396 (39.32%)	415 (41.1%)
Solicited adverse reactions (ARs)	**Total solicited adverse reactions**	**763**	**865**
	Total number of subjects	392 (38.93%)	405 (40.2%)
	Experienced solicited ARs within 30 minutes after vaccination	50 (4.97%)	49 (4.9%)
	Experienced solicited ARs within 0–7 days after vaccination	392 (38.93%)	405 (40.2%)
	Experienced solicited ARs within 0–28 days after vaccination	392 (38.93%)	405 (40.2%)

**Source*: from data on file.

Table 19. The geometric mean titre level of the receptor binding domain (RBD) antibody on day 28 after vaccination in the bridging study (NCT04916886)*

RBD Antibody	Age 18–59 years, 800L, Batch 1 (N=258)	Age 13–17 years, 800L, Batch 1 (N=172)	Age 6–12 years, 800L, Batch 1 (N=172)	Age 6–17 years, 800L, Batch 1 (N=344)
n(miss)	250 (8)	168 (4)	168 (4)	336 (8)
Mean(S)	190.62 (211.26)	270.15 (253.02)	524.52 (415.13)	397.34 (366.12)
95% CI	164.30, 216.94	231.61, 308.69	461.29, 587.76	358.05, 436.63

**Source*: from data on file. All 800L manufacturing scale; dose 0.3 ml for children and adolescents aged 6–17 years; and dose 0.5 ml for adults aged 18–59 years.

Immunosuppression

In the phase 3 clinical trial, 6 HIV-positive cases post-vaccination have been found in the SAE monitoring; 2 in the vaccine group and four in the placebo group. The 2 cases from the vaccine group and 1 from the placebo group were HIV positive on the day of study enrollment, indicating they were infected with HIV before the enrollment.

At the time of enrollment in the trial, approximately 44 000 blood samples were collected at day 0. These are being tested for evidence of HIV. As of 22 March 2022, approximately 30 761 samples have been tested, with 142 reactive samples. Participants continue to be blinded as to their vaccination status. Those who are positive are being informed of their status by the site investigator for further follow-up with their physician. The complete 6 months sera results are expected to be available after July 2022.

Breastfeeding

There are no data regarding breastmilk and therefore it is unknown whether the vaccine is excreted in human milk.

Safety related to vaccine interactions

There are no data on use of the Ad5-nCoV vaccine provided concomitantly with other vaccines.

Heterologous vaccine schedules

A single-centre, randomized, observer-blinded, parallel-controlled clinical study on sequential immunization to evaluate the safety and immunogenicity of sequential immunization with inactivated novel coronavirus vaccine (Vero cell) and Ad5-nCoV was conducted in healthy adults aged 18–59 years (NCT04892459) *(8)*. A total of four study groups were established and full booster vaccination was compared between Group A and Group B. A replacement of the second dose of inactivated vaccine was evaluated in comparison of Group C and Group D (see Table 20 for composition of groups).

Table 20. Sample sizes of all study groups in the heterologous booster trial (NCT04892459)*

Code	Group	Sample size	Basic immunization	Vaccines	Sequential immunization
A	Heterologous booster vaccination group	100	Complete 2 doses of inactivated vaccines	Ad5-nCoV (1 dose)	Heterologous booster vaccination is performed at month 3–6 after the second dose of inactivated vaccine
B	Conventional booster vaccination group	100		Inactivated vaccine (1 dose)	
C	Heterologous vaccination group	50	Complete 1 dose of inactivated vaccine	Ad5-nCoV (1 dose)	Replacement vaccination is performed at month 1–2 after the first dose of inactivated vaccine
D	Conventional vaccination group	50		Inactivated vaccine (1 dose)	

**Source*: Li J et al. 2022 *(8)*.

The clinical results demonstrate that there were differences in the case number of post-vaccination adverse reactions and adverse events between Group A (2 doses inactivated vaccine + 1 dose Ad5-nCoV) and Group B (3 doses of inactivated vaccine). The incidence of adverse reactions and adverse events in Group A was higher than those in Group B; no vaccine-related serious adverse events occurred in either of the two groups during the study. However, as regards safety results for the Ad5-nCoV vaccine, the incidence of solicited adverse reactions after the heterologous booster (34.4%) was lower than the single dose vaccination in other trials (69.0–76.4%).

At 14 days after vaccination, the GMT of neutralizing antibodies (anti-SARS-CoV-2 Wuhan strain) was 3090.13 in Group A, 8.4 times that in Group B (367.25). The GMT of neutralizing antibodies against live virus was 197.40, approximately 6 times that in Group B (33.59).

For Group C (1 dose inactivated vaccine + 1 dose Ad5-nCoV) and Group D (2 doses inactivated vaccine), S-RBD peaked at 14 days after the second dose. The S-RBD antibody GMT was 944.67 in Group C, 6.13 times that in Group D (154.15). The GMT of the neutralizing antibody was 53.45 in Group C, 4.2 times of that in Group D (12.76). For both dose regimens (2 doses inactivated vaccine + 1 dose Ad5-nCoV; and 1 dose inactivated vaccine + 1 dose Ad5-nCoV), the seroconversion rates for these antibodies were 100%, or near 100%.

In another study, seven serum specimens were obtained from individuals who had received 1 heterologous Ad5-nCoV booster dose following 2 doses of inactivated vaccine (IAV) titres against the prototype strain versus the Omicron variant. Binding, blocking and neutralizing antibody titres were markedly higher against the prototype strain than against the Omicron variant with the Ad5-nCoV booster dose inducing a 40-fold increase in Omicron-binding antibody titres compared with the no-booster control. The Ad5-nCoV booster dose led to an increase to 57% of the hACE2-receptor-blocking rate[1] compared to the control. For neutralizing antibodies against the Omicron variant, the genomic mean NT_{50} titres were below the lower limit of detection (10-fold dilution of plasma) in the control group, whereas the titres rose to 709 in the Ad5-nCoV booster group. The study also showed that the heterologous vaccine booster was superior to the homologous vaccine booster in improving the neutralizing activity against the Omicron variant (*pre-print, not peer-reviewed*) *(12)*.

The study also examined the effect of various booster vaccinations following a single-dose prime vaccination with Ad5-nCoV with serum specimens from individuals who received no booster injection (control, n=30); inactivated vaccine (IAV) booster (n=30); recombinant protein subunit vaccine (PRV) booster (n=30); or Ad5-nCoV booster (n=30) at 4–8 months following the primary Ad5-nCoV vaccination. All of the samples were collected 1 month following booster vaccination at the Chinese PLA General Hospital in Beijing The Omicron-binding antibody titres were boosted 4-fold, 25-fold and 16-fold by the booster injection of heterologous IAV and PRV vaccines or homologous Ad5-nCoV vaccine, respectively, compared with the no-booster control. For Omicron-blocking antibodies, the PRV and Ad5-nCoV booster groups exhibited an identical hACE2-receptor-blocking rate (80%), which was higher than that of the control group (3%) or IAV booster group (53%). The neutralizing NT_{50} titres for the Omicron variant in the control group and the IAV, PRV, and Ad5-nCoV booster groups were 15, 68, 313, and 228, respectively. Notably, a homologous Ad5-nCoV booster or a heterologous PRV booster induced a higher degree of neutralizing immunity against both the prototype and the Omicron strains compared with the no-booster control and inactivated vaccine booster (*pre-print, not peer-reviewed*) *(12)*.

Post licensure studies

In terms of active surveillance (or phase 4 clinical trials for the safety of Ad5-nCoV), studies are being conducted through large scale immunization campaigns in people aged 18 years and older in China. From the first subject enrollment (24 September 2021) to the lock date of analysis (16 December 2021), a total of 20 865 subjects were enrolled, including 2350 subjects aged 60 years and older.

According to the protocol of phase 4 clinical trials, the primary endpoint is the incidence of adverse events at any vaccination site (local) and non-vaccination site (systemic) within 30 minutes after vaccination, and was 1.2%; the incidence of solicited adverse events 0–7 days after vaccination was 22.3%. The secondary endpoint is the incidence of unsolicited adverse events 0–28 days after vaccination and was 0.7%. Among 20 865 subjects included in this analysis, the incidence of total adverse events was 22.4%; the incidence of solicited adverse events was 22.3%. Among solicited adverse events, the incidence of systemic adverse events and local adverse events was 12.1% and 19.9%, respectively. The incidence of unsolicited adverse events was 0.7% (Table 21). Of the solicited adverse events reported within a 30-minute timescale, the incidence was 1.1% (the incidence of local reactions and systemic reactions within 30 minutes was 0.5% and 0.8%, respectively). Within 0–7 days the incidence was 22.3%. Of the unsolicited adverse events, the incidence was 0.1% within 30 minutes; 0.7% within 0–7 days; 0.03% within 8–14 days; and 0.02% within 15–28 days (from data on file) (Table 22).

Table 21. Summary of total adverse events*

Solicited and unsolicited adverse events	Analysed population（N=20 865）		
	Number of adverse events	Number of people	Incidence（%）
Total adverse events	14 616	4673	22.4
Solicited adverse events	14 412	4652	22.3
Systemic adverse events	8635	2526	12.1
Local adverse events	5777	4155	19.9
Unsolicited adverse events	204	151	0.7

**Source*: from data on file. Note: "Systemic adverse events" refer to non-vaccination site adverse events; "Local adverse events" refer to vaccination site adverse events.

[1] The of hACE2-receptor-blocking rate is used to describe the proportion of hACE2-receptor-blocking antibody titres above the lower limit of detection (4-fold dilution of plasma).

Table 22. Summary of adverse events by time period*

Item	Analysed population（N=20 865）			
	Period	Number of adverse events	Number of people	Incidence（%）
Total adverse events	0–30 minutes	420	250	1.2
	0–7 days	14 600	4671	22.4
	8–14 days	10	7	0.0
	15–28 days	6	4	0.0
Solicited adverse events (AE)	0–30 minutes	402	235	1.1
	Systemic AE	205	101	0.5
	Local AE	197	171	0.8
	0–7 days	14 412	4652	22.3
	8–14 days	0	0	0.0
	15–28 days	0	0	0.0
Unsolicited adverse events	0–30 mins	18	17	0.1
	0–7 days	188	141	0.7
	8–14 days	10	7	0.0
	15–28 days	6	4	0.0

**Source*: from data on file.

The total incidence of solicited adverse events was 25.8% and 18.6% in females and males respectively; the incidence of systemic reactions was 14.2% (females) and 9.92% (males); and of local reactions 23.5% and 16.1%, respectively. The incidence of unsolicited adverse events was 0.9% in females and 0.6% and males. The total incidences of solicited adverse events were 23.9% for the 18–59 year age group, and 9.6% for the age group 60 years and older. For systemic reactions, incidences were 13.0% (18–59 years) and 4.7% (60 years and older); and for local reactions, 21.5% and 7.7%, respectively. The incidence of unsolicited adverse events was 0.7% in the 18–59 year age group, and 0.7% in the 60 years and older age group. The incidence of solicited adverse events in the population with comorbidities was 18.3%; 9.6% for systemic reactions; 16% for local reactions; and 1.5% for unsolicited adverse events (from data on file) (Table 23).

Table 23. Summary of adverse events with or without comorbidities*

Solicited and unsolicited adverse events	With comorbidities N=1711			Without comorbidities N=19 154		
	Number of adverse events	Number of people	Incidence %	Number of adverse events	Number of people	Incidence %
Solicited adverse events	943	313	18.29	13 469	4339	22.7
Systemic adverse events	518	164	9.59	8117	2362	12.3
Local adverse events	425	273	15.96	5352	3882	20.3
Unsolicited adverse events	40	26	1.52	164	125	0.7

**Source*: from data on file. Note: "Systemic adverse events" refer to non-vaccination site adverse events; "Local adverse events" refer to vaccination site adverse events.

The adverse events mainly occurred within 7 days after vaccination, and were characterized by fatigue, headache, myalgia, dizziness, and drowsiness. Systemic reactions included fever and local reactions such as pain, swelling and itching at the vaccination site.

In terms of passive monitoring, from 25 February 2021 to 2 January 2022 a total of 13.8 million people in China have been vaccinated with Ad5-nCoV (1 dose per person). A total of 44.4 million doses of Ad5-nCoV have been distributed outside of China. Globally, approximately 58 million doses have been administered, with no cases of HIV acquisition reported after vaccination. As of 31 December 2021, 47 cases of adverse events related to thrombosis with thrombocytopenia syndrome (TTS) have been reported (Table 24), giving a rate of 0.081 cases per 100 000 vaccinees. In comparison, the cumulative incidence of TTS following vaccination with a non-replicate adenovirus vector-based vaccine ranges from 0.5 to 6.8 cases per 100 000 vaccinees *(13)*. Of the 47 cases, 27 occurred in males and 20 in females. As regards age distribution, 25 people were aged 18–59 years; 12 were aged 60 years and older, and 10 people did not disclose their age. Of these 47 cases, 1 was classified as possibly related to vaccination, while 30 were classified as unlikely to be related (16 remained unclassified or considered unconditional due to lack of medical history or laboratory results), Table 24 (from data on file). The time intervals between vaccination and cases of TTS are shown in Table 25. Of these 47 cases, 1 was classified as "possibly" related to vaccination, while 30 cases were classified as "unlikely" to be related to the vaccination and 16 were "conditional/ unclassified" due to lack of medical history or lab results (from data on file).

Among all participants enrolled, no cases of HIV acquired after vaccination have been reported. There have been 28 cases of GBS reported (8 females and 20 males) where 11 were spontanoues reports and 11 regulatory authorities' reports, incidence rate of 0.05/100,000, where baseline incidence of GBS is 0.8-1.9/100, 000 *(14)* (from data on file). A total of 39 anaphylaxis reports were received. These were reported as anaphylactic shock cases (21 cases, henoch-schonlein purpura cases (5 cases), anaphylactic reaction cases (13 cases), The overall incidence of anaphylaxis was 0.07/100,000 (the incidence of anaphylaxis of other COVID-19 vaccines varies from 0.25-2.47/100,000 *(15–18)*. Among the 39 cases, 3 cases of Henoch-Schonlein purpura were evaluated as coincidence, and 3 cases of anaphylactic shock and 1 case of Henoch-Schonlein purpura were evaluated as adverse reactions. The causality of other cases could not be evaluated based on the limited information received (from data on file).

Table 24. Summary of cases of thrombosis with thrombocytopenia syndrome*

Adverse events	No. of cases
Cerebral infarction (CI)	21
Myocardial infarction (MI)	11 (including 1 case with CI)
Thrombotic disease	8
Platelet decreased related disease	8
Total	47 (including 1 case with CI and MI)

**Source*: from data on file.

Table 25. Time interval between vaccination and thrombosis with thrombocytopenia syndrome*

Time interval	No. of cases
0–2 days	22
3–30 days	11
>30 days	1
Unknown	13
Total	47

**Source*: from data on file.

Passive monitoring of safety data sources includes spontaneous safety reports from China, Uppsala Monitoring Centre (UMC), and overseas local Marketing Authorization Holder (MAH). The cumulative incidence of adverse events in China was 6.4 per 10 000, of which incidence of serious adverse events was 0.05 per 10 000 (Table 26). The overseas cumulative incidence of adverse events was 0.4 per 10 000, of which incidence of serious adverse events was 0.02 per 10 000 (Table 27). The reported incidence of UMC feedback data was 0.2 per 10 000, of which incidence of serious adverse events was 0.02 per 10 000 (Table 28) (from data on file).

Table 26. Summary of cases of adverse events from China*

Analysis item	Cumulative number of cases of adverse events (composition ratio) (n=8816)
Sex	
Male	4028 (45.7%)
Female	4763 (54.0%)
Unknown	25 (0.3%)
Age	
<18 years	1 (0.0%)
18–39 years	6778 (76.9%)
40–59 years	1650 (18.7%)
≥60 years	327 (3.7%)
Unknown	60 (0.7%)
Severity	
Non-serious	8741 (99.2%)
Serious – non-fatal	70 (0.8%)
Serious – death	5 (0.1%)
Causality	
Adverse reaction	8575 (97.3%)
Coincidence	175 (2.0%)
Psychogenic response	66 (0.8%)
Quality accident	0 (0%)
Vaccination accident	0 (0%)

**Source*: from data on file.

Table 27. Summary of cases of adverse events from four countries through local marketing authorization holder*

Analysis item	Cumulative number of cases of adverse events (composition ratio) (n=1562)
Country	
Pakistan	3 (0.2%)
Malaysia	24 (1.5%)
Mexico	1314 (84.1%)
Chile	221 (14.2%)
Sex	
Male	411(26.3%)
Female	1146 (73.4%)
Unknown	5 (0.32%)
Age	
18–39 years	867 (55.5%)
40–59 years	516 (33.0%)
≥60 years	166 (10.6%)
Unknown	13 (0.8%)
Seriousness	
Non-serious	1473 (94.3%)
Serious – non-fatal	67 (4.3%)
Serious – death	22 (1.4%)

**Source*: from data on file.

Table 28. Summary of cases of adverse events from Uppsala Monitoring Centre*

Analysis item	Cumulative number of cases of adverse events (composition ratio) (n=901)
Region	
Asia	819 (90.9%)
Americas	82 (9.1%)
Sex	
Male	544 (60.4%)
Female	357 (39.6%)
Age	
18–44 years	401 (44.5%)
45–64 years	403 (44.7%)
65–74 years	61 (6.8%)
≥75 years	33 (3.7%)
Unknown	3 (0.3%)
Seriousness	
Not serious	825 (91.6%)
Serious – not fatal	62 (6.9%)
Serious – death	14 (1.6%)

**Source*: from data on file.

Aerosol inhalation route for immunization (Ad5-nCoV-IH)

CanSinoBIO has now developed a nebulized inhalation route for immunization (Ad5-nCoV-IH) whereby aerosol particles for vaccine inhalation are generated through a nebulizer. The nebulized inhalation device contains an Aerogen USB Controller, an Aerogen Solo nebulizer, an Aerogen station unit and an inhalation chamber. The Aerogen USB controller, Aerogen Solo nebulizer and station unit are manufactured by Aerogen Ltd., and have been registered in many countries.

NCT04552366 – phase 1 of inhalation route

This randomized, single-centre, open-label, phase 1 trial, evaluated the safety and immunogenicity of the Ad5-nCoV vaccine administered by aerosol inhalation (Ad5-nCoV-IH) in adults (aged 18 years and older) seronegative for SARS-CoV-2 *(9)*.

The trial enrolled 144 people, with 24 people in each of six groups: (i) two-dose intramuscular injection group, (ii) nebulized inhalation high-dose group, (iii) nebulized inhalation low-dose group, (iv) intramuscular injection/nebulized inhalation (IM+IH) mixed group, (v) intramuscular injection group, and (vi) intramuscular injection high-dose group.

Safety

The study showed a better safety profile for the nebulized inhalation groups versus the intramuscular groups after the first dose; however after the second dose, the intramuscular injection + inhalation mixed group reported better safety (see Figure 3).

Figure 3. Safety results after first and second immunization for 6 study groups in phase 1 clinical study (NCT04552366) for Ad5-nCoV-IH* (9).

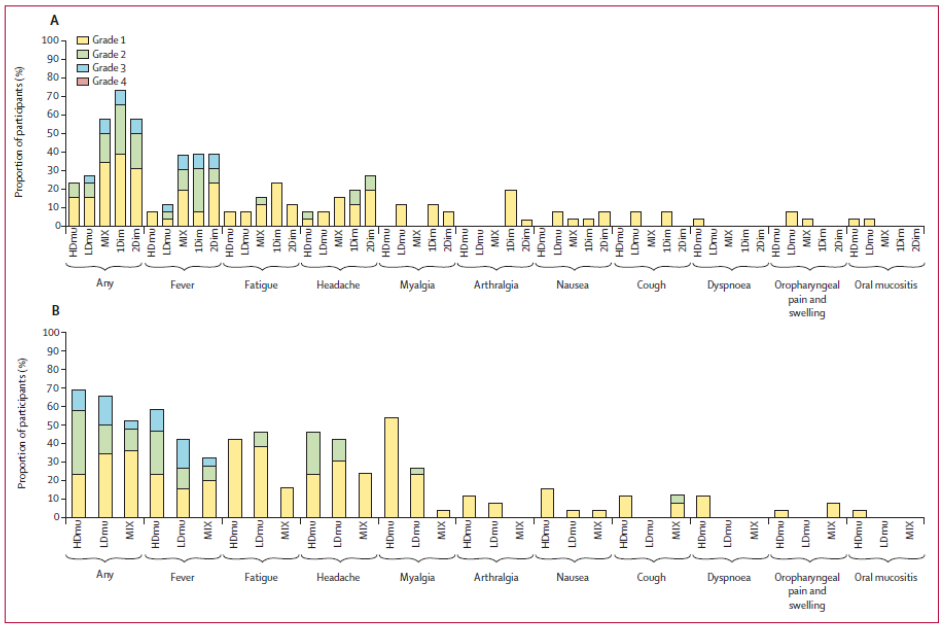


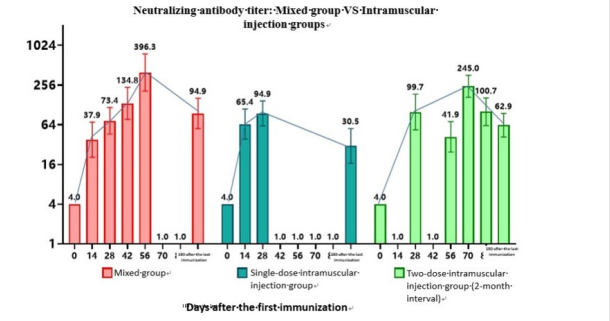
Figure 2: Solicited adverse events following Ad5-nCoV vaccination
Solicited adverse events reported within 7 days after prime (A) and booster (B) vaccination with Ad5-nCoV. The severity of solicited adverse events was graded as grade 1, grade 2, grade 3, or grade 4 according to the scale issued by the China National Medical Products of Administration (appendix 2 p 7). Participants in the 1Dim and 2Dim groups did not receive a booster vaccine. 1Dim=low-dose intramuscular injection. 2Dim=high-dose intramuscular injection. Ad5-nCoV=recombinant adenovirus type 5 carrying full-length SARS-CoV-2 spike gene. HDmu=high-dose aerosol vaccine. LDmu=low-dose aerosol vaccine. MIX=intramuscular and aerosol vaccine.

**Source*: Wu S et al. 2021 (9).

Immunogenecity

After the second dose, the intramuscular injection + inhalation mixed group exhibited better immunogenicity than other test groups. The GMT of neutralizing antibodies on day 28 after immunization was 396.3, which was about 100 times higher than the neutralizing antibody level before the first immunization and about 5 times before the second, with a positive seroconversion rate of 100%. The serum IgG, IgA, and neutralizing antibody levels in this group were significantly higher than those in other groups. At month 6 after the second immunization, the GMT remained at 96.9, with a positive seroconversion rate of 92%, higher than the level on day 28 after the first immunization (GMT: 73.4; positive seroconversion rate: 92%). No significant difference was seen between the low-dose and high-dose nebulized inhalation groups (see Figure 4) (from data on file).

Figure 4. Neutralizing antibody results of the randomized and open-label phase 1 clinical study NCT04552366*



**Source*: from data on file.

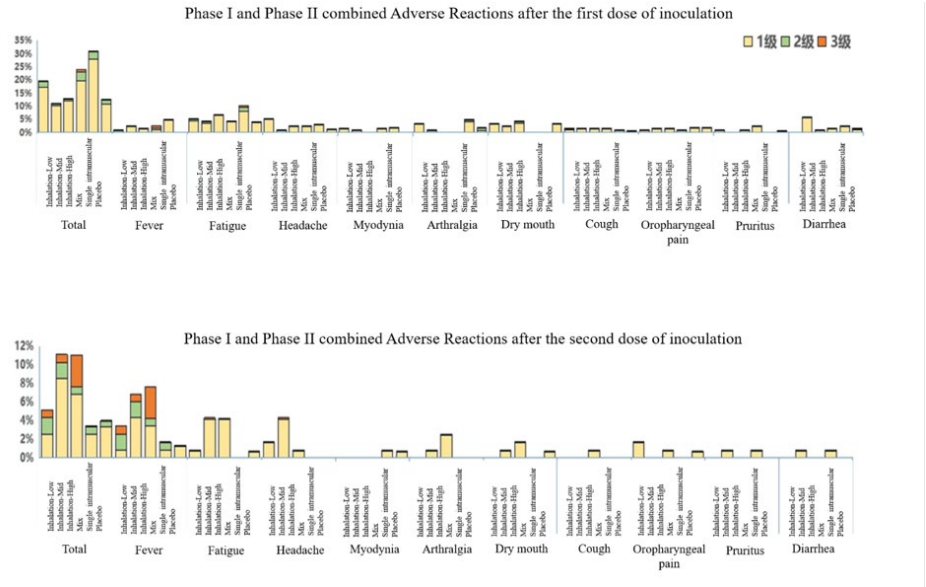
NCT04840992 – phases 1 and 2 of inhalation route

This was a phase 1 and a phase 2 randomized, double-blind, placebo-controlled study, with 120 people in phase 1 (divided into 5 groups of 24 people: low-dose group; medium-dose group; high-dose group; mixed group; and single-dose group) with a ratio of 3:1 in favour of the vaccine. There were 720 people in phase 2, divided into two age groups, 18–59 years, and 60 years and older (6 groups in each age group of 60 people in a low-dose group, medium-dose group, high-dose group, mixed group, single-dose intramuscular injection group, and single-dose group, with ratio of 5:1 in favour of the vaccine). For the mixed group (IM+IH), immunization was given after an interval of 56 days (from data on file).

Safety

In general, the adverse reactions were lower in the high-dose, medium-dose, and low-dose nebulized inhalation groups than in the intramuscular injection group using the 2-month interval immunization programme; the mixed group showed particularly safe results, with an overall incidence of adverse reactions less than 5% after the second dose. The phase 1 study showed that the incidence of adverse reactions was similar in the nebulized inhalation group to that of placebo after the first dose. One grade 3 (fever) reaction was seen in the first dose of the mixed group. The adverse reactions after the second dose in the nebulized inhalation groups and the mixed group remained at the same level as that of the placebo groups, and no grade 3 adverse reactions or vaccine-related SAEs occurred. The results for phase 2 were similar to those for phase 1. A total of four cases of grade 3 adverse reactions (all transient fever), incidence of 2% and no SAE occurred, Figure 5 (from data on file).

Figure 5. Safety results after first and second immunization for the study groups in phase 1/2 clinical study (NCT04840992)*

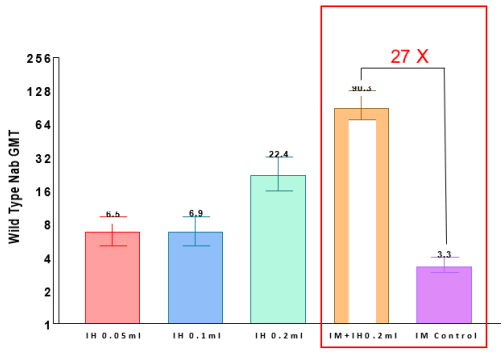


**Source:* from data on file.

Immunogenecity

From the combined analysis of the phase 1/2 data, 28 days after the two doses, the mixed group showed the best immune response in terms of the level of neutralizing antibody against real virus, which was about 27 times that of the single intramuscular injection group (Figure 6). The second best immune response was in the high-dose nebulized inhalation group, which was about 7 times that of the single-dose intramuscular injection group. The low-dose and medium-dose nebulized inhalation groups had similar levels and were twice as high as the single-dose intramuscular injection group. In terms of serum IgA antibody level, the performances of the mixed group and the high-dose nebulized inhalation group were similar; the antibody level was higher than that in the low-dose and medium-dose nebulized inhalation groups. The level of phase 1 cellular immunity was analysed; the effective cellular immunity could be induced 14 days after the first dose immunization, and the higher level of IFN-γ positive conversion rate could be over 80% after the second dose immunization. There was no significant difference between groups (from data on file).

Figure 6. Neutralizing antibody results of the phase 1/2 clinical study NCT04840992*



**Source*: from data on file.

NCT05043259 – booster using inhalation route

This randomized, open-label, parallel-controlled trial evaluated the safety and immunogenicity of heterologous booster immunization with Ad5-nCoV vaccine by aerosol inhalation (Ad5-nCoV-IH) after two-dose priming with an inactivated SARS-CoV-2 vaccine CoronaVac in adults 44 aged 18 years and older (*pre-print, not peer-reviewed*) *(10)*. There were 3 study groups: (i) low-dose heterologous booster immunization group (Group A); (ii) high-dose heterologous booster immunization group (Group B), and (iii) routine booster immunization group (Group C). The recruited subjects in groups A, B, and C were required to complete primary series vaccination with two doses of inactivated COVID-19 vaccine. At 3–9 months after primary series completion, subjects received one dose of Ad5-nCoV-IH (0.1 ml for Group A; 0.2 ml for Group B), or one dose of inactivated COVID-19 vaccine (for Group C).

Safety

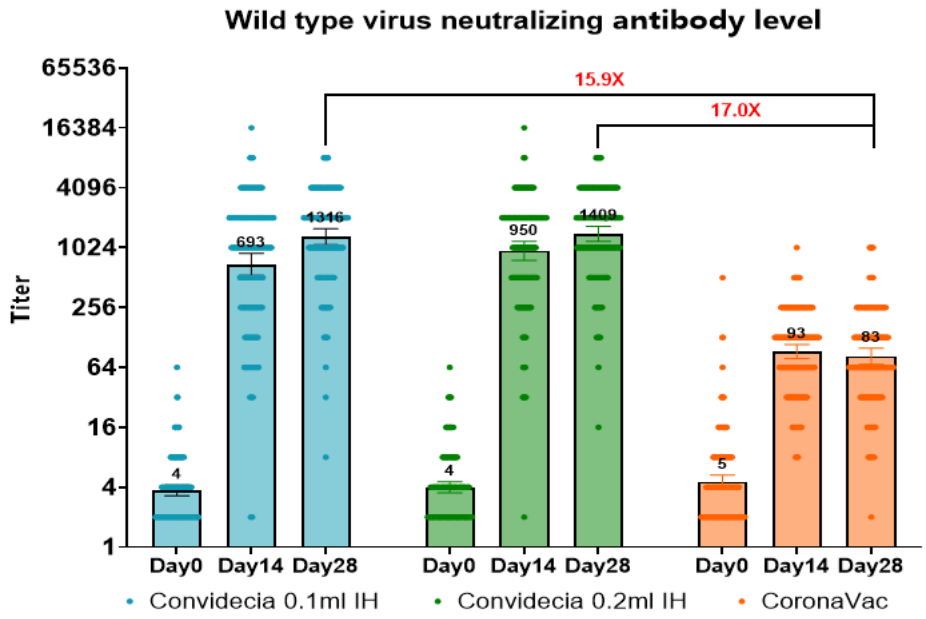
The overall rates of adverse events of the 0.1 ml and 0.2 ml nebulized inhalation booster groups 14 days after all vaccination were 19.29% and 23.57%, respectively, which were lower than the incidence of adverse events in the inactivated vaccine booster group (38.57%). The incidence of grade 3 adverse reactions of transient fever, headache or fatigue was 1.43% in both Group A and Group B (*pre-print, not peer-reviewed*) *(10)*.

Immunogenecity

The S-RBD IgG antibody level before booster immunization was close to negative. As shown in Figure 7, the GMTs of S-RBD IgG antibody in Group A and Group B reached 4630.80 and 6175.11, respectively, 14 days after the booster dose, which are 6.9 times and 9.2 times higher than booster vaccination with inactivated vaccine. The GMTs of S-RBD IgG antibody in Group A and Group B rose to 6216.98 and 6578.16 respectively, 28 days after the sequential immunization, which are 13.8 times and 14.6 times higher than the booster vaccination with inactivated vaccine (*pre-print, not peer-reviewed*) *(10)*.

The anti-SARS-CoV-2-specific neutralizing antibody level before booster immunization was close to negative. The GMT values of neutralizing antibodies in Group A and Group B reached 692.07 and 950.20, respectively, 14 days after the booster dose, which were 7.4 times and 10.2 times higher than booster vaccination with inactivated vaccine (Figure 7). The geometric mean antibody titres of neutralizing antibodies in Group A and Group B rose to 1316.28 and 1408.83 respectively, 28 days after the sequential immunization, which were 15.9 and 17.0 times higher than the booster vaccination with inactivated vaccine (*pre-print, not peer-reviewed*) *(10)*.

Figure 7. Neutralizing antibody results of the heterologous boost immunization study NCT05043259*



**Source*: from data on file*; the three colours in the graph correspond to Groups A, B and C.*

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