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Supplementary appendix

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Supplementary Material

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 of age and older: an international, multicenter, randomised, double-blinded, placebo-controlled phase 3 trial

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Appendix 3

Full List of Inclusion and Exclusion Criteria

Inclusion Criteria

1) Adults of 18 years of age, and older.
2) Able and willing (in the Investigator's opinion) to comply with all study requirements.
3) Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner/personal doctor and access all medical records when relevant to study procedures.
4) Healthy adults, or stable-healthy adults who may have a pre-existing medical condition that does not meet any exclusion criteria. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment [1].
5) For females of childbearing potential only, willingness to practice continuous effective contraception for 30 days prior to enrollment in the study, for 90 days after receiving vaccination during the study, and have a negative pregnancy test on the day(s) of screening/ vaccination (Day 0).
    a) Please note: adequate contraceptive methods is defined as Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label, such as: abstinence from penile-vaginal intercourse (when this is their preferred lifestyle), oral contraceptives (either combined estrogen and progesterone, or progesterone alone), injectable progestogen, implants of etonogestrel or levonorgestrel, estrogen vaginal ring, percutaneous contraceptive patches, intrauterine device or intrauterine system, male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject (information based on interview with the participant on her medical history), male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and male condom combined with a female diaphragm, whether with or without a vaginal spermicide (foam, gel, fil, cream, or suppository).
        i) Adequate contraception does not apply to participants of childbearing potential with same sex partners, when this is their preferred and usual lifestyle.
6) Males participating in this study who are involved in heterosexual sexual activity must agree to practice adequate contraception (see note 5a above) and refrain from donating sperm for 90 days after receiving the study vaccination.
7) Agreement to refrain from blood donation during the study.
8) Provide written informed consent.

Exclusion Criteria

1) Participation in any other COVID-19 prophylactic drug trials for the duration of the study.
    i) *Note: Participation in COVID-19 treatment trials was allowed in the event of hospitalization due to COVID-19. The study team was to be informed as soon as possible*.
2) Participation in SARS-CoV-2 serological surveys where participants are informed of their serostatus for the duration of the study.
    i) *Note: Disclosure of serostatus post enrollment may accidentally unblind participants to group allocation. Participation in this trial can only be allowed if volunteers are kept blinded to their serology results from local/national serological surveys*
3) Planned receipt of any vaccine (licensed or investigational), other than the study intervention, within 14 days before and after study vaccination.
4) Prior receipt of an investigational or licensed vaccine likely to impact on the interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus or SARS vaccines).

5) Administration of immunoglobulins and/or any blood products within the three months prior to the planned administration of the vaccine candidate.
6) Any confirmed or suspected immunosuppressive or immunodeficient state; positive HIV status; asplenia; recurrent severe infections and chronic use (more than 14 days) of immunosuppressant medication within the past 6 months. Topical steroids or short-term (course lasting ≤14 days) oral steroids are not an exclusion.
7) History of allergic disease or reactions likely to be exacerbated by any component of Ad5- nCoV.
8) Any history of angioedema.
9) Pregnancy, lactation or willingness/intention to become pregnant within 90 days after receiving study vaccine.
10) Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
11) History of serious psychiatric condition likely to affect participation in the study.
12) Bleeding disorder (e.g., factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
13) Suspected or known current alcohol or drug dependency.
14) Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well-controlled comorbidities are allowed).
15) History of laboratory-confirmed COVID-19.
16) Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e., warfarin) or novel oral anticoagulants (i.e., apixaban, rivaroxaban, dabigatran and edoxaban).
17) Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data.

Appendix 4

COVID-19 Case Severity Definitions

This study defined severe disease as a minimum of one of any of the following occurring:

1) 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)
2) Respiratory failure (defined as needing high- flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO)
3) Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
4) Significant acute renal, hepatic, or neurologic dysfunction
5) Admission to an ICU

Appendix 5

Protocol-Defined Study Outcomes

Outcomes related to later time points, along with analysis of cell-mediated immune responses will be reported in a future publication (highlighted in yellow).

Objectives	**Primary Efficacy Objective:** The primary efficacy objective 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. COVID-19 disease rates in Ad5-nCoV group will be compared with COVID-19 rates in the control group. **Primary Safety Objective**: The primary safety objective is to evaluate the incidence of serious adverse events (SAE) and medically attended adverse events (MAE) within 52 weeks after vaccination in all participants. **Secondary Efficacy Objectives:** 1. To evaluate the efficacy of Ad5-nCoV in preventing virologically confirmed (PCR positive) COVID-19 disease occurring 14 days to 52 weeks after vaccination, regardless of severity. 2. To evaluate the efficacy of Ad5-nCoV in preventing severe COVID-19 disease caused by SARS-CoV-2 infection from 14 and 28 days to 24 and 52 weeks after vaccination. ○ Severe disease is defined as: 1) 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), 2) Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO), 3) Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors), 4) Significant acute renal, hepatic, or neurologic dysfunction, 5) Admission to an ICU. 3. To evaluate the efficacy of Ad5-nCoV in different age groups from 14 and 28 days to 24 and 52 weeks after vaccination. This will be evaluated by weekly participant contact to assess for any signs or symptoms of COVID 19. 4. To evaluate the efficacy of the primary and secondary objectives #1-3 of Ad5-nCoV in preventing virologically (PCR) or serologically (four-fold increase in SARS-CoV-2 anti-N IgG from pre-immunization to post symptom, defined as Day 21–28 post illness blood test, or pre-symptom to post-symptom blood test) confirmed COVID-19 disease. **Secondary Safety Objectives**: The following secondary safety objectives will be evaluated in the efficacy-extended safety, efficacy-extended safety-immunogenicity, and efficacy-extended safety-extended immunogenicity cohorts. 1. Evaluate the incidence of solicited adverse reactions within 7 days after vaccination, in a subset of approximately 3000 participants (approximately 7%–10%). 2. Evaluate the incidence of unsolicited adverse events within 28 days after vaccination, in a subset of approximately 3000 participants (approximately 7%–10%). **Secondary Immunogenicity Objectives:** The following secondary objectives will only be evaluated in the efficacy-extended safety-immunogenicity cohort and the efficacy-extended safety-extended immunogenicity cohort.

	1. Evaluate the seroconversion rate of S-RBD IgG antibody on Day 28, and Week 24 and Week 52 after vaccination, measured by ELISA. 2. Evaluate the GMT of S-RBD IgG antibody on Day 28, and Week 24 and Week 52 after vaccination, measured by ELISA. 3. Evaluate the GMI of S-RBD IgG antibody on Day 28, and Week 24 and Week 52 after vaccination, measured by ELISA. 4. Evaluate the seroconversion rate of pseudo-virus neutralizing antibody on Day 28, Week 24 and Week 52 after vaccination. 5. Evaluate the GMT of pseudo-virus neutralizing antibody on Day 28, and Week 24 and Week 52 after vaccination. 6. Evaluate the GMI of pseudo-virus neutralizing antibody on Day 28, and Week 24 and Week 52 after vaccination. 7. Evaluate the positive rate and level of IFN-γ stimulated by peptide pool of S protein on Day 28, and Weeks 24 and Week 52 after vaccination, measured by ELISpot. 8. Evaluate the positive rate and level of IL-2, IL-4, IL-13, and IFN-γ stimulated by peptide pool of S protein on days 28, and Week 24 and Week 52 after vaccination, measured by intracellular cytokine staining (ICS). **Supportive Objectives** 1. Evaluate the severity of COVID-19 cases among vaccine recipients (based on WHO or FDA criteria) as compared to the control group, to measure antibody-mediated disease enhancement (ADE). 2. Evaluate for any evidence of SARS-CoV-2 virus shedding in COVID-19 cases that occurred 28 days to 52 weeks after vaccination (detection of viral nucleic acid every 2 days after being confirmed). 3. Perform genotyping of SARS-CoV-2 virus isolates of COVID-19 cases that occurred 28 days to 52 weeks after vaccination. 4. Evaluate incidence of suspected but unconfirmed cases of COVID-19 (either because of negative or no tests). 5. To evaluate the efficacy of Ad5-nCoV in preventing asymptomatic disease of COVID-19 (confirmed by N IgG antibody on week 52 after vaccination).

Appendix 6

Endpoint Case Definitions

Confirmed cases of COVID-19 were categorized into primary endpoint cases and secondary endpoint cases according to the time of onset after vaccination.

Primary endpoint: the participant with the clinical symptom(s) occurred not less than 28 days postvaccination and the PCR test is positive.

Secondary endpoint: the participant with the clinical symptom(s) occurred not less than 14 days postvaccination and the PCR test is positive; or 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 were reported to the Endpoint Review Committee (ERC) for final review.

Appendix 7

Characteristics of the Study Population (Safety Cohort)

		Administered Group			
		Ad5-nCoV		Placebo	
Characteristic		**N**	**%**	**N**	**%**
Randomized Group	Placebo	6*	0·0	18351	100·0
	Ad5-nCoV	18357	100·0	3*	0·0
Age at consent	N	18363		18354	
	Mean (range)	39·2 (18·0–91·5)		39·1 (18·0–93·5)	
Age distribution	18 to <45 years	12398	67·5	12385	67·5
	45 to <60 years	4121	22·4	4109	22·4
	≥60 years	1844	10·0	1860	10·1
Sex**	Male	12041	65·6	12200	66·5
	Female	6322	34·4	6154	33·5
Gender**	Male	12070	65·7	12213	66·5
	Female	6287	34·2	6136	33·4
	Transgender woman	1	0·0	0	0·0
	Transgender man	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**	Hispanic or Latino	7967	43·4	7995	43·6
	Not Hispanic or Latino	10396	56·6	10359	56·4
Race**	Missing	30	0·2	38	0·2
	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 Pacific Islander	0	0·0	1	0·0
	White	4021	21·9	4037	22·0
	Mixed race	4527	24·7	4516	24·6
BMI	N	18363		18354	
	Median (range)	25·4 (11·2–77·1)		25·4 (13·1–74·6)	
BMI Category	≥30	3475	18·9	3451	18·8
	25 to <30	6341	34·5	6369	34·7

Characteristic		Administered Group			
		Ad5-nCoV		Placebo	
		N	%	N	%
	18·5 to <25	7560	41·2	7478	40·7
	0 to <18·5	987	5·4	1056	5·8

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

Appendix 8

Vaccine Efficacy by BMI

	Total Sample size in calculation	Ad5-nCoV Group no. cases/group, %	Placebo Group no. cases/group, %	Vaccine Efficacy (95% CI)
Efficacy after Day 14				
0 to < 18.5	1766	2/848, 0.24%	10/918, 1.09%	78.00% (-0.41- 95.18)
18.5 to < 25	12004	22/60480, 0.36%	67/5956, 1.12%	68.22% (48.55- 80.37)
25 to < 30	10019	30/4988, 0.60%	75/5031, 1.49%	59.88% (38.73- 73.73)
≥ 30	5388	23/27070, 0.85%	59/2681, 2.20%	61.18% (37.14- 76.02)
Efficacy after Day 28				
0 to < 18.5	1462	2/699, 0.29%	4/763, 0.52%	44.98% (-200.45- 89.92)
18.5 to < 25	8918	10/4529, 0.22%	33/4389, 0.75%	70.98% (41.12- 85.70)
25 to < 30	7157	20/3569, 0.56%	31/3588, 0.86%	35.39% (-13.35- 63.17)
≥ 30	3713	13/1863, 0.70%	37/1850, 2.00%	64.87% (33.92- 81.33)

Appendix 9

Vaccine Efficacy by Country

	Total Sample size in calculation	Ad5-nCoV Group no. cases/group, %	Placebo Group no. cases/group, %	Vaccine Efficacy (95% CI)
Efficacy after Day 14				
Pakistan	15019	28/7509, 0.37%	90/7510, 1.20%	69.10% (52.77 - 79.78)
Mexico	11166	46/5587, 0.82%	109/5579, 1.95%	58.05% (40.80 - 70.28)
Russia	1964	2/982, 0.20%	5/982, 0.51%	60.34% (-104.42- 92.31)
Chile	922	1/461, 0.22%	7/461, 1.52%	85.87% (-14.82- 98.26)
Argentina	106	0/52, 0.00%	0/54, 0.00%	N/A
Efficacy after Day 28				
Pakistan	12479	19/6244, 0.30%	57/6235, 0.91%	66.99% (44.53- 80.36)
Mexico	7618	26/3834, 0.68%	47/3784, 1.24%	45.08% (11.33- 65.98)
Russia	781	0/394, 0.00%	1/387, 0.26%	100.00%
Chile	362	0/184, 0.00%	0/178, 0.00%	N/A
Argentina	10	0/4, 0.00%	0/6, 0.00%	N/A

Appendix 10

Serious Adverse Events (SAE) and Medically Attended Adverse Events (MAE) Following Immunization with Ad5-nCoV or Placebo, by Sex: Males

Variable	Ad5-nCoV Group (N=12,041) n, % (95% confidence interval)	Placebo Group (N=12,200) n, % (95% confidence interval)	p-value
SAE			
Total SAE	9, 0·1 (0·03, 0·1)	8, 0.1 (0·03, 0·1)	0·81
Grade 1	0, 0·0 (0·0, 0·03)	1, 0·0 (0·0, 0·05)	1·00
Grade 2	0, 0·0 (0·0, 0·03)	2, 0·0 (0·0, 0·06)	0·50
Grade 3	2, 0·0 (0·0, 0·06)	5, 0·0 (0·01, 0·1)	0·45
Grade 4	2, 0·0 (0·0, 0·06)	0, 0·0 (0·0, 0·03)	0·25
Grade 5	5, 0·0 (0·01, 0·1)	1, 0·0 (0·0, 0·05)	0·12
SAE Related to Study Product	0, 0·0 (0·0, 0·0)	0, 0·0 (0·0, 0·0)	
MAE			
Total MAE	283, 2·4 (2·1, 2·6)	248, 2·0 (1·8, 2·3)	0·10
Grade 1	244, 2·0 (1·8, 2·3)	216, 1·8 (1·5, 2·0)	0·15
Grade 2	33, 0·3 (0·2, 0·4)	35, 0·3 (0·2, 0·4	0·90
Grade 3	4, 0·03 (0·01, 0·09)	6, 0·05 (0·02, 0·1)	0·75
Grade 4	2, 0·02 (0·0, 0·06)	0, 0.0 (0·0, 0·03)	0·25
Grade 5	1, 0·01 (0·0, 0·05)	1, 0·01 (0·0, 0·05)	1·00
MAE related to study product[**]			
Total MAE	21, 0·2 (0·1, 0·3)	24, 0·2 (0·1, 0·3)	0·77
Grade 1	18, 0·2 (0·09, 0·2)	19, 0·2 (0·09, 0·2)	1·00
Grade 2	3, 0·02 (0·01, 0·07)	5, 0·04 (0·01, 0·1)	0·73
Grade 3	0, 0·0 (0·0, 0·03)	1, 0·01 (0·0, 0·05)	1·00
Grade 4	0, 0·0 (0·0, 0·03)	0, 0·0 (0·0, 0·03)	
Grade 5	0, 0·0 (0·0, 0·03)	0, 0·0 (0·0, 0·03)	

[*] Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
[**] related to study product as assessed by the local investigator

Appendix 11

Serious Adverse Events (SAE) and Medically Attended Adverse Events (MAE) Following Immunization with Ad5-nCoV or Placebo, by Sex: Females

Variable	Ad5-nCoV Group (N=6,322) n, % (95% confidence interval)	Placebo Group (N=6,154) n, % (95% confidence interval)	p-value
SAE			
Total SAE	5, 0·1 (0·03, 0.2)	2, 0·0 (0·0, 0·1)	0·45
Grade 1	0, 0·0 (0·0, 0·06)	0, 0·0 (0·0, 0·06)	
Grade 2	0, 0·0 (0·0, 0·06)	1, 0·0 (0·0, 0·09)	0·49
Grade 3	1, 0·0 (0·0, 0·09)	1, 0·0 (0·0, 0·09)	1·00
Grade 4	2, 0·0 (0·0, 0·1)	0, 0·0 (0·0, 0·06)	0·50
Grade 5	2, 0·0 (0·0, 0·1)	0, 0·0 (0·0, 0·06)	0·50
SAE related to study product	0, 0·0 (0·0, 0·0)	0, 0·0 (0·0, 0·0)	
MAE			
Total MAE	159, 2·5 (2·1, 2·9)	163, 2·7 (2·3, 3·1)	0·65
Grade 1	132, 2·1 (1·8, 2·5)	135, 2·2 (1·8, 2·6)	0·71
Grade 2	29, 0·5 (0·3, 0·7)	28, 0·45 (0·3, 0·7)	1·00
Grade 3	1, 0·02 (0·0, 0·09)_	4, 0·06 (0·02, 0·2)	0·21
Grade 4	1, 0·02 (0·0, 0·09)	0, 0·0 (0·0, 0·06	1·00
Grade 5	1, 0·02 (0·0, 0·09)	0, 0·0 (0·0, 0·06	1·00
MAE related to study product[**]			
Total MAE	19, 0·3 (0·2, 0·5)	19, 0·3 (0·2, 0·5)	1·00
Grade 1	17, 0·3 (0·2, 0·4)	14, 0·2 (0·1, 0·4)	0·72
Grade 2	5, 0·08 (0·03, 0·2)	5, 0·08 (0·03, 0·2)	1·00
Grade 3	0, 0·0 (0·0, 0·06)	0, 0·0 (0·0, 0·06)	
Grade 4	0, 0·0 (0·0, 0·06)	0, 0·0 (0·0, 0·06)	
Grade 5	0, 0·0 (0·0, 0·06)	0, 0·0 (0·0, 0·06)	

[*] Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
[**] related to study product as assessed by the local investigator

Appendix 12

SAE and MAE by Country

	Ad5-nCoV Group Sample Size	Incidence of SAE/MAE in Ad5-nCoV Group, n, % of sample size [a]	Placebo Group Sample Size	Incidence of SAE/MAE in Placebo Group, n=, % of sample size	p-value
SAE by Country					
All SAE					
Russia	1853	1, 0.1% (0.00-0.30)	1848	1, 0.1% (0.00-0.30)	1.000
Argentina	315	0, 0.0% (0.00-1.16)	316	0, 0.0% (0.00-1.16)	
Mexico	6774	3, 0.0% (0.01-0.13)	6785	6, 0.1% (0.03-0.19)	0.508
Chile	937	0, 0.0% (0.00-0.39)	939	1, 0.1% (0.00-0.59)	1.000
Pakistan	8484	10, 0.1% (0.06-0.22)	8466	2, 0.0% (0.00-0.09)	0.039
Any Grade 3 and above SAE					
Russia	1853	1, 0.1% (0.00-0.30)	1848	0, 0.0% (0.00-0.20)	1.000
Argentina	315	0, 0.0% (0.00-1.16)	316	0, 0.0% (0.00-1.16)	
Mexico	6774	3, 0.0% (0.01-0.13)	6785	4, 0.1% (0.02-0.15)	1.000
Chile	937	0, 0.0% (0.00-0.39)	939	1, 0.1% (0.00-0.59)	1.000
Pakistan	8484	10, 0.1% (0.06-0.22)	8466	2, 0.0% (0.00-0.09)	0.039
MAE by Country					
All MAE					
Russia	1853	39, 2.10% (1.50- 2.87)	1848	30, 1.62% (1.10- 2.31)	0.331
Argentina	315	5, 1.59% (0.52- 3.67)	316	3, 0.95% (0.20- 2.75)	0.505
Mexico	6774	170, 2.51% (2.15- 2.91)	6785	168, 2.48% (2.12-2.87)	0.912
Chile	937	7, 0.75% (0.30- 1.53)	939	16, 1.70% (0.98-2.75)	0.091
Pakistan	8484	221, 2.60% (2.28- 2.97)	8466	194, 2.29% (1.98-2.63)	0.196
Grade 3 and above MAE					
Russia	1853	1, 0.05% (0.00-0.30)	1848	0, 0.00% (0.00-0.20)	1.000
Argentina	315	0, 0.0% (0.00-1.16)	316	0, 0.0% (0.00-1.16)	
Mexico	6774	3, 0.04% (0.01- 0.13)	6785	4, 0.06% (0.02-0.15)	1.000
Chile	937	0, 0.00% (0.00- 0.39)	939	3, 0.32% (0.07- 0.93)	0.250
Pakistan	8484	6, 0.07% (0.03- 0.15)	8466	4, 0.05% (0.01- 0.12)	0.754
MAE related to study product					
Russia	1853	2, 0.11% (0.01- 0.39)	1848	4, 0.22% (0.06- 0.55)	0.452
Argentina	315	0, 0.0% (0.00-1.16)	316	0, 0.0% (0.00-1.16)	
Mexico	6774	33, 0.49% (0.34- 0.68)	6785	30, 0.44% (0.30-0.63)	0.707
Chile	937	1, 0.11% (0.00- 0.59)	939	3, 0.32% (0.07- 0.93)	0.625
Pakistan	8484	4, 0.05% (0.01- 0.12)	8466	6, 0.07% (0.03-0.15)	0.548
Grade 3 and above MAE related to study product					
Russia	1853	0, 0.00% (0.00- 0.20)	1848	0, 0.00% (0.00- 0.20)	
Argentina	315	0, 0.0% (0.00-1.16)	316	0, 0.0% (0.00-1.16)	
Mexico	6774	0, 0.00% (0.00- 0.05)	6785	0, 0.00% (0.00- 0.05)	
Chile	937	0, 0.00% (0.00- 0.39)	939	1, 0.11% (0.00- 0.59)	1.000
Pakistan	8484	0, 0.00% (0.00- 0.04)	8466	0, 0.00% (0.00- 0.04)	

Appendix 13

SAE Line Listing Details

Subject ID	Preferred Term/ SOC/ Verbatim Term	Onset Study Day	End Study Day	Grade	Is this AE a pre-existing condition that worsened?	Contributing factors	Seriousness	Is there a reasonable possibility that the AE may have been caused by the investigational product?	Action(s) Taken	Outcome	Did the event cause the subject to withdraw or be discontinued from the study?
71700149	Pneumonia/ Infections and infestations/ pneumonia	06JAN2021/ 16	20JAN2021/ 30	Grade 2 (Moderate)	No	Lack of efficacy of the product	Required or prolonged inpatient hospitalization	No	Hospitalization	Recovered/ resolved	No
73600072	Myocardial infarction/ Cardiac disorders/ Coronary heart disease. Posterior myocardial infarction	15JAN2021/ 4	25JAN2021/ 14	Grade 4 (Potentially life- threatening)	No	Medical History/ Other cause (physical inactivity, overweight, smoking, gender, age)	Life-threatening/ Required or prolonged inpatient hospitalization	No	Concomitant medication/ Hospitalization/ Other (Percutaneous coronary	Recovered/ resolved	No
	Coronary artery disease/ Cardiac disorders/ Coronary heart disease. Posterior myocardial infarction	15JAN2021/ 4	25JAN2021/ 14	Grade 4 (Potentially life- threatening)	No	Medical History/ Other cause (physical inactivity, overweight, smoking, gender, age)	Life-threatening/ Required or prolonged inpatient hospitalization	No	Concomitant medication/ Hospitalization/ Other (Percutaneous coronary	Recovered/ resolved	No
520200363	Suspected COVID-19/ Infections and infestations/ Suspected COVID-19	09JAN2021/ 32	12FEB2021/ 66	Grade 3 (Severe)	No	Medical History	Required or prolonged inpatient hospitalization	No	Concomitant medication/ Health care provider visit	Recovered with	No
520200419	Intestinal obstruction/ Gastrointestinal disorders/ Intestinal Obstruction	13DEC2020/ 2	07JAN2021/ 27	Grade 5 (Results in death)	No	Other cause (Intenstinal occlusion)	Death/ Required or prolonged inpatient hospitalization	No	Hospitalization	Fatal (SAEs only)	Yes
	Diaphragmatic hernia/ Gastrointestinal disorders/ Left diaphragmatic hernia	13DEC2020/ 2	07JAN2021/ 27	Grade 5 (Results in death)	No	Other cause (Intenstinal occlusion)	Death/ Required or prolonged inpatient hospitalization	No	Hospitalization	Fatal (SAEs only)	Yes
	Electrolyte imbalance/ Metabolism and nutrition disorders/ Hydroelectrolytic imbalance	28DEC2020/ 17	07JAN2021/ 27	Grade 5 (Results in death)	No	Other cause (Intenstinal occlusion)	Death/ Required or prolonged inpatient hospitalization	No	Hospitalization	Fatal (SAEs only)	Yes
	Sepsis/ Infections and infestations/ Sepsis	28DEC2020/ 17	07JAN2021/ 27	Grade 5 (Results in death)	No	Other cause (Intenstinal occlusion)	Death/ Required or prolonged inpatient hospitalization	No	Hospitalization	Fatal (SAEs only)	Yes
	Pneumonia/ Infections and infestations/ Probably intrahospital pneumonia	28DEC2020/ 17	07JAN2021/ 27	Grade 5 (Results in death)	No	Other cause (Intenstinal occlusion)	Death/ Required or prolonged inpatient hospitalization	No	Hospitalization	Fatal (SAEs only)	Yes
520400118	Appendicitis/ Infections and infestations/ appendicitis	26NOV2020/ 10	28NOV2020/ 12	Grade 3 (Severe)	No	Other cause (Patient's body itself caused the appendix inflammation)	Required or prolonged inpatient hospitalization	No	Procedure/ Hospitalization	Recovered/ resolved	No
520400446	Hypertriglycerida emia/ Metabolism and nutrition disorders/ hypertriglyceridaemia	23NOV2020/ 2	12JAN2021/ 52	Grade 4 (Potentially life- threatening)	No	Other cause (was finding)	Life-threatening	No	Concomitant medication	Recovered/ resolved	No
520500127	Craniocerebral injury/ Injury, poisoning and procedural complications/ traumatic brain injury	03JAN2021/ 24	05JAN2021/ 26	Grade 2 (Moderate)	No	Other cause (alcoholic intoxication)	Required or prolonged inpatient hospitalization	No	Hospitalization	Recovered/ resolved	No
	Spinal cord compression/ Nervous system disorders/ Medullary compression	05JAN2021/ 26	11JAN2021/ 32	Grade 1 (Mild)	No	Other procedure not required by the protocol	Required or prolonged inpatient hospitalization	No	Hospitalization	Recovered/ resolved	No
	Spinal cord compression/ Nervous system disorders/ Medullary compression	15JAN2021/ 36	12FEB2021/ 64	Grade 1 (Mild)	No	Other procedure not required by the protocol	Required or prolonged inpatient hospitalization	No	Procedure/ Hospitalization/ Other (column surgery)	Recovered/ resolved	No
521600101	Suicide attempt/ Psychiatric disorders/ Suicide attempt	10JAN2021/ 18	18JAN2021/ 26	Grade 4 (Potentially life- threatening)	No	Other cause (New Illness)	Life-threatening/ Required or prolonged inpatient hospitalization	No	Hospitalization	Recovered/ resolved	No
521800194	Intestinal obstruction/ Gastrointestinal disorders/ Intestinal Obstruction	15JAN2021/ 28	21JAN2021/ 34	Grade 3 (Severe)	No	Medical History	Required or prolonged inpatient hospitalization	No	Health care provider visit/ Hospitalization	Recovered/ resolved	No
522000496	Gastroenteritis/ Infections and infestations/ Gastroenteritis	22DEC2020/ 7	13JAN2021/ 29	Grade 2 (Moderate)	Yes	Medical History	Required or prolonged inpatient hospitalization	No	Concomitant medication/ Health care provider visit/ Hospitalization	Recovered/ resolved	No
522000616	Ruptured ectopic pregnancy/ Pregnancy, puerperium and perinatal conditions/ Ruptured ectopic pregnancy	28DEC2020/ 11	07JAN2021/ 21	Grade 3 (Severe)	No	Other cause (Rupture ectopic pregnancy)	Required or prolonged inpatient hospitalization	No	Hospitalization	Recovered/ resolved	No
560100232	Syncope/ Nervous system disorders/ Vasovagal syncope	23DEC2020/ 1	25DEC2020/ 3	Grade 3 (Severe)	No	Other cause (possible dysautonomia)	Required or prolonged inpatient hospitalization	No	Health care provider visit/ Hospitalization/ Other (laboratory test)	Recovered/ resolved	No
920101874	Myocardial infarction/ Cardiac disorders/ Sudden heart attack	03JAN2021/ 53	03JAN2021/ 53	Grade 5 (Results in death)	No	Other cause (sudden heart attack)	Death	No	Other (He was pronounced dead at the spot.)	Fatal (SAEs only)	Yes
920103094	Coma/ Nervous system disorders/ Coma	Unknown/ Unknown	23FEB2021/ 90	Grade 5 (Results in death)	No	Other cause (Coma)	Death/ Required or prolonged inpatient hospitalization	No	Health care provider visit/ Hospitalization	Fatal (SAEs only)	Yes
920103467	Epididymitis/ Infections and infestations/ Epididymitis	19DEC2020/ 21	29DEC2020/ 31	Grade 3 (Severe)	No	Other cause (Congenital anomaly/ birth defect)	Required or prolonged inpatient hospitalization	No	Concomitant medication/ Hospitalization	Recovered/ resolved	No
	Cellulitis/ Infections and infestations/ Cellulitis	19DEC2020/ 21	29DEC2020/ 31	Grade 3 (Severe)	No	Other cause (Congenital anomaly/ birth defect)	Required or prolonged inpatient hospitalization	No	Concomitant medication/ Health care provider visit/ Hospitalization	Recovered/ resolved	No
920103691	Road traffic accident/ Injury, poisoning and procedural complications/ Road traffic accident	04JAN2021/ 34	04JAN2021/ 34	Grade 5 (Results in death)	No	Other cause (Died from accident)	Death	No	None	Fatal (SAEs only)	Yes
920104944	Acute respiratory distress syndrome/ Respiratory, thoracic and mediastinal disorders/ Acute Respiratory Distress	Unknown/ Unknown	03APR2021/ 100	Grade 5 (Results in death)	No	Other cause (ARDS)	Death/ Life- threatening	No	Hospitalization	Fatal (SAEs only)	No
	Sarcoidosis/ Immune system disorders/ Sarcoidosis	Unknown/ Unknown	03APR2021/ 100	Grade 5 (Results in death)	No	Other cause (Sarcoidosis)	Death/ Life- threatening	No	Hospitalization	Fatal (SAEs only)	No
920300230	Spinal compression fracture/ Injury, poisoning and procedural complications/ L1 Compression Fracture	29DEC2020/ 55	25MAR2021/ 141	Grade 3 (Severe)	No	Other cause (Work Place Accident. L1 compression fracture)	Required or prolonged inpatient hospitalization	No	Concomitant medication/ Health care provider visit/ Hospitalization	Recovered/ resolved	No
920300258	Dermatitis exfoliative generalised/ Skin and subcutaneous tissue disorders/ Psoriasis Flare Erythroderma	14JAN2021/ 70	24MAR2021/ 139	Grade 3 (Severe)	Yes	Medical History	Required or prolonged inpatient hospitalization	No	Concomitant medication/ Health care provider visit/ Hospitalization	Recovered/ resolved	No
	Psoriasis/ Skin and subcutaneous tissue disorders/ Psoriasis Flare Erythroderma	14JAN2021/ 70	24MAR2021/ 139	Grade 3 (Severe)	Yes	Medical History	Required or prolonged inpatient hospitalization	No	Concomitant medication/ Health care provider visit/ Hospitalization	Recovered/ resolved	No
920300656	Angina unstable/ Cardiac disorders/ Unstable angina	04JAN2021/ 45	06JAN2021/ 47	Grade 3 (Severe)	Yes	Medical History	Required or prolonged inpatient hospitalization	No	Concomitant medication/ Health care provider visit/ Procedure/ Hospitalization	Recovered/ resolved	No
920301381	Death/ General disorders and administration site conditions/ Unknown Cause of Death	28DEC2020/ 18	28DEC2020/ 18	Grade 5 (Results in death)	Yes	Medical History	Death/ Life- threatening	No	Other (ER visit)	Fatal (SAEs only)	Yes
9203B00089	Acute myocardial infarction/ Cardiac disorders/ Non ST elevation Myocardial Infarction	20DEC2020/ 13	22DEC2020/ 15	Grade 4 (Potentially life- threatening)	Yes	Medical History	Life-threatening/ Required or prolonged inpatient hospitalization	No	Concomitant medication/ Health care provider visit/ Procedure/ Hospitalization	Recovered/ resolved	No
920402192	Road traffic accident/ Injury, poisoning and procedural complications/ Road traffic accident	03DEC2020/ 3	03DEC2020/ 3	Grade 5 (Results in death)	No	Other cause (Road traffic accident)	Death	No	None	Fatal (SAEs only)	Yes
920500076	Myocardial infarction/ Cardiac disorders/ Myocardial Infarction	03JAN2021/ 75	03JAN2021/ 75	Grade 5 (Results in death)	No	Other cause (Cardiac arrest)	Death	No	None	Fatal (SAEs only)	Yes

Appendix 14

Characteristics of the Study Population (Extended Safety Cohort)

		Administered Group				
		Ad5-nCoV		Placebo		
		N	%	N	%	p-value
Randomized Group	Placebo	0	0·0	1574	100·0	
	Ad5-nCoV	1585	100·0	0	0·0	
Cohort	Efficacy-Extended Safety	1324	83·5	1319	83·8	0·97
	Efficacy-Extended Safety-Immunogenicity	200	12·6	194	12·3	
	Efficacy-Extended Safety-Extended Immunogenicity	61	3·8	61	3·9	
Age at Consent	N	1585		1574		0·42
	Mean	41·8		41·4		
	Median	40·2		39·9		
	SD	15·0		14·8		
	Min	18·2		18·0		
	Max	88·9		96·5		
	Q1	29·2		29·3		
	Q3	53·2		52·0		
Age Groups	18 to <45 years	969	61·1	980	62·3	0·69
	45 to <60 years	398	25·1	393	25·0	
	≥60 years	218	13·8	201	12·8	
Sex	Male	867	54·7	817	51·9	0·12
	Female	718	45·3	757	48·1	
Gender	Male	868	54·8	818	52·0	0·17
	Female	716	45·2	756	48·0	
	Neither Male nor Female	1	0·1	0	0·0	
Child-bearing potential	Missing	1	0·1	0	0·0	0·17
	No	259	36·1	248	32·8	
	Yes	458	63·8	509	67·2	
Ethnicity	Hispanic or Latino	964	60·8	959	60·9	0·95
	Not Hispanic or Latino	621	39·2	615	39·1	
Race	Indigenous, Americas	136	8·6	136	8·6	0·98
	Asian	285	18·0	289	18·4	
	White	954	60·2	935	59·4	

		Administered Group				
		Ad5-nCoV		Placebo		
		N	%	N	%	p-value
	Mixed race	210	13·2	214	13·6	
Height (cm)	N	1585		1574		0·37
	Mean	168·8		168·5		
	Median	169·0		169·0		
	SD	9·7		9·3		
	Min	140·0		144·0		
	Max	200·0		198·0		
	Q1	162·0		162·0		
	Q3	176·0		175·0		
Weight (kg)	N	1585		1574		0·16
	Mean	75·2		74·3		
	Median	73·0		72·6		
	SD	16·2		16·3		
	Min	31·0		35·0		
	Max	135·0		154·0		
	Q1	63·0		62·5		
	Q3	85·0		84·5		
BMI	N	1585		1574		0·23
	Mean	26·3		26·1		
	Median	25·6		25·5		
	SD	4·9		4·9		
	Min	13·2		15·6		
	Max	51·1		54·5		
	Q1	23·1		22·7		
	Q3	29·1		28·9		
BMI Categories	0 to <18·5	40	2·5	48	3·0	0·62
	18·5 to <25	659	41·6	665	42·2	
	25 to <30	559	35·3	560	35·6	
	≥30	327	20·6	301	19·1	

Appendix 15

Solicited General and Injection-Site Adverse Events from Day 0 to Day 7 Postvaccination with Ad5-nCoV or Placebo, by Sex: Male

		Ad5-nCoV			Placebo			
Reactions	**Severity**	**N**	**n**	**% (95% CI)**	**N**	**n**	**% (95% CI)**	**p-value**
Total general adverse events	Any	865	522	60.3 (57.0,63.6)	815	345	42.3 (38.9,45.8)	<.001
	≥Grade 3	865	79	9.1 (7.3,11.3)	815	26	3.2 (2.1,4.6)	<.001
Fever	Any	862	121	14.0 (11.8,16.5)	814	16	2.0 (1.1,3.2)	<.001
	≥Grade 3	862	19	2.2 (1.3,3.4)	814	0	0.0 (0.0,0.5)	<.001
Drowsiness	Any	865	329	38.0 (34.8,41.4)	815	202	24.8 (21.9,27.9)	<.001
	≥Grade 3	865	35	4.0 (2.8,5.6)	815	11	1.3 (0.7,2.4)	<.001
Headache	Any	865	362	41.8 (38.5,45.2)	815	216	26.5 (23.5,29.7)	<.001
	≥Grade 3	865	37	4.3 (3.0,5.8)	815	8	1.0 (0.4,1.9)	<.001
Nausea	Any	865	93	10.8 (8.8,13.0)	814	60	7.4 (5.7,9.4)	0.017
	≥Grade 3	865	4	0.5 (0.1,1.2)	814	1	0.1 (0.0,0.7)	0.375
Diarrhea	Any	865	80	9.2 (7.4,11.4)	815	62	7.6 (5.9,9.6)	0.254
	≥Grade 3	865	5	0.6 (0.2,1.3)	815	3	0.4 (0.1,1.1)	0.727
Vomiting	Any	865	10	1.2 (0.6,2.1)	815	9	1.1 (0.5,2.1)	1.000
	≥Grade 3	865	0	0.0 (0.0,0.4)	815	0	0.0 (0.0,0.5)	
Generalized muscle aches	Any	864	335	38.8 (35.5,42.1)	814	131	16.1 (13.6,18.8)	<.001
	≥Grade 3	864	26	3.0 (2.0,4.4)	814	7	0.9 (0.3,1.8)	0.001
Total local adverse events	Any	866	475	54.8 (51.5,58.2)	816	143	17.5 (15.0,20.3)	<.001
	≥Grade 3	866	22	2.5 (1.6,3.8)	816	6	0.7 (0.3,1.6)	0.004
Redness at injection site	Any	865	44	5.1 (3.7,6.8)	815	7	0.9 (0.3,1.8)	<.001

		Ad5-nCoV			Placebo			
Reactions	**Severity**	**N**	**n**	**% (95% CI)**	**N**	**n**	**% (95% CI)**	**p-value**
	≥Grade 3	865	1	0.1 (0.0,0.6)	815	1	0.1 (0.0,0.7)	1.000
Swelling at injection site	Any	865	36	4.2 (2.9,5.7)	815	4	0.5 (0.1,1.3)	<.001
	≥Grade 3	865	1	0.1 (0.0,0.6)	815	0	0.0 (0.0,0.5)	1.000
Pain at injection site	Any	866	461	53.2 (49.8,56.6)	816	139	17.0 (14.5,19.8)	<.001
	≥Grade 3	866	21	2.4 (1.5,3.7)	816	5	0.6 (0.2,1.4)	0.003
Total solicited adverse events	Any	866	609	70.3 (67.2,73.4)	816	384	47.1 (43.6,50.6)	<.001
	≥Grade 3	866	83	9.6 (7.7,11.7)	816	28	3.4 (2.3,4.9)	<.001

Appendix 16

Solicited General and Injection-Site Adverse Events from Day 0 to Day 7 Postvaccination with Ad5-nCoV or Placebo, by Sex: Female

		Ad5-nCoV			Placebo			
Reactions	**Severity**	**N**	**n**	**% (95% CI)**	**N**	**n**	**% (95% CI)**	**p-value**
Total general adverse events	Any	717	482	67.2 (63.7,70.7)	757	384	50.7 (47.1,54.3)	<.001
	≥Grade 3	717	81	11.3 (9.1,13.8)	757	52	6.9 (5.2,8.9)	0.004
Fever	Any	716	77	10.8 (8.6,13.3)	756	9	1.2 (0.5,2.2)	<.001
	≥Grade 3	716	8	1.1 (0.5,2.2)	756	0	0.0 (0.0,0.5)	0.003
Drowsiness	Any	716	303	42.3 (38.7,46.0)	757	235	31.0 (27.8,34.5)	<.001
	≥Grade 3	716	31	4.3 (3.0,6.1)	757	22	2.9 (1.8,4.4)	0.162
Headache	Any	717	337	47.0 (43.3,50.7)	757	265	35.0 (31.6,38.5)	<.001
	≥Grade 3	717	48	6.7 (5.0,8.8)	757	22	2.9 (1.8,4.4)	<.001
Nausea	Any	716	99	13.8 (11.4,16.6)	757	89	11.8 (9.5,14.3)	0.242
	≥Grade 3	716	11	1.5 (0.8,2.7)	757	5	0.7 (0.2,1.5)	0.133
Diarrhea	Any	716	74	10.3 (8.2,12.8)	757	65	8.6 (6.7,10.8)	0.285
	≥Grade 3	716	2	0.3 (0.0,1.0)	757	3	0.4 (0.1,1.2)	1.000
Vomiting	Any	716	13	1.8 (1.0,3.1)	757	12	1.6 (0.8,2.8)	0.841
	≥Grade 3	716	1	0.1 (0.0,0.8)	757	3	0.4 (0.1,1.2)	0.625
Generalized muscle aches	Any	717	316	44.1 (40.4,47.8)	757	175	23.1 (20.2,26.3)	<.001
	≥Grade 3	717	39	5.4 (3.9,7.4)	757	9	1.2 (0.5,2.2)	<.001
Total local adverse events	Any	718	496	69.1 (65.6,72.4)	757	171	22.6 (19.7,25.7)	<.001
	≥Grade 3	718	31	4.3 (3.0,6.1)	757	4	0.5 (0.1,1.3)	<.001
Redness at injection site	Any	716	109	15.2 (12.7,18.1)	757	12	1.6 (0.8,2.8)	<.001
	≥Grade 3	716	3	0.4 (0.1,1.2)	757	0	0.0 (0.0,0.5)	0.115

		Ad5-nCoV			Placebo			
Reactions	**Severity**	**N**	**n**	**% (95% CI)**	**N**	**n**	**% (95% CI)**	**p-value**
Swelling at injection site	Any	716	76	10.6 (8.5,13.1)	757	5	0.7 (0.2,1.5)	<.001
	≥Grade 3	716	2	0.3 (0.0,1.0)	757	0	0.0 (0.0,0.5)	0.236
Pain at injection site	Any	718	478	66.6 (63.0,70.0)	757	164	21.7 (18.8,24.8)	<.001
	≥Grade 3	718	28	3.9 (2.6,5.6)	757	4	0.5 (0.1,1.3)	<.001
Total solicited adverse events	Any	718	571	79.5 (76.4,82.4)	757	411	54.3 (50.7,57.9)	<.001
	≥Grade 3	718	96	13.4 (11.0,16.1)	757	53	7.0 (5.3,9.1)	<.001

Appendix 17

Summary of Subjects with Unsolicited Adverse Events from Day 0 - Day 28 in Extended Safety Cohort

	Administered Group	SS	N	%	LCL (%)	UCL (%)	p-value
Any Adverse Event	Placebo	1574	309	19·6	17·7	21·7	0·22
	Ad5-nCoV	1585	340	21·4	19·5	23·6	
Any Grade 1 Adverse Event	Placebo	1574	229	14·6	12·8	16·4	0·88
	Ad5-nCoV	1585	234	14·8	13·1	16·6	
Any Grade 2 Adverse Event	Placebo	1574	95	6·0	4·9	7·3	0·15
	Ad5-nCoV	1585	116	7·3	6·1	8·7	
Any Grade 3 Adverse Event	Placebo	1574	33	2·1	1·5	2·9	0·17
	Ad5-nCoV	1585	46	2·9	2·1	3·9	
Any Grade 4 Adverse Event	Placebo	1574	1	0·1	0·0	0·4	0·50
	Ad5-nCoV	1585	0	0·0	0·0	0·2	
Any Grade 5 Adverse Event	Placebo	1574	0	0·0	0·0	0·2	0·50
	Ad5-nCoV	1585	2	0·1	0·0	0·5	
Any Grade 3 and above Adverse Event	Placebo	1574	33	2·1	1·5	2·9	0·12
	Ad5-nCoV	1585	48	3·0	2·2	4·0	
Any Grade 4 and above Adverse Event	Placebo	1574	1	0·1	0·0	0·4	1·0
	Ad5-nCoV	1585	2	0·1	0·0	0·5	

Appendix 18

Characteristics of the Study Population (Immunogenicity Cohort)

		Randomized Group				
		Ad5-nCoV		Placebo		
		N	%	N	%	p-value
Administered Group	Placebo	0	0·0	267	100·0	
	Ad5-nCoV	271	100·0	0	0·0	
Age at Consent	N	271		267		0·49
	Mean	42·1		41·3		
	Median	41·4		40·3		
	SD	13·7		14·0		
	Min	18·6		18·3		
	Max	78·5		82·2		
	Q1	30·8		29·6		
	Q3	52·3		52·2		
Age Groups	18 to <45 years	163	60·1	158	59·2	0·86
	45 to <60 years	78	28·8	82	30·7	
	≥60 years	30	11·1	27	10·1	
Sex*	Male	155	57·2	139	52·1	0·23
	Female	116	42·8	128	47·9	
Gender*	Male	155	57·2	139	52·1	0·28
	Female	115	42·4	128	47·9	
	Neither Male nor Female	1	0·4	0	0·0	
Child-bearing potential	No	42	36·2	40	31·3	0·41
	Yes	74	63·8	88	68·8	
Ethnicity*	Hispanic or Latino	199	73·4	197	73·8	0·93
	Not Hispanic or Latino	72	26·6	70	26·2	
Race*	Asian	44	16·2	44	16·5	0·80
	White	120	44·3	111	41·6	
	Mixed race	107	39·5	112	41·9	
Height (cm)	N	271		267		0·17
	Mean	168·7		167·6		
	Median	170·0		167·0		
	SD	9·0		9·0		
	Min	140		147		

		Randomized Group				
		Ad5-nCoV		Placebo		
		N	%	N	%	p-value
	Max	189		190		
	Q1	162·0		161·0		
	Q3	175·0		174·0		
Weight (kg)	N	271		267		0·26
	Mean	76·2		74·6		
	Median	74·0		72·0		
	SD	15·0		16·7		
	Min	50		43		
	Max	125		147·5		
	Q1	65·0		63·0		
	Q3	85·0		84·0		
BMI	N	271		267		0·57
	Mean	26·7		26·5		
	Median	25·8		25·8		
	SD	4·5		5·0		
	Min	17·5		17·0		
	Max	41·9		46·9		
	Q1	23·4		22·9		
	Q3	29·1		29·1		
BMI Categories	0 to <18·5	3	1·1	7	2·6	0·62
	18·5 to <25	107	39·5	103	38·6	
	25 to <30	105	38·7	105	39·3	
	≥30	56	20·7	52	19·5	

* Sex, gender, ethnicity, and race were determined by self-report.

Appendix 19

Antibody Response Following Immunization with Ad5-nCoV or Placebo

Antibody	Variable	Day	Ad5-nCoV		Placebo		p value
			n	**GMT (95% CI)**	**n**	**GMT (95% CI)**	
S-RBD ELISA	GMT	0	269	50·9 (45·0, 57·6)	266	49·2 (43·4, 55·8)	0·704
		28	260	1,659·4 (1,375·9, 2,001·4)	248	53·0 (46·4, 60·7)	<0·0001
	GMI	28	258	32·0 (26·9, 38·2)	247	1·1 (0·98, 1·1)	<0·0001
			n/N	**% (95% CI)**	**n/N**	**% (95% CI)**	
	Seroconversion	28	236/258	91·5 (87·4, 94·6)	6/247	2·4 (0·9, 5·2)	<0·0001
			n	**GMT (95% CI)**	**n**	**GMT (95% CI)**	
PNA	GMT	0	269	7·7 (6·7, 8·9)	266	7·5 (6·6, 8·6)	0·78
		28	259	89·6 (72·3, 111·1)	247	8·4 (7·2, 9·8)	<0·0001
	GMI	28	257	11·4 (9·7, 13·4)	246	1·1 (1·0, 1·2)	<0·0001
			n/N	**% (95% CI)**	**n/N**	**% (95% CI)**	
	Seroconversion	28	195/257	75·9 (70·2, 81·0)	8/246	3·3 (1·4, 6·3)	<0·0001

S-RBD, spike protein receptor binding domain antibody measured by enzyme-linked immunoassay; GMT, geometric mean antibody titer; GMI, geometric mean antibody increase; Seroconversion, percent with a fourfold or greater antibody rise; n, number in group; PNA, SARS-CoV-2 antibody measured by pseudovirion neutralization assay.

Appendix 20

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Appendix 21

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Appendix 22

Clinical Trial Protocol

Clinical Trial Protocol

Study Sponsor:	CanSino Biologics Inc. Beijing Institute of Biotechnology
Primary Study Product	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV)
Other Study Product	Placebo for Ad5-nCoV vaccine
Date of protocol	7 February 2021
Version	1.5
Title	Global Phase III Trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in Adults 18 years of age and older
Detailed Title	A global multicenter, randomized, double-blind, placebo -controlled, adaptive designed phase III clinical trial to evaluate the efficacy, safety and immunogenicity of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) in adults 18 years of age and older
Protocol Number	CS-CTP-AD5NCOV-III
Registration Number	NCT04526990
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STATEMENT OF COMPLIANCE

Signature Page of Sponsor's Approval for the Clinical Trial Protocol

Brief Title	Global phase III trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in adults 18 years of age and older
Official Title	A global multi-center, randomized, double-blind, placebo-controlled, adaptive designed phase III clinical trial to evaluate the efficacy, safety and immunogenicity of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) in adults 18 years of age and older
Vaccine	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV)
Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Sponsor	CanSino Biologics Inc. Beijing Institute of Biotechnology
Sponsor Person In Charge	Tao Zhu CanSino Biologics Inc. 185 South Avenue, TEDA West, Tianjin, China 300462 Tel:+86 18622657078 E-mail: tao.zhu@cansinotech.com

Sponsor Person in Charge Signature:  Date: 2021-02-07

Statement of Global PI

I agree to:

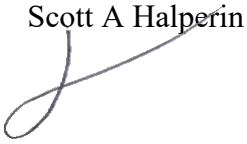
Take the full responsibilities as Global Principal Investigator (PI) of this clinical trial. Ensure that this clinical trial is conducted according to this approved protocol, or revised protocol, and the clinical trial SOPs from the sponsors.

Ensure that the investigators participating in this clinical trial understand the product information of the investigational vaccine provided by the Sponsors, and understand the duties and responsibilities related to the clinical trial as outlined in this clinical trial protocol.

Ensure that there are no changes to the clinical trial protocol without the review and written approval of the sponsors and the Institutional Review Board (IRB) unless it is due to urgent removal of immediate damages to the participants or due to the regulatory requirements (such as due to administration requirements).

I fully understand the correct usage methods of the investigational vaccine, and I fully understand the information provided by the sponsors, including but not limited to the following: Current Investigator Brochure [10] or equivalent documents.

I am familiar with and will comply with the requirements of Good Clinical Practices (GCP) and other relevant regulatory requirements.

Brief Title	Global phase III trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in adults 18 years of age and older
Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Principal Investigator	Scott A Halperin
Signature:	 Date: 10 February 2021

Statement of Global Co-PI

I agree to:

Take the full responsibilities as Global Co-Principal Investigator (co-PI) of this clinical trial. Ensure that this clinical trial is conducted according to this approved protocol, or revised protocol, and the clinical trial SOPs from the sponsors.

Ensure that the investigators participating in this clinical trial understand the product information of the investigational vaccine provided by the Sponsors, and understand the duties and responsibilities related to the clinical trial as outlined in this clinical trial protocol.

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I fully understand the correct usage methods of the investigational vaccine, and I fully understand the information provided by the sponsors, including but not limited to the following: Current Investigator Brochure [10] or equivalent documents.

I am familiar with and will comply with the requirements of Good Clinical Practices (GCP) and other relevant regulatory requirements.

Brief Title	Global phase III trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in adults 18 years of age and older
Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Co-PI	Fengcai Zhu
	Signature: Fengcai Zhu Date: 8. Feb. 2021

Statement of Global Co-PI

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Brief Title	Global phase III trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in adults 18 years of age and older
Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Co-PI	Joanne Langley
	Signature:  Date: 12 February 2021

Statement of Country Co-PI

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Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Country Co-PI	Dmitry A. Lioznov
Signature:	 Date: 11 February, 2021

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Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Country Co-PI	Aamer Ik
Signature	 Date: 12 February 2021

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Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Country Co-PI	Pedro Enrique Cahn

Signature: DocuSigned by: Pedro Cahn 9B613724D34A42C... Date: 12-feb.-2021

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Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Country Co-PI	Fernando Lanas Zanetti
	Signature: Date: Feb 12, 2021

Statement of Country Co-PI

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Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Country Co-PI	Sergio Raúl Muñoz Navarro
Signature:	 Date: 02-B-2021

Statement of Country Co-PI

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Protocol Number	CS-CTP-AD5NCOV-III
Protocol Date	7 February 2021
Version No.	1.5
Country Co-PI	Guillermo M. Ruiz-Palacios
	Signature:  Date: 19 Mar 2021

STUDY SYNOPSIS

Study Title	Global phase III trial of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in adults 18 years of age and older
Full Title	A global multicenter, randomized, double-blind, placebo -controlled, adaptive designed phase III clinical trial to evaluate the efficacy, safety and immunogenicity of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) in adults 18 years of age and older
Objectives	**Primary Efficacy Objective:** The primary efficacy objective 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. COVID-19 disease rates in Ad5-nCoV group will be compared with COVID-19 rates in the control group. **Primary Safety Objective**: The primary safety objective is to evaluate the incidence of serious adverse events (SAE) and medically attended adverse events (MAE) within 52 weeks after vaccination in all participants. **Secondary Efficacy Objectives:** 1. To evaluate the efficacy of Ad5-nCoV in preventing virologically confirmed (PCR positive) COVID-19 disease occurring 14 days to 52 weeks after vaccination, regardless of severity. 2. To evaluate the efficacy of Ad5-nCoV in preventing severe COVID-19 disease caused by SARS-CoV-2 infection from 14 and 28 days to 24 and 52 weeks after vaccination. o Severe disease is defined as: 1) 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), 2) Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO), 3) Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors), 4) Significant acute renal, hepatic, or neurologic dysfunction, 5) Admission to an ICU. 3. To evaluate the efficacy of Ad5-nCoV in different age groups from 14 and 28 days to 24 and 52 weeks after vaccination. This will be evaluated by weekly participant contact to assess for any signs or symptoms of COVID 19. 4. To evaluate the efficacy of the primary and secondary objectives #1-3 of Ad5-nCoV in preventing virologically (PCR) or serologically (four-fold increase in SARS-CoV-2 anti-N IgG from pre-immunization to post symptom, defined as Day 21-28 post illness blood test, or pre-symptom to post-symptom blood test) confirmed COVID-19 disease. **Secondary Safety Objectives**: The following secondary safety objectives will be evaluated in the efficacy-extended safety, efficacy-

extended safety-immunogenicity, and efficacy-extended safety-extended immunogenicity cohorts.

1. Evaluate the incidence of solicited adverse reactions within 7 days after vaccination, in a subset of approximately 3000 participants (approximately 7%-10%).
2. Evaluate the incidence of unsolicited adverse events within 28 days after vaccination, in a subset of approximately 3000 participants (approximately 7%-10%).

Secondary Immunogenicity Objectives:

The following secondary objectives will only be evaluated in the efficacy-extended safety-immunogenicity cohort and the efficacy-extended safety-extended immunogenicity cohort.

1. Evaluate the seroconversion rate of S-RBD IgG antibody on Day 28, and Week 24 and Week 52 after vaccination, measured by ELISA.
2. Evaluate the GMT of S-RBD IgG antibody on Day 28, and Week 24 and Week 52 after vaccination, measured by ELISA.
3. Evaluate the GMI of S-RBD IgG antibody on Day 28, and Week 24 and Week 52 after vaccination, measured by ELISA.
4. Evaluate the seroconversion rate of pseudo-virus neutralizing antibody on Day 28, Week 24 and Week 52 after vaccination.
5. Evaluate the GMT of pseudo-virus neutralizing antibody on Day 28, and Week 24 and Week 52 after vaccination.
6. Evaluate the GMI of pseudo-virus neutralizing antibody on Day 28, and Week 24 and Week 52 after vaccination.
7. Evaluate the positive rate and level of IFN-γ stimulated by peptide pool of S protein on Day 28, and Weeks 24 and Week 52 after vaccination, measured by ELISpot.
8. Evaluate the positive rate and level of IL-2, IL-4, IL-13, and IFN-γ stimulated by peptide pool of S protein on days 28, and Week 24 and Week 52 after vaccination, measured by intracellular cytokine staining (ICS).

Supportive Objectives

1. Evaluate the severity of COVID-19 cases among vaccine recipients (based on WHO or FDA criteria) as compared to the control group, to measure antibody-mediated disease enhancement (ADE).
2. Evaluate for any evidence of SARS-CoV-2 virus shedding in COVID-19 cases that occurred 28 days to 52 weeks after vaccination (detection of viral nucleic acid every 2 days after being confirmed).
3. Perform genotyping of SARS-CoV-2 virus isolates of COVID-19 cases that occurred 28 days to 52 weeks after vaccination.
4. Evaluate incidence of suspected but unconfirmed cases of COVID-19 (either because of negative or no tests).
5. To evaluate the efficacy of Ad5-nCoV in preventing asymptomatic disease of COVID-19

	(confirmed by N IgG antibody on week 52 after vaccination).
Indication	Prevention of novel coronavirus disease (COVID-19) caused by infection with the SARS-CoV-2 coronavirus
Target population	Generally healthy adults 18 years of age and older
Sample Size	This is an endpoint case driven efficacy clinical trial, with the goal of 150 COVID-19 endpoint cases. About 30,000-40,000 total participants will be enrolled into four cohorts, based on the current attack rate of COVID-19 in the study areas. A subset of approximately 3,000 participants (approximately 7%-10%) will comprise three of the cohorts.
Rationale for study	The 2019 novel coronavirus (SARS-CoV-2) is a positive non-segment single-stranded RNA virus, belonging to the Coronaviridae family of Nidovirales. There are six known coronaviruses in humans, including 229E and NL63 in the alpha genus, OC43 and HKU1 in the beta genus, Middle East respiratory syndrome-associated coronavirus (MERS-CoV), and severe acute respiratory syndrome-associated coronavirus (SARS- CoV). The coronavirus isolated from the lower respiratory tract of patients with unexplained pneumonia in Wuhan is a new type of genus β coronavirus. Following the outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and the outbreak of MERS-CoV in 2012, SARS-CoV-2 is the third highly pathogenic coronavirus. The Coronavirus Disease 2019 (COVID-19) is caused by the infection of the 2019 novel coronavirus (SARS-CoV-2) started in January 2020. World Health Organization (WHO) declared COVID-19 a worldwide pandemic on March 12, 2020. As of Oct.20, 2020, there are over 42 million cases worldwide and over 1 million deaths in 185 countries/regions [1]. China has reported 87,028 confirmed cases, the US has over 8 million cases, and Canada has over 200,000 cases [1]. As of July 27, 2020, there are over 16,114,449 cases worldwide and over 646,641 deaths in 185 countries/regions [1]. China has reported 87,028 confirmed cases, the US over 4,148,011 cases, and Canada over 113,556 [1]. The COVID-19 pandemic has brought heavy economic pressure, medical burden, and severe harm to people's lives and health. At present time, there is no effective treatment for COVID-19, and no approved vaccine to prevent this disease. There are no drugs approved specifically for COVID-19 (except approved for Emergency Authorization Use during the pandemic). It is necessary and very urgent to develop preventive vaccines against COVID-19 to meet the global needs. The vaccine candidate Ad5-nCoV, intended to prevent the COVID-19 caused by SARS-CoV-2, is jointly developed by CanSino Biologics Inc. and its collaborator, the Beijing Institute of Biotechnology. Using the replication-deficient human adenovirus type 5 as a vector, Ad5-nCoV has

	been developed through recombinant virus construction, amplification, cell culture, purification, and formulation. Ad5-nCoV expresses the specific S protein of SARS-CoV-2. It is suggested that both humoral and cellular immune responses play an important role in protective immunity according to the results of pre-clinical, phase I, and phase II studies conducted by CanSino Biologics. This study is a phase III clinical trial to evaluate the efficacy, safety, immunogenicity of one dose of Ad5-nCoV at a dose level of 5×10^{10} vp in healthy adults, aged 18 years of age and older
Testing Vaccine	**Study Product:** Ad5-nCoV manufactured by CanSino Biologics Inc. **Active Ingredients:** Replication-defective recombinant human type 5 adenovirus expressing S protein of novel coronavirus **Excipients:** Mannitol, sucrose, sodium chloride, magnesium chloride, polysorbate 80, HEPES, and glycerin **Packaging**: The vaccine is contained in a prefilled syringe **Specification:** 0.5 mL/ syringe **Dosage:** 5×10^{10}vp ($\geq$4 x10^{10} vp) **Shelf Life**: Tentatively 24 months **Storage:** It is recommended to store and ship at 2-8 ℃ (details of the temperature requirements are specified in the pharmacy manual). **Administration:** Intramuscular (IM) injection in the deltoid muscle of the upper arm. **Schedule:** A single-dose schedule is used. A second dose in all or some age cohorts may be made in response to new data from ongoing phase I/II clinical trials according to the adaptive design. **Placebo**: The placebo for this study is matching placebo for Ad5-nCoV manufactured by CanSino Biologics Inc. It contains the same ingredients except that there is no vaccine antigen. **Developers:** CanSino Biologics Inc. Beijing Institute of Biotechnology **Manufacturer**: CanSino Biologics Inc.
Study design	**Summary:** This Phase III study is a double-blind, randomized, global multi-centre, placebo-controlled, adaptive design clinical trial for 30,000-40,000 participants. All participants will receive a single dose of either the study vaccine or a placebo on Day 0 and will be followed to monitor vaccine candidate efficacy and incidence of SAE and MAE for a duration of 52 weeks. If the ongoing phase IIb trial of Ad5-nCoV demonstrates both safety and increased immunogenicity of a two dose regimen, the IDMC may recommend and/or the sponsor may decide to add additional study arms to also study a two-dose regimen in parallel. The primary efficacy objectives will then be independently assessed based on the one dose or two-dose regimen. Under the one dose regimen, there will be four cohorts in the study; the efficacy-safety cohort; the efficacy-extended safety cohort; the efficacy-extended safety-immunogenicity cohort; and the

efficacy-extended safety-extended immunogenicity cohort. Approximately 3,000 participants (7-10% of participants in select enrollment countries) will be enrolled into one of the three following cohorts; efficacy-extended safety; efficacy-extended safety-immunogenicity; or the efficacy-extended safety-extended immunogenicity cohort. These three cohorts will undergo additional monitoring, as outlined below, to provide detailed safety and immunogenicity data associated with receiving the Ad5-nCoV candidate vaccine**.** The remainder of participants will be enrolled in the fourth cohort (n≈37,000) to measure standard efficacy and safety outcomes.

Study Interventions:
All participants will be subject to the following procedures:

- **Informed consent**
  The signed informed consent must be obtained before study participation. At each subsequent participant contact requiring an intervention (such as collection of a blood sample), the participant's consent will be orally verified.
- **Check inclusion and exclusion criteria**
  All inclusion and exclusion criteria will be checked at the screening in-person visit in all four cohorts. In the efficacy-extended safety-immunogenicity and efficacy-extended safety- extended immunogenicity cohorts, inclusion and exclusion criteria will be reviewed at each in-person visit.
- **Collect demographic data and participant contact information**.
  Record participant's demographic data such as date of birth, sex, gender, height, weight and race in the participant's EDC. A current email addresses and or phone numbers will be collected for each participant. It is important to have complete and accurate contact information for each participant as the majority of participant contacts will occur electronically. Contact information may also be used to remind participants of up-coming in-person visits.
- **Medical history**
  Obtain the participant's medical history by interview and/or review of the participant's medical records and record any pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection in the EDC. This will include reviewing any health condition that may prevent the participant from enrolling in the study, such as an unstable health condition or a known positive HIV status.
- **Check contraindications, warnings and precautions to injection**
  Contraindications, warnings and precautions to injection must be checked at the beginning of the injection visit.
- **Urine Pregnancy Test/Birth Control**
  Women of child-bearing age will be asked to perform a urine pregnancy test at Day 0. The result of the urine pregnancy test must be negative in order to proceed with vaccine administration. In addition, participants who are able to become pregnant or could impregnate a partner are required to have used approved contraception for least 30 days prior to the study vaccination, and for 90 days after the study vaccination.

	• **Screening conclusion** Participants will be deemed eligible to participate upon reviewing medical history and inclusion and exclusion criteria. This will occur prior to vaccination on Day 0. • **Assess pre-injection vital signs (body temperature, blood pressure, pulse rate and respiratory rate)** The body temperature of all participants needs to be measured prior to any study product administration. Body temperature may be measured by any method (oral, axillary), but the preferred route for this study is the oral route. If the participant has a fever (fever is defined as temperature ≥ 38.0° C orally) on the day of injection, the injection visit will be rescheduled within 1 week. • **Study group and treatment number allocation** The participant will be randomized to either the experimental or placebo group at the screening in-person visit. Each participant will also be assigned a treatment identification number for blinding purposes. The number of each administered treatments must be recorded in the EDC. • **Check and record prior medications and concomitant medication/injection** Prior medications and concomitant medication/injection must be checked and recorded in the EDC. Prior medications should include any medication taken by the participant within 14 days prior to screening. Participants will be asked to avoid over-the-counter medications such as antipyretics (e.g., acetaminophen) and anti-inflammatory medications (e.g., ibuprofen, naproxen) in the 12 hours before study vaccine receipt but will be allowed to take these over-the-counter medications as needed to treat fever or other AE after vaccination. Usage of these over-the-counter medications will be recorded as concomitant medications and linked to the AE collected as solicited or unsolicited events, according to the symptom. • **Check and record intercurrent medical conditions** Any medical conditions are recorded in the EDC. • **Baseline serology** Approximately 25 mL of whole blood will be collected from each participant at Day 0 and separated for serum. The serum will be aliquoted. The first aliquot will be used to measure for baseline antibodies against SARS-CoV-2 and against HIV in the central study laboratory. The results of antibody testing from baseline serum will not be used to determine eligibility for enrollment; instead, results will solely be used for analysis and comparison purposes. Presence of pre-existing SARS-CoV-2 antibodies found in baseline serum will be used for a stratified immunogenicity and efficacy sub-analysis. The presence of HIV antibodies will be tested in all participants in the central laboratory at the end of the study, in order to do a stratified analysis of participants with previously unrecognized HIV infection. Participants who have been enrolled and immunized and then subsequently are found to have a positive HIV test, will be counseled and continue to be followed in the study. All participants, including those with an unknown HIV status, will be monitored closely for any SAE and MAE and symptoms of illness. The second aliquot will be shipped from the central study laboratory to the sponsor, where it will be stored as a back-up.

- **Injection of study vaccine**
  After completing all prerequisite procedures prior to injection, one dose of the assigned vaccine will be administered IM in the deltoid muscle of the non-dominant arm. If the investigator or delegate determines that the participant's health on the day of administration temporarily precludes administration, the visit will be rescheduled within 1 week. There will be a 30-minute wait after each vaccination to monitor for any rare anaphylactic reaction.
- **Safety participant contacts**
  Every 4 Weeks for 52 weeks there will be telephone calls following vaccination. They will be used to continuously collect any SAE and MAE data. Participants can report any AE they experience at any time during the study period; however, only SAE and MAE will be entered into the EDC. Safety participant contacts will occur Day 0 (for 30 minutes post-vaccination), and at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52.

  In the efficacy-safety cohort, safety participant contacts will be telephone calls every 4 weeks for 48 weeks, and an in-person visit for Week 52.

  In the efficacy-extended safety, efficacy-extended safety- immunogenicity, and efficacy-extended safety- extended immunogenicity cohorts, safety participant contacts will be telephone calls every 4 weeks. In-person visits will occur for Week 4 and Week 52. Participants in the efficacy-extended safety- immunogenicity, and efficacy-extended safety- extended immunogenicity cohorts will also have an in-person visit on Week 24.

- **Efficacy participant contacts**
  All participants will have efficacy participant contacts weekly, for 52 weeks following vaccination. There will be approximately 52 electronic efficacy participant contacts. All efficacy participant contacts will be emails, although other methods such as phone calls or text messages, if preferred, are acceptable. Each participant contact needs to be recorded in the study electronic case report form. The purpose of these participant contacts is to ask if the participants had any symptoms of illness they may be experiencing, regardless of severity. Any possible COVID-19 relevant symptoms will trigger laboratory testing for SARS-CoV-2 infection.

- **Illness participant contact visits (Confirmed or suspected infection during study)**
  Participants will be provided detailed instructions regarding the signs and symptoms of COVID-19 disease at each participant contact and will be instructed to seek medical attention and notify study staff should symptoms occur. Symptoms of interest include fever, cough, dyspnoea & difficulty breathing, diarrhea, nausea, vomiting, prolonged fatigue, chills, myalgia, sore throat, headache, congested/runny nose, pneumonia, difficulty swallowing, anosmia/ageusia, loss of sense of smell and taste, and neurological events.

  During the observation period of the study, if any of these symptoms develop in a participant,

	he/she should immediately follow local procedures for care of suspected COVID-19 illness and contact the study team. If a COVID-19 infection is found during the study, a case investigation will be undertaken according to locally recommended procedures. 1. If COVID-19 is suspected, the participant will have a nasal/throat swab taken. Testing for COVID-19 by PCR will be performed at the local clinical laboratory. 2. If negative, the test will be repeated in 3 days from the first testing day. 3. All attempts will be made to re-test positive samples in a national or regional reference laboratory in the study country. If the local lab is also a reference laboratory in that country, then a confirmatory sample is not required. 4. If the PCR is positive, all attempts to repeat nasal/throat swabs will be taken every 2 days and tested for COVID-19 by PCR until a negative sample is obtained. 5. A serum sample (10mL blood) will be collected at the time of illness presentation and testing for SARS-CoV-2 anti-N IgG antibodies will be performed in the central laboratory. 6. At Day 21-28 post-illness, a second serum sample will be taken and sent to the central laboratory for anti-N IgG. 7. Participants who develop COVID-19 infection post-vaccination will be carefully monitored for vaccine related disease enhancement in collaboration with their primary physician who will be encouraged to obtain specimens in accordance with the Brighton Collaboration definition (Munoz, 2020), including a serum sample tested locally for C-reactive protein (CRP), ferritin, and procalcitonin, biomarkers that have been associated with predicting more severe disease outcome in infected patients. Participants who develop COVID-19 disease will continue to be followed for other study outcomes by telephone while in isolation, and at the study center once recovered and released from isolation by public health officials. • **Final serology** Participants in all four cohorts will have an in-person visit on Week 52. Approximately 25mL of whole blood will be collected and will then be separated into serum. The serum will be aliquoted. The first aliquot will measure anti-N IgG antibodies, in the central study laboratory. The second aliquot will be shipped by the central study lab to the sponsor, where it will be stored as a back-up. The one-year antibody levels measured against anti-N IgG antibodies will be compared to the participant's baseline levels to evaluate the exploratory efficacy analysis against asymptomatic infection. **Participants in the efficacy-extended safety cohort, the efficacy-extended safety-immunogenicity cohort, and efficacy-extended safety-extended immunogenicity cohort will also have the following intervention:** • **E-diary and Diary Cards**

Participants in these cohorts will be provided with access to an e-diary or a paper diary card and a thermometer, and instructions about how to use them. The use of an e-diary instead of a paper diary card is dependent on the study site. Participants will be asked to record solicited AE for 7 days after receiving the vaccination, and unsolicited AE for 28 days, in their diary. The completed e-diary and diary cards will be reviewed and data collected at the 28-Day safety in-person visit. Non completion of the e-diary or diary cards will be investigated with the participant through telephone call(s) or any other convenient procedure. All data collected from the e-diary and diary cards will be uploaded into the EDC.

Participants in efficacy-extended safety-immunogenicity cohort will have the following:

- **Immunogenicity in-person visit**
  - **Blood collection for ELISA and pseudo-virus neutralization antibody measurement**

    Participants in this cohort will donate approximately 25mL of whole blood on Day 28 and Week 24, in addition to the whole blood collected on baseline (Day 0) and Week 52, as described above. These in-person visits will occur at the participant's local study site. Serum will be separated into two aliquots. A baseline antibody titer against SARS-CoV-2 will be established from the blood sample collected on Day 0, as outlined in the "baseline serology" description. In addition, these samples will also be used to evaluate for additional immunogenicity objectives including: the seroconversion rate of S-RBD IgG antibody, GMT of S-RBD IgG antibody, GMI of S-RBD IgG antibody, seroconversion rate of pseudo-virus neutralizing antibody, GMT of pseudo-virus neutralizing antibody, and the GMI of pseudo-virus neutralizing antibody at Day 28, Week 24, and Week 52.The second aliquot will be shipped by the central lab to the sponsor, where it will be stored as a back-up.

Participants in the efficacy-extended safety-extended immunogenicity cohort will also have the following:

- **Immunogenicity in-person visit**
  - **Blood collection for ELISA and pseudovirus neutralization antibody measurement**

    Participants in this cohort will donate approximately 25mL of whole blood on Day 28 and Week 24, in addition to the whole blood collected on baseline (Day 0) and Week 52, as described above. These in-person visits will occur at the participant's local study site. A baseline antibody titer against SARS-CoV-2 will be established from the blood sample collected on Day 0, as outlined in the "baseline serology" description. In addition, these samples will also be used to evaluate for additional immunogenicity objectives including: the seroconversion rate of S-RBD IgG antibody, GMT of S-RBD IgG antibody, GMI of S-RBD IgG antibody, seroconversion rate of pseudo-virus neutralizing antibody, GMT of pseudo-virus neutralizing antibody, and the GMI of

	pseudo-virus neutralizing antibody at Day 28, Week 24 and Week 52. o **Blood collection for ELISpot and ICS measurement** Approximately 30mL of whole blood will be collected from participants in the efficacy-extended safety-extended immunogenicity cohort, in addition to the 25mL of whole blood being collected for ELISA and pseudovirus neutralization antibody analysis. Collections will occur on Day 0 (baseline), just prior to vaccination, Day 28, and at 24 and 52 weeks post-vaccination. Blood collected at these visits will be used to evaluate the positive rate and level of IFN-γ measured by ELISpot, and the positive rate and level of IL-2, IL-4, IL-13, and IFN-γ measured by ICS on Day 28 and Weeks 24 and 52 after vaccination. PBMC will be shipped on liquid nitrogen to the central laboratory. **Study duration:** Total duration of this trial from the enrollment to the last visit will be approximately one year (52 weeks).
Visit plan	**Efficacy-Safety Cohort** All participants in the efficacy-safety cohort will have at least two planned in-person visits on Day 0 and Week 52. The first in-person visit will entail reviewing the ICF, completing a medical history of the participant, reviewing inclusion and exclusion criteria, obtaining a baseline serum for HIV antibody testing (central study laboratory), baseline SARS-CoV-2 antibody (central study laboratory), and a urine pregnancy test in women of child-bearing potential (local site laboratory). Participants will then be randomized to either the placebo or candidate vaccine group and will receive their vaccination. The participant and study nurse will remain blinded to the assigned group. Participants are required to remain at the study site for a minimum of 30 minutes after receiving the vaccine to monitor for any vaccine-related AE. All participants in this cohort will be contacted on a weekly basis to be reminded to report any signs or symptoms of illness to study staff. Participants will either be contacted by the site weekly or they will receive an automated email with a link to answer questions about whether or not they had an SAE, an MAE or COVID-19 symptoms. The reporting and monitoring of any participant illness are consistent with meeting the primary efficacy objective. If a participant becomes ill, they will be asked to immediately proceed to the site designated by their local study team where they will be assessed and treated, as deemed appropriate. Participants will also receive a telephone call every 4 weeks to evaluate for the incidence of any SAE and MAE. Further details are outlined in Section 3.8. All participants in this cohort will be asked to return to the study site on Week 52, for the final in-person visit. Approximately 25mL of blood will be collected to measure for antibodies against SARS-CoV-2, in congruence for the VE objective. **Efficacy-Extended Safety Cohort**

	All participants in the efficacy-extended safety cohort will have at least three planned in-person visits on Day 0 and Day 28, and Week 52. The first visit on Day 0 will entail reviewing the ICF, completing a medical history of the participant, reviewing inclusion and exclusion criteria, obtaining a baseline serum for HIV antibody testing (central laboratory), baseline SARS-CoV-19 antibody (central laboratory), and a urine pregnancy test in women of child-bearing potential (local laboratory). Participants will then be randomized to either the placebo or candidate vaccine group and will receive their vaccination. The participant and study nurse will remain blinded to the assigned group. Participants are required to remain at the study site for a minimum of 30 minutes after receiving the vaccine to monitor for any vaccine-related AE. Participants who are enrolled in the efficacy-extended safety cohort will be given access to an e-diary or paper diary card to record solicited AE from Day 0-7 and unsolicited AE from Day 0-28. The data in the completed e-diary or diary card will be reviewed and data will be collected at the second in-person visit on Day 28. Further details are outlined in Section 3.7 and 5.2. All participants will be contacted on a weekly basis to be reminded to report any signs or symptoms of illness to study staff. Participants will either be contacted by the site weekly or they will receive an automated message (email) with a link to answer questions about whether or not they had an SAE, an MAE or COVID-19 symptoms. The extended safety cohorts will also be asked on their day 7 contact about any events that might meet the first holding rule. The reporting and monitoring of any participant illness are consistent with meeting the primary efficacy objective. If a participant becomes ill, they will be asked to immediately proceed to the site designated by their local study team where they will be assessed and treated as deemed appropriate. Participants will also receive a telephone call every 4 weeks, to evaluate for the incidence of any SAE or MAE. All participants in this cohort will be asked to return to the study site on Week 52, for the final in-person visit. Approximately 25mL of blood will be collected to measure for antibodies against SARS-CoV-2, in congruence with the VE objective. **Efficacy-Extended Safety-Immunogenicity and Efficacy-Extended Safety-Extended Immunogenicity Cohorts** These cohorts will be enrolled in selected countries and at selected sites. All participants in the efficacy-extended safety-immunogenicity and efficacy- extended safety- extended immunogenicity cohorts will have at least four planned in-person visits on Day 0 and 28, and Week 24 and Week 52. The first visit on Day 0 will be comprised of reviewing the ICF, completing a medical history of the participant, reviewing inclusion and exclusion criteria, as well as a urine pregnancy test in women of child-bearing potential. Participants will have blood drawn pre-vaccination on Day 0 to establish baseline immunogenicity levels. Participants will then be randomized to either the placebo or candidate vaccine group and receive their vaccination. The participant and study nurse will remain blinded to the assigned group. Participants are required to remain at the study site for a minimum of

	30 minutes after receiving the vaccine to monitor for any vaccine-related AE. All participants in these cohorts will be contacted on a weekly basis to be reminded to report any signs or symptoms of illness to study staff. Participants will either be contacted by the site weekly or they will receive an automated message (email) with a link to answer questions about whether or not they had an SAE, an MAE or COVID-19 symptoms. The extended safety cohorts will also be asked on their day 7 contact about any events that might meet the first holding rule. The reporting and monitoring of any participant illness are consistent with meeting the primary efficacy objective. If a participant becomes ill, they will be asked to immediately proceed to the site designated by their local study team where they will be assessed and treated as deemed appropriate. Participants will also receive a telephone call every 4 weeks to evaluate for the incidence of any SAE. In these two cohorts, participants will have in-person visits (in addition to text or email messages) on Week 24) and Week 52. Participants who are enrolled in the efficacy-extended safety-immunogenicity and efficacy-extended safety-extended immunogenicity cohorts will be given access to an e-diary or paper diary card to record solicited AE from Day 0-7 and unsolicited AE from Day 0-28. These cohorts will review their completed e-diary or diary card with study staff at their second in-person visit on Day 28. Data collected from e-diaries and diary cards will be uploaded into the participant's EDC. Further details are outlined in Section 3.7 and 5.3. In-person visits on Day 28, Week 24 and Week 52 will also be used for blood sample collection in these two cohorts. Further details are outlined in Section 3.8 and 3.9 The efficacy-extended safety-extended immunogenicity cohort will have additional immunologic testing performed, following the same visit schedule, to evaluate T-cell response to the Ad5-nCoV vaccine. *If a participant in any cohort demonstrates signs or symptoms of illness, an unplanned in-person visit may occur for evaluation and possible treatment. If, for any reason following an electronic participant contact, the investigator would like to conduct an in-person visit with a participant, they may do so at their discretion*.
Pause and early termination	**Study Suspension Criteria** If a suspension criterion is met, the study will be put on hold, and further injections will not occur until a safety review has been conducted. Should a suspension criterion be met, the local PI will inform the global PI, Sponsors, and NRA within 24 hours. **Suspension criteria includes:** Grade 3 or greater AE occurring in >15% of participants at the global level will constitute study suspension criteria. To be included as suspension criteria, AE must begin within three days after study injection (day of injection and 2 subsequent days) and persist at Grade ≥ 3 on three consecutive days,

	depending upon symptom severity and kinetics. A suspected, unexpected serious adverse reaction (SUSAR) that is life-threatening or results in death will warrant study suspension. Other study suspension criteria include if the IDMC assessed the potential safety risks to be harmful, or if the vaccine candidate might be ineffective. **Study Early Termination Criteria** • Required by the sponsor, or • Required by the regulatory authority, or • Required by an institutional review board (IRB) **Process of Suspension of Injection and/or Study Modification** In the event that a safety signal is observed, the IDMC might recommend that the sponsor suspend injections of all group participants (early termination of study) or selected groups. In this case, for impacted groups: Participants who are already injected will continue all visits as planned. Participants who signed an informed consent but have not received any study product will be informed that their study participation will be stopped.
Statistical analysis	**Statistical Analysis Plan (SAP)** **Analysis of Demographic and Baseline Characteristics** Demographic and baseline characteristics will be summarized overall and then by treatment group using appropriate descriptive statistics. Continuous data will be summarized using the number of observations, mean, standard deviation, median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. 95% confidence intervals will be reported, but no statistical hypothesis testing will be conducted. Results will be presented for all participants. **Analysis of Efficacy** **Primary Efficacy Analysis** The primary estimate of vaccine efficacy will be based on a time to event analysis using a Cox proportional hazards model, with the log rank test used to test the hypothesis of vaccine efficacy. The primary efficacy endpoint will be assessed 3 times during the study, triggered when 50, 100 and 150 cases are observed in the combined (blinded) groups. If null hypothesis is rejected at interim analysis, further enrollment stops. Otherwise, trial enrollment continues until the next analysis is triggered. If there is early stopping of enrollment due to demonstrated benefit, follow-up of participants already enrolled in the study will continue. The primary efficacy analysis will be carried out on both intention-to-treat cohort and per-protocol cohorts.

Secondary Efficacy Objective Endpoints

1. The number of virologically confirmed (PCR positive) COVID-19 cases occurring 14 days to 52 weeks after vaccination, regardless of severity, in the Ad5-nCoV group compared to the placebo group.
2. The number of virologically confirmed (PCR positive) severe COVID-19 cases caused by SARS-CoV-2 infection from Day 28 to 24 and 52 weeks after vaccination, in the Ad5-nCoV group compared to the placebo group.
3. The number of virologically confirmed (PCR positive) severe COVID-19 cases caused by SARS-CoV-2 infection from 14 days to 24 and 52 weeks after vaccination, in the Ad5-nCoV group compared to the placebo group.
4. The number of virologically confirmed (PCR positive) SARS-CoV-19 cases in different age groups from Day 28 to 24 and 52 weeks after vaccination in the Ad5-nCoV group compared to the placebo group.
5. The number of virologically confirmed (PCR positive) SARS-CoV-19 cases in different age groups from 14 days to 24 and 52 weeks after vaccination in the Ad5-nCoV group compared to the placebo group.
6. The same endpoints of #1-5 above in virologically or serologically confirmed SARS-CoV-19 cases.

The estimate of efficacy is the relative proportion of virologically confirmed (PCR positive) COVID-19 cases occurring 28 days to 52 weeks after vaccination, regardless of severity, in the Ad5-nCoV group as compared to the placebo group. The estimate, together with 95% CI will be reported, and efficacy concluded if the lower bound of the 95% CI exceeds 30%.

Adjusted analyses will be carried out, including adjustment for country, sex, gender and age.
For each measure of vaccine efficacy, stratified analyses will be carried out with strata identified by HIV status and presence of pre-existing COVID-19 antibodies, in all participants in the central laboratory at the end of the study. Enrolled participants who had an unrecognizable HIV status who have and immunized and then subsequently are found to have a positive HIV test, will be counseled and continue to be followed in the study. All participants, including those with an unknown HIV status, will be monitored closely for any SAE and symptoms of illness.
Conclusions may be affected by early dropout if there is differential dropout in the treatment and control groups. Missing values will not be imputed. However, a sensitivity analyses will be carried out to assess the effect of drop-out. Event times for dropouts will be simulated based on the empirical distribution of event times for participants with matching covariate information. A worst-case scenario will be considered in which event times are generated only for participants in the control group. A second scenario will simulate event times for participants in either group. If any of the simulated event times precede the end of study censoring time, VE will be re-estimated in the sensitivity analysis.

Safety Analysis
Primary Safety Endpoint:

	The number of serious adverse events (SAE) and medically attended adverse events (MAE) within 52 weeks after vaccination in all participants reported in the Ad5-nCoV group compared to the placebo group. Data from all participants will be used to assess the primary safety endpoint. **Secondary Safety Objective Endpoints** 1. 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). 2. 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. All SAEs and MAEs will be listed and summarized by groups after unblinding. Additional safety data including solicited AEs (injection-site and general) occurring during the 7-day follow-up period after injection will be collected on efficacy-extended safety cohort. Unsolicited AEs will be collected from Day 0 – Day 28. For each participant, the individual local events will be aggregated into a combined event “Local”, which is the maximum severity of the individual local events. For each participant, the individual general events will be aggregated into a combined event “General”, which is the maximum severity of the individual general events. An aggregate event “Any” will be defined as the maximal severity of the combined events “Local” and “General”. In addition to being graded for severity as mild, moderate or severe, the severity of all events will be graded as "Any", which will include mild, moderate or severe events, and "Significant" which will include moderate or severe events. All statistical tests on safety performed will be 2-sided with Type I error of 5%. Missing values will not be included in the safety analyses, and there will be no imputation of missing values. No adjustments will be made for multiple comparisons. For the analysis of proportions, binomial point estimates and exact binomial confidence intervals will be calculated. Fisher’s Exact Test will be used to assess differences in rates of adverse events between treatment and control groups.

In addition, all safety data will be analysed descriptively, including unsolicited events collected through the end of the observation period.

Immunogenicity Analysis
Secondary Immunogenicity Endpoints:

1. Seroconversion rate of S-RBD IgG antibody on Day 28, Week 24 and 52 after vaccination by ELISA.
2. GMT of S-RBD IgG antibody on Day 28, Week 24 and 52 after vaccination by ELISA.
3. GMI of S-RBD IgG antibody on Day 28, Week 24 and 52 after vaccination by ELISA.
4. Seroconversion rate of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination.
5. GMT of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination.
6. GMI of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination.
7. Positive rate and level of IFN-γ by peptide pool of S protein on days 28, Week 24 and 52 after vaccination, measured by ELISpot.
8. 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).

Assessment of secondary immunogenicity endpoints 1-6 will be based on both the efficacy-extended safety- immunogenicity and efficacy-extended safety-extended immunogenicity cohorts. Secondary immunogenicity endpoints 7 and 8 will be assessed based on the efficacy-extended safety-extended immunogenicity cohort only.
Geometric mean antibody titers (GMTs) and GMI's and their two side 95% confidence intervals will be calculated by group. Analyses will be performed on the logarithmically (base 10) transformed values. Individual titers below the detection limit will be set to half the limit.

For the analysis of proportions, binomial point estimates and exact binomial confidence intervals will be calculated for each group. Rates will be compared between groups using Fisher's exact tests, and geometric means will be compared using t-tests.

All statistical tests performed for immunogenicity will be 2-sided with Type I error rate of 5%. Missing values will not be included in the immunogenicity analyses, and there will be no imputation of missing values. No adjustments will be made for multiple comparisons.
The immunogenicity analysis will be carried out on both intention-to-treat and per-protocol cohorts.

Supportive Objective Analysis
Supportive Endpoints
1. Evaluate the severity of COVID-19 cases among vaccine recipients (based on WHO criteria) as

compared to the control group, to measure antibody-mediated disease enhancement (ADE).
2. Evaluate for any evidence of SARS-CoV-2 virus shedding in COVID-19 cases that occurred 28 days to 52 weeks after vaccination (detection of viral nucleic acid every 2 days after confirmed).
3. Perform genotyping of SARS-CoV-2 virus isolates of COVID-19 cases that occurred 28 days to 52 weeks after vaccination.
4. Evaluate incidence of suspected but unconfirmed cases of COVID-19 (either because of negative or no tests).
5. To evaluate the efficacy of Ad5-nCoV in preventing asymptomatic disease of COVID-19 (confirmed by N IgG antibody on week 52 after vaccination).

Analysis of supportive endpoints
PCR confirmed positive subjects will be classified as having severe or non-severe disease. Point estimates and confidence intervals of proportions of subjects with severe disease will be reported by treatment group, and proportions will be compared between groups using Fisher's exact test. Adjusted analyses will be carried out using logistic regression.

To evaluate for virus shedding in COVID-19 cases that occurred 28 days to 52 weeks after vaccination, a Cox proportional hazards model will be used to model time to negativity from time of confirmation. The cohort for this analysis will include all PCR positive cases.

Genotypes SARS-CoV-2 virus isolates will be listed by subject and date, along with demographic data, including the study centre.

To evaluate for the incidence of suspected but unconfirmed cases of COVID-19 (either because of negative or no tests), the efficacy analysis will be repeated with two different cohorts. The first cohort will include only suspect and probable cases. The second cohort will combine both confirmed positive cases with suspected and probable cases.

The cohort for the efficacy analysis for preventing asymptomatic disease will be all subjects in the efficacy-safety cohort who were neither PCR positive nor seropositive. Proportions of demonstrated seroconversion will be estimated with confidence intervals, by treatment group, and will be compared between the vaccine and placebo groups using Fisher's exact test. Seroconversion will be defined as a 4-fold or greater increase of N IgG antibody titre at 52 weeks, as compared to Day 0.

Interim Analyses
According to the criteria for demonstrating benefit (reliably establishing VE > 30%), there will be two interim analyses. Following guidelines in the WHO Target Product Profile, the two interim analyses will be carried out when there have been 50 and 100 total endpoints. Using the O'Brien-Fleming method, benefit is established when lower bound of confidence interval of VE is > 30%. If there is early stopping due to demonstrated benefit, follow-up will continue.

	The interim analysis will be carried out by the Independent Data Monitoring Committee (IDMC) according to the statistical analysis plan. **Possible Study Design Adaptations**: Should the observed attack rate of COVID-19 be insufficient to accumulate the targeted number of endpoints by the end of the study, one or more of the following adaptations may be implemented: enlistment of new study sites, increased enrolment from active sites, or extension of the end of the study. If the ongoing phase II trial of Ad5-nCoV demonstrates both safety and increased immunogenicity of a two dose regimen, the IDMC may recommend and/or the sponsor may decide to add additional cohorts to receive a two-dose regimen. If the IDMC recommends and/or the Sponsor decides upon an adaptation to a two-dose regimen, additional enrollment in the two-dose control and treatment arms will continue until there are a total of 150 endpoint events combined in those arms. The two dose efficacy hypotheses will be the same as the one-dose efficacy hypotheses but will be assessed on comparison of the two-dose Ad5-nCoV group to the two-dose placebo group. There will be two interim analyses of the two dose regimen. The first will use the first 50 endpoints after adaptation, and the second will use the first 100 endpoints after adaptation. **Final Analysis** Efficacy and immunogenicity analyses will be carried out using according-to-protocol cohorts in addition to intention-to-treat cohorts.
Inclusion criteria	**Inclusion Criteria** ● Adults of 18 years of age, and older. ● Able and willing (in the Investigator's opinion) to comply with all study requirements. ● Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner/personal doctor and access all medical records when relevant to study procedures. ● Healthy adults, or stable-healthy adults who may have a pre-existing medical condition that does not meet any exclusion criteria. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment [4]. ● For females of childbearing potential only, willingness to practice continuous effective contraception (see glossary) for 30 days prior to enrollment in the study, for 90 days after receiving vaccination during the study, and have a negative pregnancy test on the day(s) of screening/ vaccination (Day 0). ● Males participating in this study who are involved in heterosexual sexual activity must agree to practice adequate contraception (see glossary) and refrain from donating sperm for 90 days

	after receiving the study vaccination. • Agreement to refrain from blood donation during the study • Provide written informed consent
Exclusion criteria	**Exclusion Criteria** • Participation in any other COVID-19 prophylactic drug trials for the duration of the study. Note: Participation in COVID-19 treatment trials is allowed in the event of hospitalization due to COVID-19. The study team should be informed as soon as possible. • Participation in SARS-CoV-2 serological surveys where participants are informed of their serostatus for the duration of the study. o Note: Disclosure of serostatus post enrolment may accidentally unblind participants to group allocation. Participation in this trial can only be allowed if volunteers are kept blinded to their serology results from local/national serological surveys • Planned receipt of any vaccine (licensed or investigational), other than the study intervention, within 14 days before and after study vaccination • Prior receipt of an investigational or licensed vaccine likely to impact on the interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus or SARS vaccines) • Administration of immunoglobulins and/or any blood products within the three months prior to the planned administration of the vaccine candidate • Any confirmed or suspected immunosuppressive or immunodeficient state; positive HIV status; asplenia; recurrent severe infections and chronic use (more than 14 days) of immunosuppressant medication within the past 6 months. Topical steroids or short-term (course lasting ≤14 days) oral steroids are not an exclusion. • History of allergic disease or reactions likely to be exacerbated by any component of Ad5-nCoV • Any history of angioedema • Any history of anaphylaxis to any vaccine component • Pregnancy, lactation or willingness/intention to become pregnant within 90 days after receiving study vaccine • Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ) • History of serious psychiatric condition likely to affect participation in the study • Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture • Suspected or known current alcohol or drug dependency • Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well-controlled comorbidities are allowed) • History of laboratory-confirmed COVID-19

	• Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban) • Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data.

LIST OF KEY ROLES

Key Roles/Duty	Responsible Individual	Organization
Sponsor	Tao Zhu	CanSino Biologics Inc. 185 South Avenue, TEDA West, Tianjin, China Tel: +86-18622657078 Email: tao.zhu@cansinotech.com
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Global Principal Investigator	Scott A Halperin	Canadian Center for Vaccinology Dalhousie University/IWK Health Centre 5850/5980 University Avenue Halifax, NS B3K 6R8, Canada Tel: 902-470-8141 Email:scott.halperin@dal.ca
Global Co-PI	Fengcai Zhu	Jiangsu Provincial Center for Disease Control and Prevention. 172 Jiangsu Road, Nanjing, China Tel: +86 13951994867 Email:jszfc@vip.sina.com
	Joanne Langley	Canadian Center for Vaccinology Dalhousie University/IWK Health Centre 5850/5980 University Avenue Halifax, NS B3K 6R8, Canada Telephone: 902-470-8141 Email: joanne.langley@dal.ca
Central Safety Physician	Jinbo Gou	CanSino Biologics Inc. 185 South Avenue, TEDA West District, Tianjin, China Tel: +8613032225233 Email: jinbo.gou@cansinotech.com
Central laboratory	Luc Gagnon	Nexelis 525 Cartier West Blvd Laval QC H7V 3S8

		Canada Tel: 450-239-1605 Email: luc.gagnon@nexelis.com
Central Data Manager	Donna MacKinnon-Cameron	Canadian Center for Vaccinology Dalhousie University/IWK Health Centre 5850/5980 University Avenue Halifax, NS B3K 6R8, Canada Tel: 902-470-8141 Email: donna.mackinnon-cameron@dal.ca
Central Statistician	Bruce Smith	Canadian Center for Vaccinology Dalhousie University/IWK Health Centre 5850/5980 University Avenue Halifax, NS B3K 6R8, Canada Telephone: 902-470-8141 Email: bruce.smith@dal.ca

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LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
ATP	According-to-protocol
BGTD	Biologics and Genetic Therapies Directorate, Health Canada
BMI	Body Mass Index
CCfV	Canadian Center for Vaccinology
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	Corona Virus Disease 2019
CRO	Contract Research Organization
DMP	Data Management Plan
ECMO	Extra-corpeal membrane oxygen
EDC	Electronic Data Capture
ELISA	Enzyme-linked-immunosorbent assays
FDA	Food and Drug Administration, United States
FTiH	First time in human
GCP	Good Clinical Practice
GMI	Geometric Mean Increase
GMT	Geometric Mean Titer
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Intracellular Cytokine Staining

IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MAE	Medically Attended AEs
NRA	National Regulatory Authority
PBMCs	Peripheral Blood Mononuclear Cells
PI	Principal Investigator
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Steering Committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TVC	Total Vaccinated Cohort
VE	Vaccine Efficacy
VP	Viral particles
WBC	White Blood Cells
WHO	World Health Organization

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label, such as:

- Abstinence from penile-vaginal intercourse, when this is their preferred lifestyle,
- Oral contraceptives, either combined or progesterone alone,
- Injectable progestogen,
- Implants of etonogestrel or levonorgestrel,
- Estrogen vaginal ring,
- Percutaneous contraceptive patches,
- Intrauterine device or intrauterine system,
- Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject (information based on interview with the participant on her medical history),
- Male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- Male condom combined with a female diaphragm, whether with or without a vaginal spermicide (foam, gel, fil, cream, or suppository),

Adequate contraception does not apply to participants of childbearing potential with same sex partners, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes

	failure to produce expected benefits (*i.e.* lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the participant is not. In an observer-blind study neither the participant nor study personnel performing outcome measurement are aware of treatment assignment; an unblinded staff member administers the study treatment but has no other role in the study.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.
Investigational product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigator's Brochure:	Compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human participants.

Participant:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, as a recipient of the investigational product or placebo.
Randomization:	Process of random attribution of treatment to participants in order to reduce bias of selection.
Solicited adverse event:	Adverse events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified post-administration participant contact period.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant, identified by a unique number, according to the study randomization or treatment allocation.

1. INTRODUCTION

1.1. Background

Since emerging in December 2019, the COVID-19 outbreak was deemed a Public Health Emergency of International Concern (PHEIC) by the WHO on 30 January 2020. On March 11th, 2020, COVID-19 was declared a global pandemic. As of Oct.20, 2020, there are over 42 million cases worldwide and over 1 million deaths in 185 countries/regions [1]. The COVID-19 pandemic has brought heavy economic pressure, medical burden, and severe harm to people's lives and health.

Currently, about 250 candidate vaccines against SARS-CoV-2 are in development worldwide, including mRNA vaccines, replicating or non-replicating viral vectored vaccines, DNA vaccines, autologous dendritic cell-based vaccine, and inactive virus vaccines [2]. To date, at least 17 of these vaccine candidates are under evaluation in clinical trials. There are no specific drugs or therapy approved for COVID-19 that are known to alter disease course.

One recently published trial in the UK investigated the use of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein [3]. This phase I/II single-blind, randomised, multi-site-controlled trial administered healthy adults (ages 18-55) with a 5×10^{10} viral particles (vp) dose of ChAdOx1 nCoV-19 or a control vaccine of meningococcal conjugate vaccine, at a 1:1 ratio. This candidate vaccine was found to be tolerable and immunogenic in healthy adults. Results demonstrated an increase in antibodies against SARS-CoV-2 spike protein in the ChAdOx1 nCoV-19 group, with levels peaking at Day 28 after vaccination, lasting until Day 56 in participants who received a single dose, and continuing to increase in participants who received a booster dose. An increase in cellular immune response was also demonstrated in the ChAdOx1 nCoV-19 group. Participants who received two doses of ChAdOx1 nCoV-19 demonstrated the highest humoral and cellular immune responses. The results of their phase I/II trial support moving forward with a large-scale phase III trial.

A second US clinical trial, studying a mRNA vaccine, has moved on to phase III of their trials. The study is examining the safety, efficacy, and immunogenicity of receiving two doses of an mRNA-1273 vaccine to prevent COVID-19 for up to two years [4].

1.2. Investigational vaccine

The 2019 novel coronavirus (SARS-CoV-2) is a positive non-segment single-stranded RNA virus, belonging to the Coronaviridae family of Nidovirales. There are six known coronaviruses in humans, including 229E and NL63 in the alpha genus, OC43 and HKU1 in the beta genus, Middle East respiratory syndrome-associated coronavirus (MERS-CoV), and severe acute respiratory syndrome-associated coronavirus (SARS-CoV).
The coronavirus isolated from the lower respiratory tract of patients with unexplained pneumonia in Wuhan is a new type of genus β coronavirus. Following the outbreak of severe acute

respiratory syndrome coronavirus (SARS-CoV) in 2002 and the outbreak of Middle East Respiratory Syndrome coronavirus (MERS-CoV) in 2012, SARS-CoV-2 is the third highly pathogenic coronavirus.

The vaccine candidate Ad5-nCoV, intended to prevent COVID-19 caused by SARS-CoV-2, is jointly developed by CanSino Biologics Inc. and the Beijing Institute of Biotechnology. Using the replication-deficient human adenovirus type 5 as a vector, Ad5-nCoV has been developed through recombinant virus construction, amplification and purification, and expresses the specific S protein of SARS-CoV-2. It is suggested that both humoral and cellular immune responses play an important role in protective immunity according to the results of pre-clinical, phase I and phase II studies.

Pre-clinical studies showed good immunogenicity (antibodies by ELISA and neutralization, cell mediated immunity) in mice, guinea pigs, rats, and cynomolgus monkeys. Protection by the Ad5-nCoV vaccine has been demonstrated in transgenic mice, ferrets and rhesus monkeys. Toxicology studies have been completed and have not demonstrated any concerns (see Investigator Brochure [10] for full details of the pre-clinical studies).

Phase I trials found that the Ad5-vectored COVID-19 vaccine was tolerable in healthy adults [5]. The study was designed and carried out as a dose-escalation, single-centre, open-label, non-randomised clinical trial. 108 healthy adults participated in the phase I portion of the study and were divided into low, medium, and high-dose Ad5-nCoV vaccine groups. Participants received a dose on Day 0. A total of 87% of participants reported at least 1 AE during the first 7 days after receiving the vaccine. The most common local AE was pain at the injection site, while fatigue, headache and fever were the most frequently reported systemic AE. Most reported AE were classified as mild to moderate and were self-limiting. However, there were 5 incidences of a Grade 3 fever in the high dose group. There was also higher occurrence of severe fever, fatigue, muscle pain, or joint pain, (which might be associated with viremia caused by Ad5 vector infection) in participants who received the of 1.5×10^{11} viral particles. For this reason, the low (5×10^{10} vp per mL) and medium dose (1×10^{11} vp per mL) were selected to progress to phase II trials. No SAE were recorded within 28 days of receiving the vaccine.

All three doses of the Ad5-nCoV vaccine demonstrated good immunogenicity in participants [5]. Anti-RBD antibodies were present in all groups after Day 14 and had at least a 4-fold increase in 97%, 94% and 100% of participants in the low, medium, and high doses respectively. Both ELISA and neutralizing antibodies increased significantly at 14 days post vaccination and peaked at 28 days post vaccination, in all three groups. A rapid T-cell response was observed in all groups by Day 14 as well.

On July 20th, 2020 the Phase II results of the Ad5-nCoV clinical trial were published. 508 healthy adults ≥ 18 years of age were randomized into three groups to receive Ad5-nCoV vaccine at either 1×10^{11} vp per mL or 5×10^{10} vp per mL, or a placebo vaccine in a 2:1:1 ratio,

respectively [2]. The main objectives of this study were to assess the immunogenicity and safety of receiving the Ad5-nCoV vaccine, and to determine the appropriate dose to be administered for the efficacy study (currently, phase III).

The data produced from the phase II clinical trial further supported the safety and tolerability of receiving an Ad5-nCoV vaccine in healthy adults [2]. There were no SAE recorded in any of the study groups within 28 days of vaccination. Participants in both the 1×10^{11}vp and 5×10^{10} vp groups commonly reported mild to moderate adverse reactions, when solicited by study staff. Injection site pain was the most frequently reported solicited reaction; 57% of the 1×10^{11} vp dose and 56% of the 5×10^{10}vp group reported pain within 14 days of vaccination. A total of 9% of participants in the 1×10^{11}vp had a Grade 3 adverse reaction, which was significantly higher than those who received 5×10^{10} vp vaccine (p=0.0011) or placebo (p=0.0004). The most commonly reported Grade 3 adverse reaction was a fever; however, fevers were self-limiting. There was no difference in the incidence of unsolicited adverse reactions between the three groups.

Both doses of Ad5-nCoV vaccine administered in the phase II study induced a robust immune response to SARS-CoV-2, with overall comparable immunogenicity between the doses [2]. Beginning Day 14, RBD-specific ELISA antibody responses were detectable in both groups and peaked at 656.5 (575.2-749.2) in the 1×10^{11}vp group, and 571.0 (467.6- 697.3) in the 5×10^{10}vp group, on Day 28 post vaccination. While the placebo group showed no increase in antibodies from baseline, 96% of the 1×10^{11}vp group and 97% of the 5×10^{10}vp group demonstrated seroconversion of the RBD-specific ELISA antibodies at Day 28. There was seroconversion of neutralising antibodies in 59% and 47% of participants in the 1×10^{11}vp and 5×10^{10} vp dose groups, respectively. There was a significant positive T-cell response in both the 1×10^{11}vp and 5×10^{10}vp dose groups by Day 28, although the difference was not significant between the doses. A positive specific T-cell response, measured by IFNγ-ELISpot, was found in 90% of the 1×10^{11} vp group and 88% of participants in the 5×10^{10} vp group. At Day 28, 95% of participants in the 1×10^{11} viral particles dose group and 91% of the recipients in the 5×10^{10} viral particles dose group showed either cellular or humoral immune responses.

It was found that the 5×10^{10} vp group produced a similar immune response to the 1×10^{11}vp group, but with a better safety profile [2]. From the data produced in the Phase I and II trials, it has been determined that the best dose for the Ad5-nCoV vaccine is 5×10^{10} vp.

1.3. Rationale for the study

Largely attributable to globalization, without a prophylactic vaccine against SARS-CoV-2, COVID-19 will persist as a pandemic threat [2]. The few published clinical trials support the need for further researching of the efficacy of receiving vaccines that will protect against SARS-CoV-2 infections [3].

This study is a phase III clinical trial to collect sufficient efficacy and safety data through the cooperation of global clinical trial sites to support the final registration of the candidate vaccine.

One dose of Ad5-nCoV at 5×10^{10}vp will be administered to healthy adults older than 18 years of age and compared to a placebo control group for efficacy of the vaccine in preventing SARS-CoV-2.

The Adenovirus type 5 platform has been successfully used by CanSino Biologics in its licensed Ebola virus vaccine. Two phase I clinical trials in China and one phase II clinical trial in Sierra Leone of Recombinant Ebola Virus Disease Vaccine (Adenovirus Type 5 Vector, rAd5) were conducted. The safety data are summarized below.

Between December 2014 and January 2015, a randomized, double-blinded, placebo-controlled, phase I clinical trial of single dose rAd5 Ebola vaccine was conducted in Jiangsu Province, China, to evaluate the safety, tolerability and immunogenicity in healthy people aged between 18 to 60 years. The vaccine was well tolerated with an adverse event reported in over 60% of participants after their primary immunization, and 71% of participants after the booster dose 6 months later [6, 7]. Local adverse reactions were pain, induration, and redness, swelling and itching. Systemic adverse reactions were fever, headache, fatigue, vomiting, diarrhea, myalgia, joint pain, sore throat and cough [6, 7]. Between March and August of 2015, a randomized, single center, open-label phase I clinical trial of rAd5 Ebola vaccine was conducted in Zhejiang Province, China, to evaluate its safety and immunogenicity in healthy Africans in China [8]. The safety results showed that solicited local adverse reactions were pain, swelling, induration and redness, mucosal damage, itching and rash at the injection site [8]. From October 2015, a randomized, single center, double-blinded, placebo-controlled phase II clinical trial of rAd5 Ebola vaccine was conducted in Sierra Leone [9], to evaluate its safety and immunogenicity in healthy Africans. The safety results showed that solicited local adverse reactions were mainly pain [9]. For full study details, please see articles referenced. Most of the adverse reactions were mild and self-limited. The above results indicated that the strength and extent of adverse reactions are acceptable and the rAd5 Ebola vaccine in healthy adults is tolerable and safe.

Immunogenicity of the rAd5 Ebola vaccine was demonstrated in all of the reported studies [6-9]. Higher antibody titers were demonstrated in participants who had low or absent pre-existing antibodies against adenovirus type 5; however, a significant immune response also occurred in individuals with pre-existing antibodies. These differences diminished after a booster dose of the rAd5 Ebola vaccine at 6 months [6-9].

Phase I and Phase II studies of the Adenovirus type 5 platform expressing SARS-CoV-2 spike protein have now been completed and demonstrate good safety and immunogenicity. A phase III trial to test the efficacy of the Ad5-nCoV vaccine is warranted.

2. STUDY OBJECTIVES

2.1 Primary Objectives

Primary Efficacy Objective:

The primary efficacy objective 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. COVID-19 disease rates in Ad5-nCoV group will be compared with COVID-19 rates in the control group. This objective will be measured in all participants who receive a dose of either study vaccine or placebo in the study.

Efficacy Hypothesis

A sequential-monitoring-adjusted 95% lower bound of the confidence interval on vaccine efficacy (VE) exceeds 30%， the point estimate for VE will be at least 50%, in agreement with the minimum requirement given in the WHO Target Product Profile.

Null hypothesis (H_0): Lower bound of 95% CI of VE≤30%

Alternative hypothesis (H_1): Lower bound of 95% CI of VE＞30%

Primary Safety Objective:

The primary safety objective is to evaluate the incidence of serious adverse events (SAE) and medically attended adverse events (MAE) within 52 weeks after vaccination in all participants.

2.2 Secondary Objectives

Secondary Efficacy Objectives:

1. To evaluate the efficacy of Ad5-nCoV in preventing virologically confirmed (PCR positive) COVID-19 disease occurring 14 days to 52 weeks after vaccination, regardless of severity.
2. To evaluate the efficacy of Ad5-nCoV in preventing severe COVID-19 disease caused by SARS-CoV-2 infection from 14 and 28 days, to 24 and 52 weeks after vaccination.
   Severe disease is defined as: 1) 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), 2) Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO), 3) Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors), 4) Significant acute renal, hepatic, or neurologic dysfunction, 5) Admission to an ICU.
3. To evaluate the efficacy of Ad5-nCoV in different age groups from 14 and 28 days, to 24 and 52 weeks after vaccination. This will be evaluated by weekly participant contacts to assess for any signs or symptoms of COVID-19.

4. To evaluate the efficacy of the primary and secondary objectives #1-3 of Ad5-nCoV in preventing virologically (PCR) or serologically (four-fold increase in SARS-CoV-2 anti-N IgG from pre-immunization to post symptom, defined as Day 21-28 post illness blood test, or pre-symptom to post-symptom blood test) confirmed COVID-19 disease.

Secondary Safety Objectives:

The following secondary safety objectives will be evaluated in the efficacy-extended safety, and efficacy-extended safety-immunogenicity, and efficacy-extended safety-extended immunogenicity cohorts.

1. Evaluate the incidence of solicited adverse reactions within 7 days after vaccination, in a subset of approximately 3000 participants (approximately 7%-10%).
2. Evaluate the incidence of unsolicited adverse events within 28 days after vaccination, in a subset of approximately 3000 participants (approximately 7%-10%).

Secondary Immunogenicity Objectives:

The following secondary objectives will only be evaluated in the efficacy-extended safety-immunogenicity cohort and the efficacy-extended safety-extended immunogenicity cohort.

1. Evaluate the seroconversion rate of S-RBD IgG antibody on Day 28, Week 24 and Week 52 after vaccination, measured by ELISA.
2. Evaluate the GMT of S-RBD IgG antibody on Day 28, Week 24 and Week 52 after vaccination, measured by ELISA.
3. Evaluate the GMI of S-RBD IgG antibody on Day 28, Week 24 and Week 52 after vaccination, measured by ELISA.
4. Evaluate the seroconversion rate of pseudo-virus neutralizing antibody on Day 28, Week 24 and Week 52 after vaccination.
5. Evaluate the GMT of pseudo-virus neutralizing antibody on Day 28, Week 24 and Week 52 after vaccination.
6. Evaluate the GMI of pseudo-virus neutralizing antibody on Day 28, Week 24 and Week 52 after vaccination.
7. Evaluate the positive rate and level of IFN-γ stimulated by peptide pool of S protein on Day 28, and Weeks 24 and Week 52 after vaccination, measured by ELISpot.
8. Evaluate the positive rate and level of IL-2, IL-4, IL-13, IFN-γ stimulated by peptide pool of S protein on Day 28, and Weeks 24 and Week 52 after vaccination, measured by intracellular cytokine staining (ICS).

2.3 Supportive Objectives

1. Evaluate the severity of COVID-19 cases among vaccine recipients (based on WHO criteria) as compared to the control group, to measure antibody-mediated disease

enhancement (ADE).
2. Evaluate for any evidence of SARS-CoV-2 virus shedding in COVID-19 cases that occurred 28 days to 52 weeks after vaccination (detection of viral nucleic acid every 2 days after being confirmed).
3. Perform genotyping of SARS-CoV-2 virus isolates of COVID-19 cases that occurred 28 days to 52 weeks after vaccination.
4. Evaluate incidence of suspected but unconfirmed cases of COVID-19 (either because of negative or no tests).
5. Evaluate the efficacy of Ad5-nCoV in preventing asymptomatic disease of COVID-19 (confirmed by N IgG antibody on week 52 after vaccination).

3. STUDY DESIGN

3.1 Summary

This Phase III study is an endpoint case driven, double-blind, randomized, global, multi-centre, placebo-controlled, adaptive design clinical trial, with the goal of about 150 COVID-19 endpoint cases. Approximately 30,000-40,000 total participants will be enrolled into four cohorts, based on the current attack rate of COVID-19.

All participants will receive a single dose of either the study vaccine or a placebo vaccine on Day 0 and will be followed to monitor vaccine candidate efficacy and incidence of SAE for a duration of 52 weeks. If the ongoing phase II trial of Ad5-nCoV demonstrates both safety and increased immunogenicity of a two dose regimen, IDMC and/or the Sponsor may recommend the addition of a two-dose regimen to the study. The primary efficacy objective will then be assessed independently based on the one-dose and two-dose regimens. In the current one-dose study design, there will be four cohorts in the study: the efficacy-safety cohort (n≈37, 000) and three study subset cohorts (approximately 3,000 participants [7-10% from select enrollment countries]). These three subset cohorts will be: efficacy-extended safety, efficacy-extended safety-immunogenicity, and the efficacy-extended safety-extended immunogenicity cohort. These three subset cohorts, in addition to measuring standard safety and efficacy, will undergo additional monitoring as outlined below, to provide extended safety and immunogenicity data associated with receiving the 5×10^{10}vp Ad5-nCoV vaccine ($\geq 4 \times 10^{10}$ VP)**.**

Candidate Vaccine: Ad5-nCoV

Placebo control: Placebo for Ad5-nCoV

Vaccination schedule: A single-dose schedule is used. A second dose in all or some age cohorts may be made in response to new data from ongoing phase I/II clinical trials according to the adaptive design.

Data collection: This clinical trial will use a single, designated Electronic Data Capture System (EDC) in all participating countries.

Safety Precautions: Safety precautions will be outlined in detail in this section, as well as Section 7.

3.2 Adaptive Design

The adaptive design will allow for responding to changes in standards of prevention and care, and uncertainties about the course of the pandemic in different geographic locations and populations. Various adaptive features will assure that the trial achieves results in a defined and short period. These adaptive features are:

1. **Choice of study population**

   If deemed necessary to increase the likelihood that the study will identify efficacious vaccines, the blinded Steering Committee may also modify the number of study sites and the sample size at all or selected study sites. Some sites may use a mobile trial structure, allowing flexible redirection to populations with high attack rates.

   During the clinical trial process, if the COVID-19 attack rate in a certain country shows a rapid decline due to local epidemic prevention measures. With the approval of the clinical trial steering committee, the local sample size may be reduced, and the sample size of countries with higher attack rates will likely increased.

2. **Adjustment of vaccination schedule**

   In accordance with the adaptive design of the study, the vaccination schedule may be adjusted as the clinical trial progresses. It is currently planned that participants will receive a single dose of the vaccine. However, addition of a two-dose schedule would be considered if the ongoing phase II trial of Ad5-nCoV demonstrates both safety and increased immunogenicity of a two dose regimen.

   - After adaptive adjustment of the vaccination schedule, a second, independent primary efficacy endpoint will be added: “the efficacy of preventing virologically confirmed (PCR positive) COVID-19 disease between 14 days and 52 weeks after two doses of vaccination, regardless of severity”.

   After the decision to adjust the vaccination schedule, the safety, immunogenicity and efficacy participant contact requirements will be updated in the form of clinical trial protocol version upgrade.

3.3 Randomization & Treatment Allocation

An interactive web response system (IWRS) will be used to randomize participants in global clinical trial. This system will be able to dynamically adjust the distribution of sample size according to the actual situation in different sites (such as COVID-19 attack rate, etc.) during the trial.

Participants will be randomly assigned to Ad5-nCoV group and control group in a ratio of 1:1.

3.4 Blinding

This is double-blinded clinical trial. The sponsor will provide investigational product and identical appearing placebo to investigators responsible for vaccine administration according to the prompts in the IWRS system.

Emergency unblinding decisions are expected to be rare and could be justified only when that information is needed for the future clinical management of that participant. The decision of emergency unblinding must be approved by the Local PI, the global PI and the sponsor after sufficient evaluation.

3.5 Study Groups

Participants will be randomized to receive either the candidate vaccine or the placebo. While efficacy outcomes and serious adverse events will be collected on all participants, approximately 3,000 participants (7-10% from each participating country) enrolled will comprise three additional cohorts to collect detailed safety data (the efficacy-extended safety cohort) or extended safety and immunogenicity data (the efficacy-extended safety-immunogenicity cohort and the efficacy-extended safety-extended immunogenicity cohort). Of these 3000 participants, 600 participants within the extended immunogenicity cohorts will undergo blood sampling on Days 0 and 28, and 24 and 52-weeks post immunization for immunogenicity testing (efficacy-extended safety-immunogenicity cohort). Of these 600, 200 participants will be in the efficacy-extended safety-extended immunogenicity cohort and will undergo additional T-cell testing.

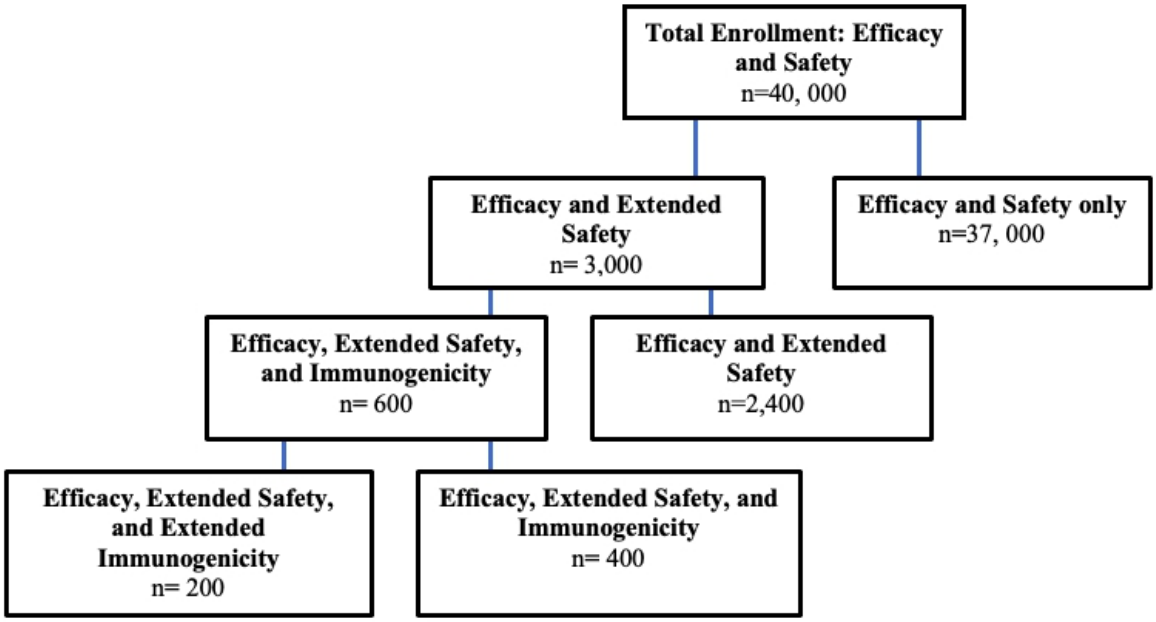

Figure 1. Cohort of study participants

3.6 Sampling/Study Schedule (Based on Cohort)

Efficacy-Safety Cohort

All participants in the efficacy-safety cohort will have at least two planned in-person visits on Day 0 and Week 52. The first in-person visit will entail reviewing the ICF, completing a medical history of the participant, reviewing inclusion and exclusion criteria, obtaining a baseline serum for HIV antibody testing (central laboratory), baseline SARS-CoV-19 antibody (central laboratory), and a urine pregnancy test in women of childbearing potential (local site or laboratory). Participants will then be randomized to either the placebo or candidate vaccine group and will receive their vaccination. The participant and study nurse will remain blinded to the assigned group. Participants are required to remain at the study site for a minimum of 30 minutes after receiving the vaccine to monitor for any vaccine-related AE.

All participants in this cohort will be contacted on a weekly basis to be reminded to report any signs or symptoms of illness to study staff. Participants will either be contacted by the site weekly or they will receive an automated message (email) with a link to answer questions about whether or not they had an SAE, an MAE or COVID-19 symptoms. The reporting and monitoring of any participant illness are consistent with meeting the primary efficacy objective. If a participant becomes ill, they will be asked to immediately proceed to the site designated by their local study team where they will be assessed and treated, as deemed appropriate. Participants will also receive a telephone call every 4 weeks to evaluate for the incidence of any SAE and MAE. Further details are outlined in Section 3.8.

All participants in this cohort will be asked to return to the study site on Week 52, for the final in-person visit. Approximately 25mL of whole blood will be collected to measure for antibodies against SARS-CoV-2, in congruence for the VE objective

If a participant demonstrates signs or symptoms of illness, an unplanned in-person visit may occur for evaluation and possible treatment. If, for any reason following a participant contact, the investigator would like to conduct an in-person visit with a participant, they may do so at their discretion

Efficacy-Extended Safety Cohort

All participants in the efficacy-extended safety cohort will have at least three planned in-person visits on Day 0 and Day 28, and Week 52. The first visit on Day 0 will entail reviewing the ICF, completing a medical history of the participant, reviewing inclusion and exclusion criteria, obtaining a baseline serum for HIV antibody testing (central study laboratory), baseline SARS-CoV-19 antibody (central laboratory), and a urine pregnancy test in women of child-bearing potential (local site or laboratory). Participants will then be randomized to either the placebo or candidate vaccine group and receive their vaccination. The participant and study nurse will remain blinded to the assigned group. Participants are required to remain at the study site for a minimum of 30 minutes after receiving the vaccine to monitor for any vaccine-related AE.

Participants who are enrolled in the efficacy-extended safety cohort will be given access to an e-diary or a paper diary card to record solicited AE from Day 0-7 and unsolicited AE from Day 0-28. These cohorts will review their completed e-diary or diary card with study staff at their second in-person visit on Day 28. Data collected from e-diaries and diary cards will be uploaded into the participant's EDC. Further details are outlined in Section 3.7 and 5.3.

All participants will be contacted on a weekly basis to be reminded to report any signs or symptoms of illness to study staff. Participants will either be contacted by the site weekly or they will receive an automated message (email) with a link to answer questions about whether or not they had an SAE, an MAE or COVID-19 symptoms. They will also be asked on their Day 7 contact about any events that might meet a holding rule. The reporting and monitoring of any participant illness are consistent with meeting the primary efficacy objective. If a participant becomes ill, they will be asked to immediately proceed to the site designated by their local study team where they will be assessed and treated as deemed appropriate. Participants will also receive a telephone call every 4 weeks, to evaluate for the incidence of any SAE and MAE.

All participants in this cohort will be asked to return to the study site on Week 52, for the final in-person visit. Approximately 25mL of whole blood will be collected to measure for antibodies against SARS-CoV-2, in congruence for the VE objective.

If a participant demonstrates signs or symptoms of illness, an unplanned in-person visit may occur for evaluation and possible treatment. If, for any reason following a participant contact, the investigator would like to conduct an in-person visit with a participant, they may do so at their discretion

Efficacy-Extended Safety-Immunogenicity and Efficacy-Extended Safety-Extended Immunogenicity Cohorts

These cohorts will be enrolled in selected countries. All participants in the efficacy-extended safety cohort will have at least three planned in-person visits on Day 0 and Day 28, and Week 52. The first visit on Day 0 will entail reviewing the ICF, completing a medical history of the participant, reviewing inclusion and exclusion criteria, and a urine pregnancy test in women of child-bearing potential (local site or laboratory). Participants will have blood drawn pre-vaccination on Day 0 to establish obtaining a baseline serum for HIV antibody testing (central laboratory), baseline SARS-CoV-19 antibody (central laboratory), and baseline immunogenicity levels. Participants will then be randomized to either the placebo or candidate vaccine group and receive their vaccination. The participant and study nurse will remain blinded to the assigned group. Participants are required to remain at the study site for a minimum of 30 minutes after receiving the vaccine to monitor for any vaccine-related AE.

All participants in these cohorts will be contacted on a weekly basis to be reminded to report any signs or symptoms of illness to study staff. Participants will either be contacted by the site weekly or automated message (email) with a link to answer questions about whether or not they had an SAE, an MAE or COVID-19 symptoms. The reporting and monitoring of any participant illness are consistent with meeting the primary efficacy objective. If a participant becomes ill, they will be asked to immediately proceed to the site designated by their local study team where they will be assessed and treated as deemed appropriate. Participants will also receive a telephone call every 4 weeks to evaluate for the incidence of any SAE and MAE. In these two cohorts, participants will have their two of in-person visits (in addition to weekly contact) on Week 24 and Week 52.

Participants who are enrolled in the efficacy-extended safety-immunogenicity and efficacy-extended safety-extended immunogenicity cohorts will be given access to an e-diary or paper diary card to record solicited AE from Day 0-7 and unsolicited AE from Day 0-28. These cohorts will review their completed e-diary or diary card with study staff at their second in-person visit on Day 28. Data collected from e-diaries and diary cards will be uploaded into the participant's EDC. Further details are outlined in Section 3.7 and 5.3.

In-person visits on Day 28, Week 24 and Week 52 will also be used for blood sample collection in these two cohorts to assess for detailed immunogenicity response. Further details are outlined in Section 3.8 and 3.9

The efficacy-extended safety-extended immunogenicity cohort will have additional immunologic testing performed, following the same visit schedule, to evaluate T-cell response to the Ad5-nCoV vaccine.

If a participant demonstrates signs or symptoms of illness, an unplanned in-person visit may occur for evaluation and possible treatment. If, for any reason following a participant contact, the investigator would like to conduct an in-person visit with a participant, they may do so at their discretion.

Table 1. In-Person Visits For Efficacy-Safety Cohort

Intervention	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
	Day 0	**Day 28**	**Week 24**	**Week 52**
Visit window	**-**	**+7 days**	**+14 days**	**+14 days**
Informed Consent	●			
Review Consent				●
Collect Demographic and Participant Contact Information	●			
Urine Pregnancy test- women of childbearing potential	●			
Review Inclusion and Exclusion criteria	●			
Medical History	●			
	Clinical Trial Protocol	**Clinical Trial Protocol**	**Clinical Trial Protocol**	**Clinical Trial Protocol**
	Clinical Trial Protocol	**Clinical Trial Protocol**	**Clinical Trial Protocol**	**Clinical Trial Protocol**
Check Contraindications to vaccine	●			
	Clinical Trial Protocol	**Clinical Trial Protocol**	**Clinical Trial Protocol**	**Clinical Trial Protocol**

	Clinical Trial Protocol	**Clinical Trial Protocol**	**Clinical Trial Protocol**	**Clinical Trial Protocol**
Screening conclusion	●			
Pre-injection vital signs	●			
Study group and treatment number allocation	●			
Check and record prior medications and concomitant medication/injection	●			
Check and record intercurrent medical conditions	●			
Blood Sample Collected for ELISA testing (~25mL)	●[a]			●
Administration of Study Product	●			
Safety participant contact (Phone call or in-person visit)	Every 4 weeks			
Efficacy participant contact (message) [(b)]	Weekly from Day 7-week 52 (visit window: +3 days)			
Study conclusion				●

● *is used to indicate a study procedure.*

[(a)]: Serum sample will be also used for a post-hoc analyses to assess for presence of HIV antibodies in all participants.

[(b)]: If in certain countries or local study sites it is preferable, a phone-call or text instead of email for efficacy patient contact is acceptable.

Table 2. In-Person Visits For Efficacy-Extended Safety Cohort

Intervention	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
	Day 0	**Day 28**	**Week 24**	**Week 52**
Visit window	**-**	**+7 days**	**+14 days**	**+14 days**
Informed Consent	●			

Review Consent				●
Collect Demographic and Participant Contact Information	●			
Urine Pregnancy test- women of childbearing potential	●			
Review Inclusion and Exclusion criteria	●			
Medical History	●			
Check Contraindications to vaccine	●			
Screening conclusion	●			
Pre-injection vital signs	●			
Study group and treatment number allocation	●			
Check and record prior medications and concomitant medication/injection	●			
Check and record intercurrent medical conditions	●			
Blood Sample Collected for ELISAtesting (~25mL)	●[a]			●
Administration of Study Product	●			
Extended Safety participant contact: in-person visit	●	●		
E-diary access or paper diary card provided to participant	●			
E-diary or diary card reviewed with participant and data collected and uploaded to EDC		●		
Safety participant contact (Phone call or in-person visit)	Every 4 weeks			
Efficacy participant contact (message) [(b]	Weekly from Day 7-week 52 (visit window: +3 days)			

Study conclusion				●

● *is used to indicate a study procedure.*

(a): Serum sample will be also used for a post-hoc analyses to assess for presence of HIV antibodies in all participants

(b): If in certain countries or local study sites it is preferable, a phone-call or text instead of email for efficacy patient contact is acceptable.

Table 3. In-Person Visits For Efficacy-Extended Safety-Immunogenicity Cohort

Intervention	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
	Day 0	**Day 28**	**Week 24**	**Week 52**
Visit window	**-**	**+7 days**	**+14 days**	**+14 days**
Informed Consent	●			
Re-confirm Consent		●	●	●
Collect Demographic and Participant Contact Information	●			
Urine Pregnancy test- women of childbearing potential	●			
Review Inclusion and Exclusion criteria	●	●	●	●
Medical History	●			
	Clinical Trial Protocol	**Clinical Trial Protocol**	**Clinical Trial Protocol**	**Clinical Trial Protocol**
	Clinical Trial Protocol	**Clinical Trial Protocol**	**Clinical Trial Protocol**	**Clinical Trial Protocol**
Check Contraindications to vaccine	●			
Screening conclusion	●			
Pre-injection vital signs	●			

Study group and treatment number allocation	●			
Check and record prior medications and concomitant medication/injection	●			
Check and record intercurrent medical conditions	●			
Administration of Study Product	●			
Safety participant contact (Phone call or in-person visit)	Every 4 weeks			
Efficacy participant contact (message) [(b)]	Weekly from Day 7- week 52 (visit window: +3 days)			
Extended Safety participant contact: in-person visit	●	●		
E-diary access or paper diary card provided to participant	●			
E-diary or diary card reviewed with participant and data collected and uploaded to EDC		●		
Immunogenicity participant contact: in-person visit	●	●	●	●
Blood Sample Collected for ELISA and neutralizing antibody testing (~25mL)	●[a]	●	●	●
Study conclusion				●

● *is used to indicate a study procedure.*

[(a)]: Serum sample will be also used for a post-hoc analyses to assess for presence of HIV antibodies in all participants.

[(b)]: If in certain countries or local study sites it is preferable, a phone-call or or text instead of email for efficacy patient contact is acceptable.

Table 4. In-Person Visits For Efficacy-Extended Safety-Extended Immunogenicity Cohort

Intervention	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**

	Day 0	**Day 28**	**Week 24**	**Week 52**
Visit window	**-**	**+7 days**	**+14 days**	**+14 days**
Informed Consent	●			
Review Consent		●	●	●
Collect Demographic and Participant Contact Information	●			
Urine Pregnancy test- women of childbearing potential	●			
Review Inclusion and Exclusion criteria	●	●	●	●
Medical History	●			
Check and record prior medications and concomitant medication/injection	●			
Check and record intercurrent medical conditions	●			
Check Contraindications to vaccine	●			
Pre-injection vital signs	●			
Study group and treatment number allocation	●			
Screening conclusion	●			
Administration of Study Product	●			
Safety participant contact (Phone call or in-person visit)	Every 4 weeks (Day 28 is in person)			
Efficacy participant contact (message) [(b)]	Weekly from Day 7- week 52 (visit window: +3 days)			
Extended Safety participant contact: in-person visit	●	●		
E-diary access or paper diary card provided to participant	●			
E-diary or diary card reviewed with		●		

participant and data collected and uploaded to EDC				
Immunogenicity participant contact: in-person visit	●	●	●	●
Blood Sample Collected for ELISA and neutralizing Antibody testing (~25mL)	●[a]	●	●	●
Blood Sample Collection for ELISpot and ICS testing (~30mL)	●	●	●	●
Study conclusion				●

● *is used to indicate a study procedure.*

(a): Serum sample will be also used for a post-hoc analyses to assess for presence of HIV antibodies in all participants.
(b): If in certain countries or local study sites it is preferable, a phone-call or or text instead of email for efficacy patient contact is acceptable

Detailed description of study procedures and interventions is outlined in Section 5.1 for efficacy-safety cohort, 5.2 for efficacy-extended safety cohort, 5.3 for efficacy-extended safety-immunogenicity cohort, and 5.4 for efficacy-extended safety-extended immunogenicity cohort.

3.7 Safety and Extended Safety Participant Contacts

These participant contacts will be used to closely monitor for the incidence of SAE in all participants. The incidence of local and systemic AE in the efficacy-extended safety cohort, the efficacy-extended safety-extended-immunogenicity cohort, and the efficacy-extended safety-extended immunogenicity cohort will also be evaluated.

Frequent contact is planned between study staff and participants to allow for early identification of any SAE. This is a prudent step to ensure that any participants who may have an unrecognized positive HIV status or other undiagnosed health condition are followed carefully for signs and symptoms of infection or occurrence of a SAE.

Every 4 weeks for 52 weeks there will be telephone contacts to continuously collect SAE and MAE data until one-year post vaccination. Adverse events may also be reported at any time during the study period by participants. Safety participant contacts will occur on Day 0 (for 30 minutes post-vaccination), Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. These safety participant contacts will be through phone calls in the efficacy-safety cohort. Week 52 will be a final in-person visit.

In the efficacy-extended safety cohort, safety participant contacts will be an in-person visit on Day 28 and Week 52), and via phone calls at Week 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52.

Participants in the efficacy-extended safety-immunogenicity cohort and the efficacy-extended safety-extended immunogenicity cohort will have in-person safety participant contacts on Day 28, Week 24 and Week 52, and phone calls at Week 8, 12, 16, 20, 28, 32, 36, 40, 44 and 48.

Participants in the efficacy-extended safety, efficacy-extended safety-immunogenicity, and the efficacy-extended safety-extended immunogenicity cohorts will also be given access to an e-diary or a paper diary card to record solicited AE from Day 0-7 and unsolicited AE from Day 0-28. These cohorts will review their completed e-diary or diary card with study staff at their second in-person visit on Day 28. Data collected from e-diaries and diary cards will be uploaded into the participant's EDC. Further details are outlined in Section 5.3.

The visit window for safety participant contact at 28 days is +7 days.
The visit window for safety (SAE) participant contact from Weeks 8-52 is +7 days.

Note: A safety participant contact, and an immunogenicity participant contact can be combined, meaning that safety participant phone call can be replaced by an in-person visit, depending on the date and the cohort.

3.8 Efficacy participant contacts

Efficacy participant contacts will occur for all participants on a weekly basis. Text messages will remind participants to report any signs or symptoms of infection to the study staff. These participant contacts can also be in-person, by phone, via the Internet or any other suitable method. Each contact needs to be recorded in the study electronic case report form.

Any reported COVID-19 relevant symptoms will trigger laboratory testing for SARS-CoV-2 infection. The SARS-CoV-2 nucleic acid test is performed with a throat or nasal swab and repeated within 3 days if the result is negative. PCR SARS-CoV-2 tests will be done at local laboratories or at study site laboratories. Every effort will be made to verify positive PCR tests in a national or regional reference laboratory. Participants with a positive nasal/throat PCR will have it repeated at the local laboratory every two days until negative (if possible). A serum specimen will be collected at the time of illness presentation and be repeated 3-4 weeks later for SARS-CoV-2 anti-N IgG antibodies to be performed in the study central laboratory for all subjects presented with suspected COVID-19 symptoms, regardless of the result of PCR SARS-CoV-2 test.

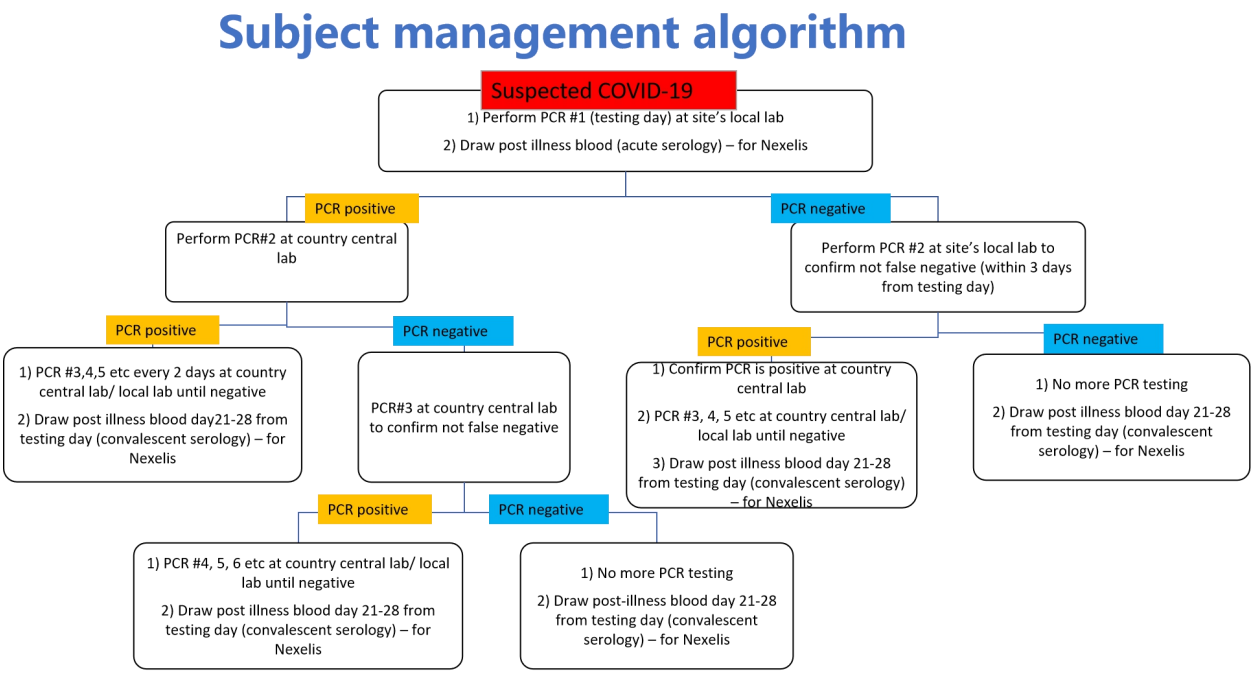

Figure 2. Procedure algorithm of Efficacy participant contacts

COVID-19 cases diagnosed within 28 days post vaccination will be documented but not be included as a case for primary endpoint. After COVID-19 diagnosis, participants will be referred locally for management, as required. Data to determine whether these participants meet criteria for severe COVID-19 or if they receive antivirals that could modify the likelihood of severe COVID-19 will be collected. Blinded study participant contact for COVID-19 disease is planned to last for at least 52 weeks.

Participants in the efficacy-safety cohort will have efficacy participant contact via email, text, or phone on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168, 175, 182, 189, 196, 203, 210, 217, 224, 231, 238, 245, 252, 259, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, 336, 343, 350, and 357. Participant contacts on Days 28, 56, 84, 112, 140, 168, 196, 224, 252, 280, 308, and 336, will be a phone call, in addition to the email or text message. Day 364 (week 52) will be an in-person visit for final blood collection for VE testing.

Participants in the efficacy-extended safety cohort will have efficacy participant contact via email, text or phone message on Days 7, 14, 21, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168, 175, 182, 189, 196, 203, 210, 217, 224, 231, 238, 245, 252, 259, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, 336, 343, 350, and 357. Participant contacts on Days 56, 84, 112, 140, 168, 196, 224, 252, 280, 308, and 336, will be a phone call, in addition to the email or text message, to combine safety and efficacy participant contacts. Day 28 will be an in-person visit to accommodate for the extended safety participant contact. Day 364 (week 52) will be an in-person visit for final blood collection to be used for VE testing.

Participants in the efficacy- extended safety-immunogenicity and efficacy-extended safety-extended immunogenicity cohorts will have participant contacts via email, text, or phone message on Days 7, 14, 21, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161,175, 182, 189, 196, 203, 210, 217, 224, 231, 238, 245, 252, 259, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, 336, 343, 350, and 357. Participant contacts on Days 56, 84, 112, 140, 196, 224, 252, 280, 308, and 336 will have a phone call, in addition to an email or text message. Day 28, 168 (week 24), and 364 (week 52) will be an in-person visit to accommodate the extended safety participant contact and immunological testing, in addition to the standard safety and efficacy participant contact visit.

The visit window for Efficacy participant contact is +3 days.

Case definitions for surveillance：

Suspect case

Subject with any of the following symptoms (or signs) is reported as suspected case：

Fever, cough, dyspnoea & difficulty breathing, anosmia/ageusia, chills, myalgia, sore throat, prolonged fatigue, diarrhea, nausea, vomiting, headache, congested/runny nose, pneumonia, difficulty swallowing, loss of sense of smell and taste, and neurological events.

Probable case

1. A suspect case for whom testing for the COVID-19 virus is inconclusive.

OR

2. A suspect case for whom testing could not be performed for any reason.

Confirmed case

A suspect case with laboratory confirmation of COVID-19 infection (including PCR positive result OR 4 folds 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: the participant with the clinical symptom(s) occurred not less than 28 days post-vaccination and the PCR test is positive.

Secondary endpoint: the participant with the clinical symptom(s) occurred not less than 14 days post-vaccination and the PCR test is positive; or 4 folds 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.

3.9 Immunogenicity In-Person Visits

The main immunogenicity in-person visits will only be carried out in the efficacy-extended safety-immunogenicity cohort and efficacy-extended safety- extended immunogenicity cohort of approximately 600 participants. Participants within these two cohorts will return to the study site on Day 28, Week 24, and Week 52 for collection of venous blood samples for antibody testing. Approximately 25mL of serum will be collected for ELISA and neutralizing antibody testing on Day 28, Week 24, and Week 52. Approximately 30mL of whole blood will be collected on Day 28, and Week 24 and Week 52 for ELISpot testing and intracellular cytokine staining (ICS) in the efficacy-extended safety-extended immunogenicity cohort (n=200).

The visit window for immunogenicity participant contact of Day28 is +7 days.

The visit window for immunogenicity participant contact of Week 24, and Week 52 is +14 days.

Telephone visits and face-to-face visits at the same time point can be combined into one face-to-face visits.

4. STUDY POPULATION

The trial will recruit 30,000-40, 000 participants, aged 18 years old and older, whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on surveillance data and epidemiologic modeling. Recruitment should support the generalizability of results, including by important characteristics such as age (including elderly). Participants must meet inclusion/exclusion criteria. Participants will be enrolled at many centres globally.

Participants will be enrolled at various study sites across five countries: Argentina, Chile, Pakistan, Russia, and Mexico. Depending on success of participant enrollment, as well as the COVID-19 attack rate in each country, this list may be revised to include additional countries.

According to the results of negotiations with target countries, enrollment in each country is expected to fall within the following ranges:

TABLE 5. EXPECTED SAMPLE SIZE AT EACH STUDY SITE

Cohort	Total sample size	Pakistan	Mexico	Chile	Argentina	Russia
Total	40000-54000	18000	15000	5000	8000	8000
Efficacy-Safety cohort	37000-51000	17400	13950	4650	7370	7630
Efficacy-extended safety cohort	2400	500	800	300	480	320
Efficacy-extended safety-immunogenicity cohort	400	50	150	50	100	50
Efficacy-extended safety-extended immunogenicity cohort	200	50	100	0	50	0

4.1 Inclusion Criteria

1. Adults of 18 years of age, and older.
2. Able and willing (in the Investigator's opinion) to comply with all study requirements.
3. Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner/personal doctor and access all medical records when relevant to study procedures.

4. Healthy adults, or stable-healthy adults who may have a pre-existing medical condition that does not meet any exclusion criteria. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment [4].
5. For females of childbearing potential only, willingness to practice continuous effective contraception (see glossary) for 30 days prior to enrollment in the study, for 90 days after receiving vaccination during the study, and have a negative pregnancy test on the day(s) of screening/ vaccination (Day 0).
6. Males participating in this study who are involved in heterosexual sexual activity must agree to practice adequate contraception (see glossary) and refrain from donating sperm for 90 days after receiving the study vaccination.
7. Agreement to refrain from blood donation during the study
8. Provide written informed consent

4.2 Exclusion Criteria

1. Participation in any other COVID-19 prophylactic drug trials for the duration of the study. *Note: Participation in COVID-19 treatment trials is allowed in the event of hospitalization due to COVID-19. The study team should be informed as soon as possible.*

2. Participation in SARS-CoV-2 serological surveys where participants are informed of their serostatus for the duration of the study.

   Note: Disclosure of serostatus post enrolment may accidentally unblind participants to group allocation. Participation in this trial can only be allowed if volunteers are kept blinded to their serology results from local/national serological surveys

3. Planned receipt of any vaccine (licensed or investigational), other than the study intervention, within 14 days before and after study vaccination

4. Prior receipt of an investigational or licensed vaccine likely to impact on the interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus or SARS vaccines)

5. Administration of immunoglobulins and/or any blood products within the three months prior to the planned administration of the vaccine candidate

6. Any confirmed or suspected immunosuppressive or immunodeficient state; positive HIV status; asplenia; recurrent severe infections and chronic use (more than 14 days) of immunosuppressant medication within the past 6 months. Topical steroids or short-term (course lasting ≤14 days) oral steroids are not an exclusion.

7. History of allergic disease or reactions likely to be exacerbated by any component of Ad5-nCoV

8. Any history of angioedema

9. Any history of anaphylaxis to any vaccine component
10. Pregnancy, lactation or willingness/intention to become pregnant within 90 days after receiving study vaccine
11. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
12. History of serious psychiatric condition likely to affect participation in the study
13. Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
14. Suspected or known current alcohol or drug dependency
15. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well-controlled comorbidities are allowed)
16. History of laboratory-confirmed COVID-19
17. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
18. Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data.

4.3 Recruitment

Participants will be recruited through invitations to persons in the study center's participant database (who have previously indicated their willingness to be contacted regarding future studies) by mail and email, advertising using local print and radio media, social media, e-mail, notification through the study sites' websites, through offices of local physicians, and in universities and health care settings. The numbers of persons who express interest in participating but are ineligible or declined participation, and reasons, will be recorded in the Screening Log.

5. STUDY PROCEDURES AND INTERVENTIONS

In-person visits will take place at selected local study sites in countries that are enrolled in the trial, as well as through electronic (text message) and telephone calls. These facilities will be authorized by the institution to continue to do research related to COVID-19 disease during the pandemic. Scheduling during the pandemic will be arranged to minimize any social contact except with study staff. Study staff will screen potential participants for respiratory or other COVID-19 symptoms over the phone and again upon the participant's arrival at the study center. Staff will wear medical masks at all times when interacting with participants to protect the

participant and themselves from the potential of virus transmission in an asymptomatic individual, according to local institutional policies. These institution-wide precautions are meant to minimize the likelihood of a COVID-19 outbreak at the clinical trial site putting participants and staff at-risk, and to preserve the integrity of the study. These procedures will remain in place as long as the host institutional polices require them; study policies will continue to change to align with the host institution's policies.

5.1 Study Intervention Descriptions for Efficacy-Safety Cohort

All participants will be subject to the following procedures:

- **Informed consent**
  The signed informed consent must be obtained before study participation. At each subsequent participant contact requiring an intervention (such as collection of a blood sample), the participant's consent will be verified.
- **Check inclusion and exclusion criteria**
  All inclusion and exclusion criteria will be checked at the screening in-person visit in all four cohorts.
- **Collect demographic data and participant contact information**
  Record demographic data such as date of birth, sex, gender, height, weight and race in the participant's EDC. Current email addresses and or phone numbers will be collected for each participant. It is important to have complete and accurate contact information for each participant as the majority of participant contacts will occur electronically. Contact information may also be used to remind participants of up-coming in-person visits
- **Medical history**
  Obtain the participant's medical history by interview and/or review of the participant's medical records and record any pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection in the EDC. This will include reviewing any health condition that may prevent the participant from enrolling in the study, such as an unstable health condition or known positive HIV status.
- **Check contraindications, warnings and precautions to injection**
  Contraindications, warnings and precautions to injection must be checked at the beginning of each injection visit.
- **Urine Pregnancy Test/Birth Control**
  Women of child-bearing age will be asked to perform a urine pregnancy test at Day 0. The result of the urine pregnancy test must be negative in order to proceed with vaccine administration. In addition, participants who are able to become pregnant or could impregnate a partner are required to have used approved contraception least 30 days prior to the study vaccination and for 90 days after the study vaccination
- **Screening conclusion**
  Participants will be deemed eligible to participate upon reviewing medical history and inclusion and exclusion criteria, this will occur prior to vaccination on Day 0.

- **Assess pre-injection vital signs (body temperature, blood pressure, pulse rate and respiratory rate)**
  The body temperature of all participants needs to be measured prior to any study product administration. Body temperature may be measured by any method (oral, axillary), but the preferred route for this study is the oral route. If the participant has a fever (fever is defined as temperature ≥ 38.0° C orally) on the day of injection, the injection visit will be rescheduled within 1 week.
- **Study group and treatment number allocation**
  The participant will be randomized to either the experimental or placebo group at the screening in-person visit. Each participant will also be assigned a treatment identification number for blinding purposes. The number of each administered treatments must be recorded in the EDC.
- **Baseline serology**
  Approximately 25 mL of whole blood will be collected from each participant at Day 0 and separated for serum. The serum will be aliquoted. The first aliquot will be used to measure for baseline antibodies against SARS-CoV-2 and against HIV in the central study laboratory. The results of antibody testing from baseline serum will not be used to determine eligibility for enrollment; instead, results will solely be used for analysis and comparison purposes. Presence of pre-existing SARS-CoV-2 antibodies found in baseline serum will be used for a stratified immunogenicity and efficacy sub-analysis. The presence of HIV antibodies will be tested in all participants in the central laboratory at the end of the study, in order to do a stratified analysis of participants with previously unrecognized HIV infection. Participants who have been enrolled and immunized and then subsequently are found to have a positive HIV test, will be counseled and continue to be followed in the study. All participants, including those with an unknown HIV status, will be monitored closely for any SAE and symptoms of illness. The second aliquot will be shipped from the central lab to the sponsor, where it will be stored as a back-up
- **Check and record prior medications and concomitant medication/injection**
  Prior medications and concomitant medication/injection must be checked and recorded in the EDC. Prior medications should include any medication taken by the participant within 14 days prior to screening. Participants will be asked to avoid over-the-counter medications such as antipyretics (e.g., acetaminophen) and anti-inflammatory medications (e.g., ibuprofen, naproxen) in the 12 hours before study vaccine receipt but will be allowed to take these over-the-counter medications as needed to treat fever or other adverse events after vaccination. Usage of these over-the-counter medications will be recorded as concomitant medications and linked to the adverse event collected as solicited or unsolicited events according to the symptom.
- **Check and record intercurrent medical conditions**
  Any medical conditions are recorded in the EDC.
- **Injection of study vaccine**

After completing all prerequisite procedures prior to injection, one dose of the assigned vaccine will be administered IM in the deltoid muscle of the non-dominant arm. If the investigator or delegate determines that the participant's health on the day of administration temporarily precludes administration, the visit will be rescheduled within 1week. There will be a 30-minute wait after each vaccination to monitor for any rare anaphylactic reaction.

- **Safety participant contacts**
  Every 4 weeks for 52 weeks there will be telephone calls (Weeks 4-52) to continuously collect any SAE and MAE data. Participants can report any AE they experience at any time during the study period but only SAE and MAE will be entered into the EDC. Safety participant contacts in this cohort will occur Day 0 (for 30 minutes post-vaccination), and Week 4, 8, 12, 16, 20, 24, 32, 36, 40, 44 and 48. The final safety participant contact will occur as an in-person visit on Week 52.
- **Efficacy participant contacts**
  All participants will have efficacy participant contacts weekly for 52 weeks following vaccination. There will be approximately 52 electronic efficacy participant contacts. All efficacy participant contacts will be email messages, although other electronic methods such as by phone, text message, the Internet are suitable, if preferred. Each participant contact needs to be recorded in the study electronic case report form. The purpose of these participant contacts is to serve as a reminder to participants to report any symptoms of illness they may be experiencing, regardless of severity. Any possible COVID-19 relevant symptoms will trigger laboratory testing for SARS-CoV-2 infection.

- **Illness participant contact visits (Confirmed or suspected infection during study)**
  Participants will be provided detailed instructions regarding the signs and symptoms of COVID-19 disease at each participant contact and will be instructed to seek medical attention and notify study staff should symptoms occur. Symptoms of interest please refer to 3.8 efficacy participate contact. During the observation period of the study, if any of these symptoms develop in a participant, he/she should immediately follow local procedures for care of suspected COVID-19 illness and contact the study team. Specimen collection for the study will follow the study illness visit algorithm (see Figure 2). The participant's nasopharyngeal/throat swab will be collected and tested for COVID-19 infection in either a local clinical or study site laboratory. If negative, the test will be repeated in 3 days. All attempts will be made to re-test positive samples in a national or regional reference laboratory in the study country. Repeat nasal/throat swabs will be taken every 2 days until a negative sample is obtained (if possible). A serum taken at the time of illness presentation and 2-3 weeks later will be collected for SARS-CoV-2 anti-N IgG antibodies to be performed in the study central laboratory for all subjects presented with suspected COVID-19 symptoms regardless of the result of PCR SARS-CoV-2. If a COVID-19 infection is found during the study, a case investigation will be undertaken according to locally recommended procedures. Participants who develop COVID-19 infection post-vaccination

will be carefully monitored for vaccine related disease enhancement in collaboration with their primary physician, who will be encouraged to obtain specimens in accordance with the Brighton Collaboration definition (Munoz, 2020). This monitoring may include testing for C-reactive protein (CRP), ferritin, and procalcitonin, biomarkers that have been associated with predicting more severe disease outcome in infected patients. Participants who develop COVID-19 disease will continue to be followed for other study outcomes by telephone while in isolation, and at the study center once recovered and released from isolation by public health officials.

- **Final serology**
  Participants in all four cohorts will have an in-person visit on Week 52. Approximately 25 mL of whole blood will be collected from each participant and separated for serum. The serum will be aliquoted. The first aliquot will measure antibodies against SARS-CoV-2, in the central study laboratory. The second aliquot will be shipped by the central lab to the sponsor, where it will be stored as a back-up. The one-year antibody levels measured against SARS-CoV-2 will be compared to the participant's baseline levels to evaluate the exploratory efficacy analysis against asymptomatic infection.

5.2 Study Intervention Descriptions for Efficacy-Extended Safety Cohort

All participants will be subject to the following procedures:

- **Informed consent**
  The signed informed consent must be obtained before study participation. At each subsequent participant contact requiring an intervention (such as collection of a blood sample), the participant's consent will be verified.
- **Check inclusion and exclusion criteria**
  All inclusion and exclusion criteria will be checked at the screening in-person visit in all four cohorts.
- **Collect demographic data and participant contact information**
  Record demographic data such as date of birth, sex, gender, height, weight and race in the participant's EDC. Current email addresses and or phone numbers will be collected for each participant. It is important to have complete and accurate contact information for each participant as the majority of participant contacts will occur electronically. Contact information may also be used to remind participants of up-coming in-person visits.
- **Medical history**
  Obtain the participant's medical history by interview and/or review of the participant's medical records and record any pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection in the EDC. This will include reviewing any health condition that may prevent the participant from enrolling in the study, such as an unstable health condition or known positive HIV status.

- **Check contraindications, warnings and precautions to injection**
  Contraindications, warnings and precautions to injection must be checked prior to administering the study injection.
- **Urine Pregnancy Test/Birth Control**
  Women of child-bearing age will be asked to perform a urine pregnancy test at Day 0. The result of the urine pregnancy test must be negative in order to proceed with vaccine administration. In addition, participants who are able to become pregnant or could impregnate a partner are required to have used approved contraception least 30 days prior to the study vaccination and for 90 days after the study vaccination
- **Screening conclusion**
  Participants will be deemed eligible to participate upon reviewing medical history and inclusion and exclusion criteria, this will occur prior to vaccination on Day 0.
- **Assess pre-injection vital signs (body temperature, blood pressure, pulse rate and respiratory rate)**
  The body temperature of all participants needs to be measured prior to any study product administration. Body temperature may be measured by any method (oral, axillary), but the preferred route for this study is the oral route. If the participant has a fever (fever is defined as temperature ≥ 38.0° C orally) on the day of injection, the injection visit will be rescheduled within 1 week.
- **Study group and treatment number allocation**
  The participant will be randomized to either the experimental or placebo group at the screening in-person visit. Each participant will also be assigned a treatment identification number for blinding purposes. The number of each administered treatments must be recorded in the EDC.
- **Baseline serology**
  Approximately 25 mL of whole blood will be collected from each participant at Day 0 and separated for serum. The serum will be aliquoted. The first aliquot will be used to measure for baseline antibodies against SARS-CoV-2 and against HIV in the central study laboratory. The results of antibody testing from baseline serum will not be used to determine eligibility for enrollment; instead, results will solely be used for analysis and comparison purposes. Presence of pre-existing SARS-CoV-2 antibodies found in baseline serum will be used for a stratified immunogenicity and efficacy sub-analysis. The presence of HIV antibodies will be tested in all participants in the central laboratory at the end of the study, in order to do a stratified analysis of participants with previously unrecognized HIV infection. Participants who have been enrolled and immunized and then subsequently are found to have a positive HIV test, will be counseled and continue to be followed in the study. All participants, including those with an unknown HIV status, will be monitored closely for any SAE and symptoms of illness. The second aliquot will be shipped from the central lab to the sponsor, where it will be stored as a back-up
- **Check and record prior medications and concomitant medication/injection**

Prior medications and concomitant medication/injection must be checked and recorded in the EDC. Prior medications should include any medication taken by the participant within 14 days prior to screening. Participants will be asked to avoid over-the-counter medications such as antipyretics (e.g., acetaminophen) and anti-inflammatory medications (e.g., ibuprofen, naproxen) in the 12 hours before study vaccine receipt but will be allowed to take these over-the-counter medications as needed to treat fever or other adverse events after vaccination. Usage of these over-the-counter medications will be recorded as concomitant medications and linked to the adverse event collected as solicited or unsolicited events according to the symptom.

- **Check and record intercurrent medical conditions**
  Any medical conditions are recorded in the EDC.
- **Injection of study vaccine**
  After completing all prerequisite procedures prior to injection, one dose of the assigned vaccine will be administered IM in the deltoid muscle of the non-dominant arm. If the investigator or delegate determines that the participant's health on the day of administration temporarily precludes administration, the visit will be rescheduled within 1 week. There will be a 30-minute wait after each vaccination to monitor for any rare anaphylactic reaction.
- **E-Diary and Diary Cards**
  Participants in this cohort will be provided with access to an e-diary or a paper diary card and a thermometer, and instructions about how to use them. The use of an e-diary instead of a paper diary card is dependent on the study site. Participants will be asked to record solicited AE for 7 days after receiving the vaccination, and unsolicited AE for 28 days, in their diary. The completed e-diary and diary cards will be reviewed, and data collected at the 28-Day safety in-person visit. Non completion of the e-diary or diary cards will be investigated with the participant through telephone call(s) or any other convenient procedure. All data collected from the e-diary and diary cards will be uploaded into the EDC.
- **Safety participant contacts**
  Every 4 weeks for 52 weeks there will be telephone calls (Week 4-52) to continuously collect any SAE and MAE data. Participants can report any AE they experience at any time during the study period but only SAE and MAE will be entered into the EDC. Safety participant contacts will occur Day 0 (for 30 minutes post-vaccination), Day 28 (to collect the diary), Month 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12. Safety participant contacts will be a telephone call from Weeks 4-52, and as an in-person visit Month 1 (Day 28) and 12.
- **Efficacy participant contacts**
  All participants will have efficacy participant contacts weekly for 52 weeks following vaccination. There will be approximately 52 electronic efficacy participant contacts. All efficacy participant contacts will be text messages, although other electronic method such as by phone, e-mail, the Internet is suitable, if preferred. Each participant contact needs to be recorded in the study electronic case report form. The purpose of these participant contacts is to serve as a reminder to participants to report any symptoms of illness they may be

experiencing, regardless of severity. Any possible COVID-19 relevant symptoms will trigger laboratory testing for SARS-CoV-2 infection.

- **Illness participant contact visits (Confirmed or suspected infection during study)**
  Participants will be provided detailed instructions regarding the signs and symptoms of COVID-19 disease at each participant contact and will be instructed to seek medical attention and notify study staff should symptoms occur. Symptoms of interest please refer to 3.8 efficacy participate contact. During the observation period of the study, if any of these symptoms develop in a participant, he/she should immediately follow local procedures for care of suspected COVID-19 illness and contact the study team. Specimen collection for the study will follow the study illness visit algorithm (see Figure 2). The participant's nasopharyngeal/throat swab will be collected and tested for COVID-19 infection in either a local clinical or study site laboratory. If negative, the test will be repeated in 3 days. All attempts will be made to re-test positive samples in a national or regional reference laboratory in the study country. Repeat nasal/throat swabs will be taken every 2 days until a negative sample is obtained (if possible). A serum taken at the time of illness presentation and 2-3 weeks later will be collected for SARS-CoV-2 anti-N IgG antibodies to be performed in the study central laboratory. If a COVID-19 infection is found during the study, a case investigation will be undertaken according to locally recommended procedures. Participants who develop COVID-19 infection post-vaccination will be carefully monitored for vaccine related disease enhancement in collaboration with their primary physician who will be encouraged to obtain specimens in accordance with the Brighton Collaboration definition (Munoz, 2020). This monitoring may include testing for C-reactive protein (CRP), ferritin, and procalcitonin, biomarkers that have been associated with predicting more severe disease outcome in infected patients. Participants who develop COVID-19 disease will continue to be followed for other study outcomes by telephone while in isolation, and at the study center once recovered and released from isolation by public health officials.
- **Final serology**
  Participants in all four cohorts will have an in-person visit on Week 52. Approximately 25 mL of whole blood will be collected from each participant and separated for serum. The serum will be aliquoted. The first aliquot will measure antibodies against SARS-CoV-2, in the central study laboratory. The second aliquot will be shipped by the central study lab to the sponsor, where it will be stored as a back-up. The one-year antibody levels measured against SARS-CoV-2 will be compared to the participant's baseline levels to evaluate the exploratory efficacy analysis against asymptomatic infection.

5.3 Study Intervention Descriptions for Efficacy-Extended Safety-Immunogenicity Cohort

All participants will be subject to the following procedures:

- **Informed consent**
  The signed informed consent must be obtained before study participation. At each

subsequent participant contact requiring an intervention (such as collection of a blood sample), the participant's consent will be verified.

- **Check inclusion and exclusion criteria**
  All inclusion and exclusion criteria will be checked at the screening in-person visit in all four cohorts. In the efficacy-extended safety-immunogenicity and efficacy-extended safety-extended immunogenicity cohorts, inclusion and exclusion criteria will be reviewed at each in-person visit.
- **Collect demographic data and participant contact information**
  Record demographic data such as date of birth, sex, gender, height, weight and race in the participant's EDC. Current email addresses and or phone numbers will be collected for each participant. It is important to have complete and accurate contact information for each participant as the majority of participant contacts will occur electronically. Contact information may also be used to remind participants of up-coming in-person visits.
- **Medical history**
  Obtain the participant's medical history by interview and/or review of the participant's medical records and record any pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection in the EDC. This will include reviewing any health condition that may prevent the participant from enrolling in the study, such as an unstable health condition or known positive HIV status.
- **Baseline serology**
  Approximately 25 mL of whole blood will be collected from each participant at Day 0 and separated for serum. The serum will be aliquoted. The first aliquot will be used to measure for baseline antibodies against SARS-CoV-2 and against HIV in the central study laboratory. The results of antibody testing from baseline serum will not be used to determine eligibility for enrollment; instead, results will solely be used for analysis and comparison purposes. Presence of pre-existing SARS-CoV-2 antibodies found in baseline serum will be used for a stratified immunogenicity and efficacy sub-analysis. The presence of HIV antibodies will be tested in all participants in the central laboratory at the end of the study, in order to do a stratified analysis of participants with previously unrecognized HIV infection. Participants who have been enrolled and immunized and then subsequently are found to have a positive HIV test, will be counseled and continue to be followed in the study. All participants, including those with an unknown HIV status, will be monitored closely for any SAE and symptoms of illness. The second aliquot will be shipped from the central lab to the sponsor, where it will be stored as a back-up.
- **Check contraindications, warnings and precautions to injection**
  Contraindications, warnings and precautions to injection must be checked prior to administering the study injection.
- **Urine Pregnancy Test/Birth Control**
  Women of child-bearing age will be asked to perform a urine pregnancy test at Day 0. The result of the urine pregnancy test must be negative in order to proceed with vaccine

administration. In addition, participants who are able to become pregnant or could impregnate a partner are required to have used approved contraception least 30 days prior to the study vaccination and for 90 days after the study vaccination

- **Screening conclusion**
  Participants will be deemed eligible to participate upon reviewing medical history and inclusion and exclusion criteria, this will occur prior to vaccination on Day 0.
- **Assess pre-injection vital signs (body temperature, blood pressure, pulse rate and respiratory rate)**
  The body temperature of all participants needs to be measured prior to any study product administration. Body temperature may be measured by any method (oral, axillary), but the preferred route for this study is the oral route. If the participant has a fever (fever is defined as temperature ≥ 38.0° C orally) on the day of injection, the injection visit will be rescheduled within 1 week.
- **Study group and treatment number allocation**
  The participant will be randomized to either the experimental or placebo group at the screening in-person visit. Each participant will also be assigned a treatment identification number for blinding purposes. The number of each administered treatments must be recorded in the EDC
- **Check and record prior medications and concomitant medication/injection**
  Prior medications and concomitant medication/injection must be checked and recorded in the EDC. Prior medications should include any medication taken by the participant within 14 days prior to screening. Participants will be asked to avoid over-the-counter medications such as antipyretics (e.g., acetaminophen) and anti-inflammatory medications (e.g., ibuprofen, naproxen) in the 12 hours before study vaccine receipt but will be allowed to take these over-the-counter medications as needed to treat fever or other adverse events after vaccination. Usage of these over-the-counter medications will be recorded as concomitant medications and linked to the adverse event collected as solicited or unsolicited events according to the symptom.
- **Check and record intercurrent medical conditions**
  Any medical conditions are recorded in the EDC.
- **Injection of study vaccine**
  After completing all prerequisite procedures prior to injection, one dose of the assigned vaccine will be administered IM in the deltoid muscle of the non-dominant arm. If the investigator or delegate determines that the participant's health on the day of administration temporarily precludes administration, the visit will be rescheduled within 1 week. There will be a 30-minute wait after each vaccination to monitor for any rare anaphylactic reaction.
- **E-diary and Diary Cards**
  Participants in this cohort will be provided with access to an e-diary or a paper diary card and a thermometer, and instructions about how to use them. The use of an e-diary instead of a paper diary card is dependent on the study site. Participants will be asked to record

solicited AE for 7 days after receiving the vaccination, and unsolicited AE for 28 days, in their diary. The completed e-diary and diary cards will be reviewed, and data collected at the 28-Day safety in-person visit. Non completion of the e-diary or diary cards will be investigated with the participant through telephone call(s) or any other convenient procedure. All data collected from the e-diary and diary cards will be uploaded into the EDC.

- **Safety participant contacts**
  Every 4 weeks for 52 weeks there will be telephone calls (Week 8-52) to continuously collect any SAE and MAE data. Participants can report any AE they experience at any time during the study period but only SAE and MAE will be entered into the EDC. Safety participant contacts will occur Day 0 (for 30 minutes post-vaccination), Day 28 (to collect the diary), Month 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12. Safety participant contacts will be a telephone call from Week 8, 12, 16, 20, 32, 36, 40, 44 and 48, and as an in-person visit Month 1 (Day 28), 6, and 12.
- **Efficacy participant contacts**
  All participants will have efficacy participant contacts weekly for 52 weeks following vaccination. There will be approximately 52 electronic efficacy participant contacts. All efficacy participant contacts will be text messages, although other electronic method such as by phone, e-email, the Internet is suitable, if preferred. Each participant contact needs to be recorded in the study electronic case report form. The purpose of these participant contacts is to serve as a reminder to participants to report any symptoms of illness they may be experiencing, regardless of severity. Any possible COVID-19 relevant symptoms will trigger laboratory testing for SARS-CoV-2 infection.
- **Illness participant contact visits (Confirmed or suspected infection during study)**
  Participants will be provided detailed instructions regarding the signs and symptoms of COVID-19 disease at each participant contact and will be instructed to seek medical attention and notify study staff should symptoms occur. Symptoms of interest please refer to 3.8 efficacy participate contact. During the observation period of the study, if any of these symptoms develop in a participant, he/she should immediately follow local procedures for care of suspected COVID-19 illness and contact the study team. Specimen collection for the study will follow the study illness visit algorithm (see Figure 2). The participant's nasopharyngeal/throat swab will be collected and tested for COVID-19 infection in either a local clinical or study site laboratory. If negative, the test will be repeated in 3 days. All attempts will be made to re-test positive samples in a national or regional reference laboratory in the study country. Repeat nasal/throat swabs will be taken every 2 days until a negative sample is obtained (if possible). A serum taken at the time of illness presentation and 2-3 weeks later will be collected for SARS-CoV-2 anti-N IgG antibodies to be performed in the study central laboratory. If a COVID-19 infection is found during the study, a case investigation will be undertaken according to locally recommended procedures. Participants who develop COVID-19 infection post-vaccination will be carefully monitored for vaccine related disease enhancement in collaboration with their primary physician who will be

encouraged to obtain specimens in accordance with the Brighton Collaboration definition (Munoz, 2020). This monitoring may include testing for C-reactive protein (CRP), ferritin, and procalcitonin, biomarkers that have been associated with predicting more severe disease outcome in infected patients. Participants who develop COVID-19 disease will continue to be followed for other study outcomes by telephone while in isolation, and at the study center once recovered and released from isolation by public health officials.

- **Immunogenicity in-person visit**
    - **Blood collection for ELISA Antibody measurement**
      Participants in this cohort will donate approximately 25mL of serum on Day 28 and Week 24, in addition to the serum collected on baseline (Day 0) and Week 52, as described above. These in-person visits will occur at participants' local study site. A baseline antibody titer against SARS-CoV-2 will be established from the blood sample collected on Day 0, as outlined in the "baseline serology" description. In addition, these samples will also be used to evaluate for additional immunogenicity objectives. Serum collected from this cohort will be analyzed for the seroconversion rate of S-RBD IgG antibody, GMT of S-RBD IgG antibody, GMI of S-RBD IgG antibody, seroconversion rate of pseudo-virus neutralizing antibody, GMT of pseudo-virus neutralizing antibody, and the GMI of pseudo-virus neutralizing antibody at Day 28, Week 24, and Week52. The second aliquot will be shipped by the central lab to the sponsor, where it will be stored as a back-up
- **Final serology**
  Participants in all four cohorts will have an in-person visit on Week 52. Approximately 25 mL of whole blood will be collected from each participant and separated for serum into two aliquots. The first aliquot will measure antibodies against SARS-CoV-2, in the central study laboratory. The second aliquot will be shipped by the central lab to the sponsor, where it will be stored as a back-up. The one-year antibody levels measured against SARS-CoV-2 will be compared to the participant's baseline levels to evaluate the exploratory efficacy analysis against asymptomatic infection.

The visit window for immunogenicity in-person visits of Day28 is +7 days.
The visit window for immunogenicity in-person visits of Week 24, and Week 52 is + 14 days.

5.4 Study Intervention Descriptions for Efficacy-Extended Safety-Extended Immunogenicity Cohort

All participants will be subject to the following procedures:

- **Informed consent**
  The signed informed consent must be obtained before study participation. At each subsequent participant contact requiring an intervention (such as collection of a blood sample), the participant's consent will be verified.

- **Check inclusion and exclusion criteria**
  All inclusion and exclusion criteria will be checked at the screening in-person visit in all four cohorts. In the efficacy-extended safety-immunogenicity and efficacy-extended safety-extended immunogenicity cohorts, inclusion and exclusion criteria will be reviewed at each in-person visit.
- **Collect demographic data and participant contact information**
  Record demographic data such as date of birth, sex, gender, height, weight and race in the participant's EDC. Current email addresses and or phone numbers will be collected for each participant. It is important to have complete and accurate contact information for each participant as the majority of participant contacts will occur electronically. Contact information may also be used to remind participants of up-coming in-person visits.
- **Medical history**
  Obtain the participant's medical history by interview and/or review of the participant's medical records and record any pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection in the EDC. This will include reviewing any health condition that may prevent the participant from enrolling in the study, such as an unstable health condition or known positive HIV status.
- **Baseline serology**
  Approximately 25 mL of whole blood will be collected from each participant at Day 0 and separated for serum. The serum will be aliquoted. The first aliquot will be used to measure for baseline antibodies against SARS-CoV-2 and against HIV in the central study laboratory. The results of antibody testing from baseline serum will not be used to determine eligibility for enrollment; instead, results will solely be used for analysis and comparison purposes. Presence of pre-existing SARS-CoV-2 antibodies found in baseline serum will be used for a stratified immunogenicity and efficacy sub-analysis. The presence of HIV antibodies will be tested in all participants in the central laboratory at the end of the study, in order to do a stratified analysis of participants with previously unrecognized HIV infection. Participants who have been enrolled and immunized and then subsequently are found to have a positive HIV test, will be counseled and continue to be followed in the study. All participants, including those with an unknown HIV status, will be monitored closely for any SAE and symptoms of illness. The second aliquot will be shipped from the central lab to the sponsor, where it will be stored as a back-up.
- **Check contraindications, warnings and precautions to injection**
  Contraindications, warnings and precautions to injection must be checked at the beginning of each injection visit.
- **Urine Pregnancy Test/Birth Control**
  Women of child-bearing age will be asked to perform a urine pregnancy test at Day 0. The result of the urine pregnancy test must be negative in order to proceed with vaccine administration. In addition, participants who are able to become pregnant or could

impregnate a partner are required to have used approved contraception least 30 days prior to the study vaccination and for 90 days after the study vaccination

- **Assess pre-injection vital signs (body temperature, blood pressure, pulse rate and respiratory rate)**
  The body temperature of all participants needs to be measured prior to any study product administration. Body temperature may be measured by any method (oral, axillary), but the preferred route for this study is the oral route. If the participant has fever (fever is defined as temperature ≥ 38.0° C orally) on the day of injection, the injection visit will be rescheduled within 1 week.
- **Study group and treatment number allocation**
  Study group and treatment number will be allocated within each step. The number of each administered treatment must be recorded in the EDC.
- **Screening conclusion**
  Participants will be deemed eligible to participate upon reviewing medical history and inclusion and exclusion criteria, this will occur prior to vaccination on Day 0.
- **Check and record prior medications and concomitant medication/injection**
  Prior medications and concomitant medication/injection must be checked and recorded in the EDC. Prior medications should include any medication taken by the participant within 14 days prior to screening. Participants will be asked to avoid over-the-counter medications such as antipyretics (e.g., acetaminophen) and anti-inflammatory medications (e.g., ibuprofen, naproxen) in the 12 hours before study vaccine receipt but will be allowed to take these over-the-counter medications as needed to treat fever or other adverse events after vaccination. Usage of these over-the-counter medications will be recorded as concomitant medications and linked to the adverse event collected as solicited or unsolicited events according to the symptom.
- **Check and record intercurrent medical conditions**
  Any medical conditions that have arisen are recorded in the EDC.
- **Injection of study vaccine**
  After completing all prerequisite procedures prior to injection, one dose of the assigned vaccine will be administered IM in the deltoid muscle of the non-dominant arm. If the investigator or delegate determines that the participant's health on the day of administration temporarily precludes administration, the visit will be rescheduled within 1 week. There will be a 30-minute wait after each vaccination to monitor for any rare anaphylactic reaction.

- **Safety participant contacts**
  Every 4 weeks there will be telephone calls (Weeks 8-52) to continuously collect any SAE and MAE data. Participants can report any AE they experience at any time during the study period but only SAE and MAE will be entered into the EDC. Safety participant contacts will occur Day 0 (for 30 minutes post-vaccination), Day 28 (to collect the diary), Month 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12. Safety participant contacts will be a telephone call from Months 2,

3, 4, 5, 7, 8, 9, 10 and 11, and as an in-person visit Month 1 (Day 28), Week 24, and Week 52.

- **E-diary and Diary Cards**
  Participants in this cohort will be provided with access to an e-diary or a paper diary card and a thermometer, and instructions about how to use them. The use of an e-diary instead of a paper diary card is dependent on the study site. Participants will be asked to record solicited AE for 7 days after receiving the vaccination, and unsolicited AE for 28 days, in their diary. The completed e-diary and diary cards will be reviewed, and data collected at the 28-Day safety in-person visit. Non completion of the e-diary or diary cards will be investigated with the participant through telephone call(s) or any other convenient procedure. All data collected from the e-diary and diary cards will be uploaded into the EDC.
- **Efficacy participant contacts**
  All participants will have efficacy participant contacts weekly for 52 weeks following vaccination. There will be approximately 52 electronic efficacy participant contacts. All efficacy participant contacts will be text messages, although other electronic method such as by phone, e-email, the Internet is suitable, if preferred. Each participant contact needs to be recorded in the study electronic case report form. The purpose of these participant contacts is to serve as a reminder to participants to report any symptoms of illness they may be experiencing, regardless of severity. Any possible COVID-19 relevant symptoms will trigger laboratory testing for SARS-CoV-2 infection.
- **Illness participant contact visits (Confirmed or suspected infection during study)**
  Participants will be provided detailed instructions regarding the signs and symptoms of COVID-19 disease at each participant contact and will be instructed to seek medical attention and notify study staff should symptoms occur. Symptoms of interest please refer to 3.8 efficacy participate contact. During the observation period of the study, if any of these symptoms develop in a participant, he/she should immediately follow local procedures for care of suspected COVID-19 illness and contact the study team. Specimen collection for the study will follow the study illness visit algorithm (see Figure 2). The participant's nasopharyngeal/throat swab will be collected and tested for COVID-19 infection in either a local clinical or study site laboratory. If negative, the test will be repeated in 3 days. All attempts will be made to re-test positive samples in a national or regional reference laboratory in the study country. Repeat nasal/throat swabs will be taken every 2 days until a negative sample is obtained (if possible). A serum taken at the time of illness presentation and 2-3 weeks later will be collected for SARS-CoV-2 anti-N IgG antibodies to be performed in the study central laboratory for all subjects presented with suspected COVID-19 symptom, regardless on the outcome of PCR SARS-CoV-2 test. If a COVID-19 infection is found during the study, a case investigation will be undertaken according to locally recommended procedures. Participants who develop COVID-19 infection post-vaccination will be carefully monitored for vaccine related disease enhancement in collaboration with their primary physician who will be encouraged to obtain specimens in accordance with the

Brighton Collaboration definition (Munoz, 2020). This monitoring may include testing for C-reactive protein (CRP), ferritin, and procalcitonin, biomarkers that have been associated with predicting more severe disease outcome in infected patients. Repeat nasal/throat swabs will be taken every 2 days until a negative sample is obtained. Participants who develop COVID-19 disease will continue to be followed for other study outcomes by telephone while in isolation, and at the study center once recovered and released from isolation by public health officials.

- **Immunogenicity in-person visit**
  - **Blood collection for ELISA Antibody measurement**
  - Participants in this cohort will donate approximately 25mL of whole blood on Day 28 and Week 24, in addition to the whole blood collected on baseline (Day 0) and Week 52, as described above. Whole blood will be separated into serum, and then aliquoted. These in-person visits will occur at participants' local study site. A baseline antibody titer against SARS-CoV-2 will be established from the blood sample collected on Day 0, as outlined in the "baseline serology" description. In addition, these samples will also be used to evaluate for additional immunogenicity objectives. Serum collected from this cohort will be analyzed for the seroconversion rate of S-RBD IgG antibody, GMT of S-RBD IgG antibody, GMI of S-RBD IgG antibody, seroconversion rate of pseudo-virus neutralizing antibody, GMT of pseudo-virus neutralizing antibody, and the GMI of pseudo-virus neutralizing antibody at Day 28, Week 24, and Week 52. The second aliquot will be shipped by the central lab to the sponsor, where it will be stored as a back-up.
  - **Blood collection for ELISpot and ICS measurement**
    Approximately 30mL of whole blood will be collected from participants in the efficacy-extended safety-extended immunogenicity cohort, in addition to the 25mL being collected for ELISA antibody analysis. Collections will occur on Day 0 (baseline), just prior to vaccination, Day 28, and at 24- and 52-weeks post-vaccination. Blood collected at these visits will be used to evaluate the positive rate and level of IFN-γ measured by ELISpot, and the positive rate and level of IL-2, IL-4, IL-13, and IFN-γ measured by ICS on Day 28 and Weeks 24 and 52 after vaccination. PBMC will be shipped on dry ice to the central laboratory.
- **Final serology**
  Participants in all four cohorts will have an in-person visit on Month 12. Approximately 25 mL of whole blood will be collected from each participant and separated for serum into two aliquots. The first aliquot will measure antibodies against SARS-CoV-2, in the central study laboratory. The second aliquot will be shipped by the central lab to the sponsor, where it will be stored as a back-up. The one-year antibody levels measured against SARS-CoV-2 will be compared to the participant's baseline levels to evaluate the exploratory efficacy analysis against asymptomatic infection.

The visit window for immunogenicity in-person visits of Day28 is +7 days.
The visit window for immunogenicity in-person visits of Week 24, and Week 52 is + 14 days

5.5 Study conclusion

Upon study conclusion (52 weeks post-vaccination), the investigators will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the EDC.

Participants who received placebo will be offered the candidate vaccine once the vaccine has been authorized for use in their country.

6. STUDY PRODUCT AND ADMINISTRATION

6.1 Description of Study Product

Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector). This vaccine, Ad5-nCoV, is a replication-defective recombinant human type 5 adenovirus expressing novel coronavirus S protein, which is produced by viral amplification in HEK293SF-3F6 cells, purification and formulation with addition of proper excipients. The product is used for prevention from infection caused by novel coronavirus.

Active Ingredients:	Replication-defective recombinant human type 5 adenovirus expressing S protein of novel coronavirus
Excipients:	Mannitol, sucrose, sodium chloride, magnesium chloride, polysorbate 80, HEPES, and glycerin
Packaging:	The vaccine is contained in a prefilled syringe
Specification:	0.5 mL/syringe
Dosage：	5×10^{10}vp ($\geq$4 x 10^{10} vp)
Shelf Life:	Tentatively 24 months
Storage:	This vaccine should be stored and transported at 2-8℃.
Administration:	Intramuscular injection in the deltoid muscle of the upper arm.
Schedule:	A single-dose schedule is planned. A second dose in all or some age cohorts may be made in response to new data from ongoing phase I/II clinical trials according to the adaptive design.
Manufacturer:	CanSino Biologics Inc. 185 South Ave., TEDA West District, Tianjin, China Postal code: 300462

Tel: 86-022-58213600
Fax: 86-022-58213677

Website: www.cansinotech.com

Developers: CanSino Biologics Inc.
Beijing Institute of Biotechnology

Contraindications to the Study Vaccine

(1) Allergic reaction to any component of this vaccine.
(2) Acute illness, acute phase of chronic disease, and fever.
(3) Pregnant and lactating women.
(4) People with thrombocytopenia or hemorrhagic diseases, immune-suppressive therapy or immune dysfunction, and uncontrolled seizure disorder and other progressive neurological disorders

Warnings and Precautions

1. This vaccine is strictly prohibited to be administered by intravascular injection.
2. Epinephrine and other drugs as well as equipment should be in place when the vaccine is used, in case emergency treatment of severe allergic reactions will be needed. Those who are immunized with this vaccine should be observed for at least 30 minutes at the site.
3. As with all vaccines, this vaccine may not produce 100% protection in the vaccinated population.
4. The vaccine must be stored in the place not accessible by children.
5. The vaccine should be shaken before injection. It should not be used under following circumstances: presence of foreign objects, cracked vaccine syringe, unclear label or expired, or any other abnormal appearance of the vaccine.
6. No disinfectant in contact with the vaccine when injection.

6.2 Description of Control Product

The placebo contains the same excipients except the vaccine antigens and it will appear identical to Ad5-nCoV vaccine, and is manufactured and tested by CanSino Biologics Inc. The placebo is contained in a prefilled syringe, with a volume of 0.5 mL/ syringe.

6.3. Product Oversight

Product accountability
A product accountability log will be maintained by study staff to document the number of ssyringes of product received and the disposition of each dose.

Replacement doses
Replacements will be from the study stock.

Return of Unused Products
Following verification of product accountability, all empty syringes will be destroyed as per site policy. At the end of the study, all unused clinical trial vaccine material will be returned to the sponsor or disposed of according to the site's standard operating procedure.

Dosage and administration of study products by the study nurse
A study nurse at each clinical site will be responsible for the administration of the IM vaccine into the patient's deltoid muscle. Because the candidate vaccine and placebo will both come in prefilled 0.5mL syringes and look identical, the study nurse does not need to be unblinded. Participants will not be told which study product they are receiving. Products will be administration according to the prompts in the IWRS system.

Contraindications to administration of the product

The following events constitute contraindications to administration of the study products at that point in time. If any contraindication is present at the time scheduled for injection, the participant may be injected at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator.

- Acute disease and/or fever at the time of administration.
- Fever is defined as temperature ≥ 38.0°C, taken orally
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered the product.

Concomitant medications/products and concomitant administration

At each participant contact over the phone or in-person, the investigator should question the participant about any medication/product taken and injection received by the participant.

Recording of prior and concomitant medications/products and concomitant administration

The following prior and concomitant medications/products/vaccines must be recorded in the EDC if administered during the indicated recording period:

- All concomitant medications/products, except vitamins and dietary supplements, administered from 14 days prior to screening up to 28 days following any dose of study product.
- Any concomitant vaccination administered in the period starting from screening up to study end.

- Prophylactic medication (*i.e.* medication administered in the absence of ANY symptom and in anticipation of a reaction to the injection). *E.g.* an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring.

- Any concomitant medication/product/vaccine relevant to a SAE* or administered at any time during the study period for the treatment of a SAE*, or administered at any time during the study for treatment of an adverse event leading to study termination, or treatment of an adverse event requiring a medically attended visit.

**SAEs that are required to be reported per protocol.*

Concomitant medications/products/vaccines that may lead to the elimination of a participant from according-to-protocol (ATP) analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the according-to-protocol (ATP) analysis:

- Any investigational or non-registered product (drug or vaccine) other than the study product(s) used during the study period.
- A vaccine not foreseen by the study protocol administered during the period starting from 14 days before injection and ending 14 days after a study vaccine injection. It should be noted that in case an emergency mass vaccination for a unforeseen public health threat other than COVID-19 is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is authorized by the regulatory authority and used according to its package insert and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunosuppressants or other immune-modifying drugs administered chronically (*i.e.* more than 14 days) during the study period (for corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent). Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drug administered at any time during the study period (*e.g.* infliximab).
- Immunoglobulins and/or any blood products administered during the study period.

Intercurrent medical conditions that may lead to elimination of a participant from ATP analyses

At each participant contact subsequent to the injection visit, it must be verified if the participant has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the EDC.

Participants may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (*e.g.* confirmed influenza infection) or if they become diagnosed with an immunological disorder.

7. SAFETY

A primary objective of this study focuses on the tolerability and safety of receiving one dose of 5×10^{10}vp Ad5-nCoV vaccine. This will be measured by the incidence of SAE and MAE within 52 weeks of receiving the vaccine.

A secondary outcome is to monitor for any solicited AE (*local* injection site reactions and *general* reactions within the seven days following vaccination) and unsolicited AE within 28 days after vaccination, in approximately 3000 participants in the efficacy-extended safety, efficacy-extended safety-immunogenicity, or efficacy-extended safety-extended immunogenicity cohorts.

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE, MAE, or SAE as provided in this protocol. Each participant will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

Table 6. Adverse Event Reporting:

Cohorts	**30 min observation**	**Day 0-7**	**Day 8-29**	**Beyond day 29 until week 52**
Efficacy-safety cohort	Post injection AE or SAE only	SAE and MAE only	SAE and MAE only	SAE and MAE only
Efficacy-extended safety cohort	Post injection AE or SAE only	Solicited AEs and unsolicited AEs SAE and MAE	Any unsolicited AE only SAE and MAE	SAE and MAE only
Efficacy-extended safety-immunogenicity cohort	Post injection AE or SAE only	Solicited AE and unsolicited AEs SAE and MAE	Any unsolicited AE only SAE and MAE	SAE and MAE only
Efficacy-extended safety-extended	Post injection AE or SAE only	Solicited AEs and unsolicited AEs SAE and MAE	Any unsolicited AE only SAE and MAE	SAE and MAE only

immunogenicity cohort				

7.1 Definitions of an adverse event

An **AE** is "an untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product." A medical attended AE (MAE) is an AE that requires a visit with the healthcare system. A serious AE (SAE) is an untoward medical occurrence that results in death, is life-threatening (that is, there was a risk of death at the time of the event), requires hospitalization or prolongation of existing hospitalization occurs, results in disability/incapacity, or is a congenital anomaly/birth defect in the offspring of a study subject.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with product administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described below.

All other AEs will be recorded as unsolicited AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection. These events will be recorded in the medical history.

Solicited adverse events

A ***solicited*** **adverse event** (AE) is a pre-specified outcome that the participant is asked to record as present or not, and if present, to apply an intensity rating. Solicited AE are collected daily from Days 0 to 7 following administration of the study vaccine. An *unsolicited* event is one that the participant identifies when asked in a non-leading manner if there have been any changes in their health since the last participant contact. Unsolicited AE are collected during participant contacts in the extended safety cohorts.

Solicited AEs (Solicited local (injection-site) and general AEs) occurring during the 7-day participant contact period after injection will be recorded.

Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

- Pain at injection site
- Redness at injection site
- Swelling at injection site

Solicited general adverse events

The following general AEs will be solicited:

- Drowsiness
- Fever
- Headache
- Nausea
- Diarrhea
- Vomiting
- Generalized muscle aches

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the EDC.

Definition of a serious adverse event

An SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

Note: In general, hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity,

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Congenital anomaly/birth defects,

Note: Medical judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, congenital anomaly/birth defects, blood dyscrasias, or convulsions that do not result in hospitalisation.

Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Although routine clinical laboratory monitoring is not a part of this phase III trial, a participant may undergo laboratory testing for other reasons as part of their normal medical care. In absence

of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology,) or other abnormal assessments (e.g. physical examination findings) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE. Stable and or chronic health conditions that were present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, abnormal laboratory findings associated with existing health condition, unless judged by the investigator as more severe than expected for the participant's condition, will not be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

7.2 Detection of adverse events

All participants will be instructed on the recognition of symptoms and signs by the study staff. Monitoring for any signs or symptoms of COVID-19 is instrumental in evaluating the efficacy of the candidate vaccine. All participants will be monitored for the incidence of SAE and MAE up to 52 weeks after receiving the vaccination, via a phone call every 4 weeks. Participants will be instructed to contact study staff by phone (24 hours a day), if a MAE or SAE occurs.

Within the efficacy-extended safety cohort, efficacy-extended safety-immunogenicity, and efficacy-extended safety-extended immunogenicity cohorts, 3,000 participants will be monitored for incidence of local and systemic AE, in addition to monitoring for SAE. These participants will be instructed on how to take their temperature orally, as well as to record any symptoms in their e-diary or diary card for 28 days after receiving the vaccination. A thermometer and given access to an e-diary or a paper diary card to record solicited AE from Day 0-7 and unsolicited AE from Day 0-28. These cohorts will review their completed e-diary or diary card with study staff at their second in-person visit on Day 28. Data collected from e-diaries and diary cards will be uploaded into the participant's EDC.

AE Type	**Solicited AEs/ Unsolicited AEs/MAE/SAEs**
Method of 'solicited' participant contact	E-diary or diary card**
Method of 'unsolicited' participant contact	E-diary or diary card**
Method for reporting SAEs/MAEs	SAE report forms
Method for reporting pregnancies	Pregnancy report forms

***Will occur only in efficacy and extended safety cohort, and efficacy, extended safety, and immunogenicity/extended immunogenicity cohorts*

Time period for detecting and recording adverse events and serious adverse events

In the extended safety cohorts, all AEs starting within 28 days following administration of the dose of the study product/placebo must be recorded into the appropriate section of the EDC, irrespective of intensity or whether or not they are considered injection related.

The time period for collecting and recording SAEs and MAEs in all participants will begin at the first receipt of study product/comparator and will end on Day 364.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study product. SAEs that are related to the investigational product will be collected and recorded from the time of the first receipt of study product/comparator until the participant is discharged from the study.

In addition to the above-mentioned reporting requirements and in order to fulfill international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) will be collected and recorded from the time the participant consents to participate in the study until she/he is discharged from the study.

Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

Evaluation of adverse events and serious adverse events

Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the participants should be asked a non-leading question such as:

'*Have you acted differently or felt different in any way since receiving the product or since the last visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the EDC.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

Assessment of adverse events

Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:
The maximum intensity of local injection site redness/swelling will be scored as follows:
0: ≤ 20 mm
1: > 20 - ≤ 50 mm
2: > 50 - ≤ 100 mm
3: > 100 mm

The grade of fever will be scored as follows (oral temperatures*):
1: ≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
2: > 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
3: > 39.0°C (102.2°F) - ≤ 40.0°C (104°F)
4: > 40.0°C (104°F)
*oral temperature=axillary temperature+0.2°C

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity should be assigned to one of the following categories:

- Grade 1 (mild) = An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Grade 2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.
- Grade 3 (severe) = An AE which prevents normal, everyday activities
- Grade 4= An adverse event that is potentially life threatening.
- Grade 5=An AE which results in death.

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the predefined outcomes.

Assessment of causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the IB and/or PI to determine his/her assessment.

There may be situations when a SAE has occurred, but the investigator has minimal information to include in the initial SAE report. However, it is very important that the investigator always assesses causality for every event prior to submission of the SAE report. The investigator may

change his/her opinion of causality in light of participant contact information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple products, it may not be possible to determine the causal relationship of general AEs to the individual products administered. The investigator should, therefore, assess whether the AE could be causally related to injection rather than to the individual products.

All solicited local (injection site) reactions will be considered causally related to injection. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

YES: There is a reasonable possibility that the product(s) contributed to the AE.

NO: There is no reasonable possibility that the AE is causally related to the administration of the study product(s). There are other, more likely causes and administration of the study product(s) is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious', additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the product, if applicable.
- Erroneous administration.
- Other cause (specify).

Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

Medically attended AEs (MAEs)

For each solicited and unsolicited symptom the participant experiences, the participant will be asked if they received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the in the EDC.

Prompt reporting of SAE, SUSAR and other events to IDMC, Research Ethics Board (REB)

SAEs will be reported promptly to the Independent Data Monitoring Committee and REB within the timeframes described in this protocol once the investigator determines that the event meets the protocol definition of a SAE. SAEs will be collected throughout the study. If an SAE is confirmed as a SUSAR, then the sponsor will report it to the IDMC.

TABLE 7. TIMEFRAMES FOR SUBMITTING SAE TO THE RESEARCH ETHICS BOARD

Type of Event	**Initial Reports**		**Participant contact of Relevant Information on a Previous Report**	
	Timeframe	**Documents**	**Timeframe**	**Documents**
SAEs	24 hours*	SAE report	24 hours*	SAE report

* Timeframe allowed after receipt or awareness of the information.

Table 8 TIMEFRAMES FOR SUBMITTING SUSAR TO THE IDMC

Type of Event	**Initial Reports**		**Participant contact of Relevant Information on a Previous Report**	
	Timeframe	**Documents**	**Timeframe**	**Documents**
SUSAR	2 days*	SAE report	7 days*	SAE report

* Timeframe allowed after receipt or awareness of the information.

Contact information for reporting serious adverse events and Back-up Study Contact for Reporting SAEs

24/24 hour and 7/7-day availability:

Email: cansino-pv@TigermedGrp.com

Details and contact information will be described in a separate Pharmacovigilance Agreement.

Completion and transmission of SAE reports

Once an investigator becomes aware that a SAE has occurred in a study participant, the investigator (or designate) must complete the information in the SAE report as thoroughly as possible with all available details of the event, WITHIN 24 HOURS. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report.

Updating of SAE information after freezing of the participant's EDC

When additional SAE information is received after freezing of the participant's EDC, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report is provided to the REB.

Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to the in accordance with the procedures detailed in this protocol. CanSino Biologics, Inc., as the clinical trial sponsor, has a legal responsibility to promptly notify the appropriate health agency about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other participants are met. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation. All of these notifications will occur within 24 hours of the Investigator becoming aware of the SAE.

7.3 Participant contact of adverse events and serious adverse events

Participant contacts during the study

After the initial AE/SAE report, the investigator is required to proactively follow each participant and provide additional relevant information on the participant's condition to the REB.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

With the exception of MAEs, all AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 28 days after vaccination.

Participant contact after the participant is discharged from the study

The investigator will follow participants:

- With SAEs, or participants withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained,

or the participant is lost to participant contact, defined as four attempts to contact by phone/email at different times of the day have been unsuccessful and a letter has been sent to the address with no reply.

- With MAE until the end of the study or the participants are lost to participant contact.
- With other non-serious AEs, until Day 28 after injection or they are lost to participant contact.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to the REB using a paper SAE and/or pregnancy report as applicable.

The manufacturer of the investigational product may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a participant dies during participation in the study or during a recognized participant contact period, the REB will be provided with any available post-mortem findings, including histopathology.

7.4 Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medications administered for the treatment of an AE should be recorded in the participant's EDC.

Unblinding

Unblinding procedure (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the investigational product/product, prior to regulatory reporting.

Emergency unblinding

Emergency unblinding is performed by contacting the Country/Regional CRO who has access to the participant's individual Unblinding of a participant's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the study treatment is essential for the clinical management or welfare of the participant, as judged by the investigator.

Emergency unblinding is performed by contacting the Country/Regional CRO who has access to the participant's individual study treatment.

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to the REB.

Arrangements will be made to obtain the treatment assignment list from the study unblinded nurse pharmacist such that only that participant's assignment is unblinded.

Participant card

Study participants must be provided with the telephone number of the main contact for information about the clinical trial. Participants must be instructed to keep participant cards in their possession at all times.

The investigator (or designate) must therefore provide a "participant card" to each participant. In an emergency situation this card serves to inform the responsible attending physician that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator.

8. PARTICIPANT COMPLETION AND WITHDRAWAL

8.1 Participant completion

A participant who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

8.2 Participant withdrawal

Participants who are withdrawn because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn as result of a SAE/AE until resolution of the event. Withdrawals will not be replaced, unless the withdrawal is prior to the first dose of study vaccine.

Participant withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any participant who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the participant will be used for the analysis.

A participant is considered a 'withdrawal' from the study when no study procedure has occurred, no participant contact has been performed and no further information has been collected for this participant from the date of withdrawal/last contact.

Investigators will make an attempt to contact those participants who do not return for scheduled visits or participant contact.

Information relative to the withdrawal will be documented in the EDC. The investigator will document whether the decision to withdraw a participant from the study was made by the

participant, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE
- Non-serious AE
- Protocol violation (specify)
- Consent withdrawal, not due to an AE*
- Moved from the study area.
- Lost to participant contact.
- Other (specify).

**In case a participant is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the participant, in the EDC.*

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn from the study as result of a SAE/AE until resolution of the event.

Participant withdrawal from investigational product

A 'withdrawal' from the investigational product refers to any participant who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A participant withdrawn from the investigational product may not necessarily be withdrawn from the study as further study procedures or participant contact may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational product will be documented on the Product Administration screen of the EDC. The investigator will document whether the decision to discontinue further injection/treatment was made by the participant, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE
- Non-serious AE
- Other (specify)

9. OUTCOME MEASURES AND STATISTICAL METHODS

9.1 Study Hypotheses

Efficacy will be concluded if the lower bound of the sequential-monitoring-adjusted 95% confidence interval on vaccine efficacy (VE) exceeds 30%, in agreement with the minimum requirement given in the WHO Target Product Profile.

Null hypothesis (H_0): Lower bound of 95% CI of VE≤30%

Alternative hypothesis (H_1): Lower bound of 95% CI of VE＞30%

Vaccine efficacy will be calculated using a Cox proportional hazards model as

VE = 1 – hazard ratio = $1 - \frac{hazard \in treatment group}{hazard \in placebo group}$

The primary efficacy endpoint will be formally assessed 3 times during the study with possible early rejection of null hypothesis, when 50, 100 and 150 cases are observed. A Lan-DeMets alpha-spending function is used to control the overall type I error at 2.5%.

9.2 Sample Size Estimation

The efficacy cohort includes all vaccinated participants in the clinical trial.

The trial is endpoint driven, as the main analysis for Ad5-nCoV versus the control arm is triggered by the occurrence of a total of 150 cases of COVID- 19 across these two arms, at which point the results will be reported, but blinded follow-up will continue.

Following Schoenfeld (1972), in order to achieve power $1-\beta$ at $\Delta_1 > \Delta_0$, when testing H_0 vs H_1 at level α with proportional allocation to the treatment and control arms, the required number of endpoint events is

$$\frac{4\left(z_{1-\alpha} + z_{1-\beta}\right)^2}{(log(\Delta_1) - log\,(\Delta_0))^2}$$

When testing at one sided level $\alpha = 0.025$, with $\Delta_0 = 0.7$ corresponding to VE=30%, and to achieve 90% power when true vaccine efficacy is 60%, corresponding to $\Delta_1 = 0.4$, the required number of endpoint events is 135.

An adjustment for 2 interim monitoring analyses increases the required number of events to 138. See Jennison and Turnbull (2003), table 2.4, for details.

A total of 150 endpoint events will provide in excess of 90% power as suggested in the WHO guideline.

9.3 Study Population and Analysis Sets

9.3.1 Study Population

All Enrolled Cohort

The All Enrolled Cohort will be defined as all screened participants who provide informed consent and demographic and/or baseline screening assessments, regardless of the participant's randomization and treatment status in the study.

Efficacy-Safety Cohort

All participants in the All Enrolled Set who receive at least one study injection. This is an intention-to-treat cohort, with participants grouped as randomized.

Efficacy-Extended Safety Cohort

All participants in the Efficacy-Safety Cohort having three planned in-person visits on Day 0, Day 28 and Week 52.

Efficacy-Extended Safety-Immunogenicity and Efficacy-Extended Safety-Extended Immunogenicity Cohorts

Participants in the efficacy-extended safety-immunogenicity and efficacy-extended safety-extended immunogenicity cohorts will have at least four planned in-person visits on Day 0, 28, Week 24 and Week 52.

9.3.2 Analysis Sets

Full Analysis Set/Intent-to-Treat Set

The full analysis set consists of all participants in the Efficacy-Safety cohort, regardless of their protocol adherence and continued participation in the study. Participants will be analyzed according to their randomized treatment. Participants who withdraw from the study will be included up to the date of their study withdrawal.

Per-protocol Analysis Set

The per-protocol analysis set for efficacy includes subjects in the full analysis set who receive the correct treatment, the correct number of doses, and who do not have a major protocol deviation. Detailed definition of this analysis set including definition of major protocol deviations will be described in the Statistical Analysis Plan prior to the first interim analysis.

Safety Analysis Set

The safety analysis set consists of all participants in the Efficacy-Safety cohort. The participants who receive incorrect treatment will be assigned to the treatment group they actually receive.

9.4 Statistical Analysis

This purpose of this section is to describe various planned analyses in this study. Details of statistical methods will be included in the Statistical Analysis Plan, which will be finalized prior to the first interim analysis.

9.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized overall and then by treatment group using appropriate descriptive statistics. Continuous data will be summarized using the number of observations, mean, standard deviation, median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. 95% confidence intervals will be reported, but no statistical hypothesis testing will be conducted. Results will be presented for all participants.

9.4.2 Efficacy Analysis

Primary Efficacy Analysis

The primary estimate of vaccine efficacy and testing of hypotheses will be based on a time to event analysis using a Cox proportional hazards model. The primary efficacy endpoint will be assessed 3 times during the study, triggered when 50, 100 and 150 cases are observed in the combined (blinded) groups. A Lan-DeMets alpha-spending function approximating O'Brien and Fleming boundaries $2 - 2\Phi\left(z_{1-\alpha/2}\sqrt{3/k}\right)$ is used to control the overall type I error at 2.5%.

Critical value, associated significance level and error spending at each analysis is shown in the following table:

Analysis	Critical Values (Significance Level)	Error Spending	Cumulative Error Spending
First	3.7103 (0.00010351)	0.00010351	0.00010351
Second	2.5114 (0.00601267)	0.00594488	0.00604839
Final	1.9930 (0.02313072)	0.01895161	0.025

If the test statistic is larger than the corresponding critical value at interim analysis (first or second), null hypothesis is rejected and further trial enrollment stops. Otherwise, trial enrollment continues until the next analysis is triggered. In addition to formal hypothesis testing, confidence intervals on vaccine efficacy will be reported at interim and final analyses.

If there is early stopping of enrollment due to demonstrated benefit, follow-up of participants already enrolled in the study will continue.

The interim analysis will be carried out by the IDMC, according to the statistical analysis plan.

The primary efficacy analysis will be carried out on both intention-to-treat and per-protocol cohorts.

Secondary Efficacy Analysis

Secondary efficacy endpoints are

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

nCoV group compared to the placebo group.

3. The number of virologically confirmed (PCR positive) severe COVID-19 cases caused by SARS-CoV-2 infection from 14 days to 24 and 52 weeks after vaccination, in the Ad5-nCoV group compared to the placebo group.
4. The number of virologically confirmed (PCR positive) SARS-CoV-19 cases in different age groups from Day 28 to 24 and 52 weeks after vaccination in the Ad5-nCoV group compared to the placebo group.
5. The number of virologically confirmed (PCR positive) SARS-CoV-19 cases in different age groups from 14 days to 24 and 52 weeks after vaccination in the Ad5-nCoV group compared to the placebo group.
6. The same endpoints of #1-5 above in virologically or serologically confirmed SARS-CoV-19 cases.

Secondary efficacy analyses will also be based on Cox proportional hazard model.

An adjusted analysis will be carried out for the primary objective, including adjustment for country, sex, gender, and age. A stratified analysis for the primary objective will be carried out with strata identified by HIV status and presence of pre-existing COVID-19 antibodies. Participants who have been enrolled and immunized and then subsequently are found to have a positive HIV test, will be counseled and continue to be followed in the study. All participants, including those with an unknown HIV status, will be monitored closely for any SAE and symptoms of illness.

Conclusions may be affected by early dropout if there is differential dropout in the treatment and control groups. Missing values will not be imputed; however, a sensitivity analysis for the primary objective will be carried out to assess the effect of drop-out. Event times for dropouts will be simulated based on the empirical distribution of event times for participants with matching covariate information. A worst-case scenario will be considered in which event times are generated only for participants in the control group. A second scenario will simulate event times for participants in either group. If any of the simulated event times precede the end of study censoring time, VE will be re-estimated in the sensitivity analysis.

The efficacy analysis will be performed based on the Intent-to-Treat Analysis Set and the Per-protocol Analysis Set.

9.4.3 Safety Analysis

Primary Safety Endpoint:

The number of serious adverse events (SAE) within 52 weeks after vaccination in all participants reported in the Ad5-nCoV group compared to the placebo group. Data from all participants will be used to assess the primary safety endpoint.

Secondary Safety Objective Endpoints

1. The incidence of solicited adverse reactions within 7 days after vaccination (in two of the

cohorts, of about 3000 participants only, approximately 7%-10% of total).
2. The incidence of unsolicited adverse events within 28 days after vaccination (in two of the cohorts, of about 3000 participants only, approximately 7%-10% of total).

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

All SAEs will be listed and summarized by groups after unblinding.

Additional safety data including solicited AEs (injection-site and general) occurring during the 7-day follow-up period after injection will be collected on efficacy-extended safety cohort. Unsolicited AEs will be collected from Day 0 – Day 28.

For each participant, the individual local events will be aggregated into a combined event "Local", which is the maximum severity of the individual local events. For each participant, the individual general events will be aggregated into a combined event "General", which is the maximum severity of the individual general events. An aggregate event "Any" will be defined as the maximal severity of the combined events "Local" and "General". In addition to being graded for severity as mild, moderate or severe, the severity of all events will be graded as "Any", which will include mild, moderate or severe events, and "Significant" which will include moderate or severe events.

All statistical tests on safety performed will be 2-sided with Type I error of 5%. Missing values will not be included in the safety analyses, and there will be no imputation of missing values. No adjustments will be made for multiple comparisons.

For the analysis of proportions, binomial point estimates and exact binomial confidence intervals will be calculated.

Fisher's Exact Test will be used to assess differences in rates of adverse events between treatment and control groups.

In addition, all safety data will be analysed descriptively, including unsolicited events collected through the end of the observation period.

The Safety analysis with be performed based on the Safety Analysis Set.

9.4.4 Immunogenicity Analysis

Secondary Immunogenicity Endpoints:

1. Seroconversion rate of S-RBD IgG antibody on Day 28, Month 6 and 12 after vaccination by ELISA.
2. GMT of S-RBD IgG antibody on Day 28, Week 24 and 52 after vaccination by ELISA.
3. GMI of S-RBD IgG antibody on Day 28, Week 24 and 52 after vaccination by ELISA.
4. Seroconversion rate of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination.

5. GMT of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination.
6. GMI of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination.
7. Positive rate and level of IFN-γ by peptide pool of S protein on days 28, Week 24 and 52 after vaccination, measured by ELISpot.
8. 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).

Assessment of secondary immunogenicity endpoints 1-6 will be based on both the efficacy-extended safety- immunogenicity and efficacy-extended safety-extended immunogenicity cohorts. Secondary immunogenicity endpoints 7 and 8 will be assessed based on the efficacy-extended safety-extended immunogenicity cohort only.

Geometric mean antibody titers (GMTs) and GMI's and their two side 95% confidence intervals will be calculated by group. Analyses will be performed on the logarithmically (base 10) transformed values. Individual titers below the detection limit will be set to half the limit.

For the analysis of proportions, binomial point estimates and exact binomial confidence intervals will be calculated for each group. Rates will be compared between groups using Fisher's exact tests, and geometric means will be compared using t-tests.

All statistical tests performed for immunogenicity will be 2-sided with Type I error rate of 5%.

Missing values will not be included in the immunogenicity analyses, and there will be no imputation of missing values. No adjustments will be made for multiple comparisons.

Both per-protocol and intent-to-treat immunogenicity analyses will be carried out. The immunogenicity analysis sets will consist of subsets of subjects in the intent-to-treat and per-protocol sets who also fall into the efficacy-extended safety-immunogenicity or efficacy-extended safety-extended immunogenicity cohort, as appropriate to the endpoint analyzed. The per-protocol immunogenicity analysis set will exclude subjects whose samples were drawn outside of protocol specified time windows.

9.4.5 Analysis of supportive endpoints

Supportive Endpoints

1. Evaluate the severity of COVID-19 cases among vaccine recipients (based on WHO criteria) as compared to the control group, to measure antibody-mediated disease enhancement (ADE).

2. Evaluate for any evidence of SARS-CoV-2 virus shedding in COVID-19 cases that occurred 28 days to 52 weeks after vaccination (detection of viral nucleic acid every 2 days after confirmed).

3. Perform genotyping of SARS-CoV-2 virus isolates of COVID-19 cases that occurred 28 days to 52 weeks after vaccination.

4. Evaluate incidence of suspected but unconfirmed cases of COVID-19 (either because of negative or no tests).

5. To evaluate the efficacy of Ad5-nCoV in preventing asymptomatic disease of COVID-19 (confirmed by N IgG antibody on month 12 after vaccination).

Analysis of supportive endpoints

PCR confirmed positive subjects will be classified as having severe or non-severe disease. Point estimates and confidence intervals of proportions of subjects with severe disease will be reported by treatment group, and proportions will be compared between groups using Fisher's exact test. Adjusted analyses will be carried out using logistic regression.

To evaluate for virus shedding in COVID-19 cases that occurred 28 days to 52 weeks after vaccination, a Cox proportional hazards model will be used to model time to negativity from time of confirmation. The cohort for this analysis will include all PCR positive cases.

Genotypes SARS-CoV-2 virus isolates will be listed by subject and date, along with demographic data, including the study centre.

To evaluate for the incidence of suspected but unconfirmed cases of COVID-19 (either because of negative or no tests), the efficacy analysis will be repeated with two different cohorts. The first cohort will include only suspect and probable cases. The second cohort will combine both confirmed positive cases with suspected and probable cases.

The cohort for the efficacy analysis for preventing asymptomatic disease will be all subjects in the efficacy-safety cohort who were neither PCR positive nor seropositive. Proportions with demonstrated seroconversion will be estimated with confidence intervals, by treatment group, and will be compared between the vaccine and placebo groups using Fisher's exact test. Seroconversion will be defined as a 4-fold or greater increase of N IgG antibody titre at 52 weeks, as compared to Day 0.

9.5 Possible Study Design Adaptations

Should the observed attack rate of COVID-19 be insufficient to accumulate the targeted number of endpoints by the end of the study, one or more of the following adaptations may be implemented: enlistment of new study sites, increased enrolment from active sites, or extension of the end of the study.

If the ongoing phase II trial of Ad5-nCoV demonstrates both safety and increased immunogenicity of a two dose regimen, the IDMC may recommend and/or the sponsor may decide to add additional cohorts to receive a two-dose regimen.

If the IDMC recommends and/or the Sponsor decides upon an adaptation to a two-dose regimen, additional participants will be randomized into either a two-dose treatment group or a two-dose placebo group and enrollment will continue until there are a total of 150 endpoint events

combined in those arms. The window for 2nd injection will be 2 months +/- 2 weeks. The two dose efficacy hypotheses will be the same as the one-dose efficacy hypotheses but will be assessed on comparison of the two-dose Ad5-nCoV group to the two-dose placebo group. There will be two interim analyses of the two dose regimen. The first will use the first 50 endpoints after adaptation, and the second will use the first 100 endpoints after adaptation. The primary efficacy objectives will then be independently assessed based on the one dose or two-dose regimen.

10. DATA MANAGEMENT

10.1 General Requirements

The data management of this clinical trial will follow the **CDISC** standard. A designated person (Central Data Manager) will be responsible for the data management of global clinical trial and develop a core data management plan approved by the global PI and the sponsor. The local PI of each participating country along with the Sponsor will identify a local CRO to monitor data entry and ensure compliance with the CDISC standard.

10.2 Electronic Data Capture System

This clinical trial will use a single, designated Electronic Data Capture System (EDC) in all participating countries. The local PI of each country must ensure that its research team is well trained in EDC system operation skills.

11. STUDY HOLDING RULES AND SAFETY MONITORING

The study in its entirety may be terminated prematurely with reasonable justification by Study Steering Committee, National Regulatory Authority (NRA), or the Ethics Committee with oversight responsibilities at any time, and/or individual participants may terminate their participation prematurely, or have their participation be terminated by the Investigator.
An Independent Data Monitoring Committee (IDMC) will be established to review the safety data of every participant with a GRADE 4 adverse. Meetings will also be held should a participant have an adverse event meeting a “holding rule”. The review will be conducted using blinded data.

11.1 Study Suspension Criteria

If a suspension criteria is activated, the study will be put on hold, and further injections will not be administered until a safety review has been conducted. Should a suspension criteria be activated, the local PI will inform the global PI, Sponsors, and NRA within 24 hours.

Suspension criteria includes:

- More than 15% of participants at the global level experience a Grade 3 AE beginning

within 3 days after study injection (day of injection and 2 subsequent days) and persisting at Grade ≥ 3 on three consecutive days depending upon symptom severity and kinetics.
- A suspected, unexpected serious adverse reaction (SUSAR) occurs that is life-threatening or results in death.
- The IDMC assessed the potential safety risks in clinical studies.
- The IDMC assessed that the vaccine candidate might be ineffective.

11.2 Study Early Termination Criteria

- Required by the sponsor, or
- Required by the regulatory authority, or
- Required by an institutional review board (IRB)

11.3 Process of Suspension of Injection and/ or Study Modification

In the event that a safety signal is observed, the IDMC might decide to cancel injection of all groups (early termination of study) or selected groups.
In this case, for impacted groups:

- Participants who are already injected will continue all visits as planned.
- Participants who signed an informed consent but have not received any study product will be informed that their study participation will be stopped.

Details of the IDMC functioning are described in the IDMC Charter.

12. STUDY GOVERNANCE

The study will be managed by a global CRO under the direction of the nominated PI and the Steering Committee. It is the global CRO's responsibility to oversee all study site activities. In countries where the global CRO does not have adequate presence to manage study activities, it will be their responsibility of the global CRO to coordinate a local CRO engaged to manage the site-specific activities. There will also be a designated IDMC to continuously monitor and review data from safety and efficacy trials.

12.1 Study Steering Committee

A Study Steering Committee (SC) will be established by the sponsor as the management decision-making body for this clinical trial. The SC will provide guidance to the Global CRO who will be responsible to ensure that the conduct of the trial in each site is harmonized with respect to important aspects such as data collection, laboratory tests, and implementation of vaccination. Approval, revision, adaptive adjustment of the clinical trial protocol, and major issues such as suspension and termination of clinical trials all be decided by SC.

The composition of SC is as follows:

- Representatives from the sponsor

- Global PI and co-PI
- Central Safety Physician
- Central Statistician

12.2 Global PIs and Local PI

Both the global PI and co-PI and the local PIs are selected by the sponsor.

The main responsibilities of Global PI are:

- Assisting the sponsor to formulate the clinical trial protocol.
- In the course of clinical trials, coordinating the progress of each clinical trial participating country, and making recommendations for adaptive adjustment according to changes in circumstances (e.g., COVID-19 attack rate).
- When necessary, working with local PIs to resolve issues that arise in the course of clinical trials.
- Preparing study reports for global clinical trial.
- Working with the Study Statistician to finalize the Statistical Analysis Plan (SAP)

The main responsibilities of the local PIs are:

- Drafting local implementation documents and informed consent form (ICF) based on the clinical trial protocol and ICF.
- Submission of protocol, ICF, and other study documentation to the local IRB
- Conducting clinical trials based on the approved implementation protocol.
- Solving the problems that occurred during the clinical trial.
- Preparing study reports for the sub-center clinical trial.

12.3 Endpoint Review Committee

The Endpoint Review Committee (ERC) will be blinded to the treatment assignments. Each endpoint case (including primary and secondary endpoint case) will be reviewed independently by two ERC members; if their adjudications conflict, the endpoint will also be reviewed by a third member and the endpoint will be adjudicated by the majority vote. Members of the ERC will be appointed by the Study Steering Committee. Each positive laboratory result will be

reviewed by the ERC. A detailed outline of ERC regulations and endpoint case criteria, in addition to the criteria defined below, will be available in the ERC charter.

Endpoints cases are defined by any of the following events:

1. A participant has an illness visit and virological confirmation (positive PCR test). PCR SARS-CoV-2 tests are permitted to be carried out at local study sites. Every effort will be made to verify positive PCR tests in a central reference laboratory.
2. A participant has an illness visit and serological confirmation of SARS-CoV-2. A positive serology test is defined by a four-fold rise or greater to N antibody titers in association with the illness.
3. A participant has illness visit and both virological and serological confirmation.
4. A participant who does not present with any symptoms (does not have any illness visits) but demonstrates seroconversion to the N antigen between the day 0 and Week 52 visits.

12.4 Independent Data Monitoring Committee

The sponsor will establish an Independent Data Monitoring Committee (IDMC) consisting of at least 3 members to review global clinical trial safety and efficacy data. The IDMC core members will include an independent safety physician, clinical trial experts, an independent expert physician, infectious disease clinicians, biostatisticians, and epidemiologists who are not otherwise involved in the conduct of the project.
IDMC's main responsibilities are:

- Reviewing the reported safety data in the participants after vaccination.
- Assessing the safety, if necessary, in the context of efficacy, of the investigational vaccine to safeguard the interests of trial participants.
- Conducting interim analysis and terminate the trial early (for benefit or futility) when sufficient evidence of efficacy is obtained.
- Monitoring the overall conduct of the clinical trial to protect its validity and credibility.

13. ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with all regulatory requirements. The trial will be conducted in accordance with the latest version of the Declaration of Helsinki, GCP, ICH regulatory guidelines, and requirements regarding ethical committee review, informed consent, and other statutes and regulations regarding the protection of the rights and welfare participants participating in the study.

Each enrollment site and local investigator will be responsible for submitting this protocol, the informed consent document, and all recruiting materials to their local independent Research Ethics Board (REB) for review and approval.

No changes will be made to the protocol without REB approval, except where necessary to eliminate apparent immediate hazards to participants.

Participants will be able to withdraw their consents to participate at any time without giving a reason and with assurance that their care will not be affected in any way. The investigators may withdraw a participant if, in the investigator's clinical judgment, it is in the best interest of the participant or if the participant is unable to comply with study requirements.

13.1 Benefits/Potential Risks

A complete description of the potential risks and benefits can be found in the informed consent document and Investigator Brochure [10].

13.2 Informed Consent Process and Documentation

The investigator or designate will be responsible for presenting a full description of the research project including risks/benefits, and how personal health information may be used and disclosed in research. A written informed consent/authorization will then be obtained from the participant prior to the screening procedures and injection. The principal investigator or designate will also be responsible for maintaining up-to-date records of the consent forms and providing a copy to the participant.

Participants will be encouraged and will have ample opportunity to have their questions answered before and after consenting to participate.

13.3 Modification of the Protocol

No modifications of the protocol may be made by study personnel without consultation the principal investigator. Any protocol amendment will be submitted to the appropriate local regulatory authority and to the Research Ethics Board(s) for approval.

13.4 Interruption of the Trial

Study suspension and early termination are described in Section 12.

13.5 Confidentiality of Data and Access to Participant Records

Confidentiality will be maintained within legal limits in the review of medical records and consent forms, which may contain the identity of the participant. Such records will be coded only with the participant's initials and study number.

13.6 Monitoring

The sponsor will select a Contract Research Organization (CRO) in each participating country to monitor clinical trials, following the implementation protocol, where they are unable to monitor themselves. The local CRO should have a clinical trial quality management system and experience in the management of vaccine clinical trials. Where the Global CRO has the capability, it may perform the monitoring. Monitors will follow their local enrollment sites SOP for clinical trial monitoring.

The study will be monitored once the first participant has been enrolled, during the study at appropriate intervals, and after the last participant has completed the study. The monitoring visit schedule will be determined by the monitor and principal investigator based on the frequency of enrolments and participant contact visits. A monitor visit tracking form and report will be required for each monitoring visit. A copy of the monitor report will be sent to the global CRO for review.

13.7 Auditing

Audits or inspections may be made by the REB to ensure that the study has been conducted in accordance with the protocol, FDA, ICH/GCP, and the participating Country's regulatory health authority. Audits may also be performed by a Country's regulatory health authority at any point.

13.8 Archiving

The investigators will retain all source documents and study records on site, including consent forms and copies of case report forms for 25 years after completion of the study.

13.9 Stipends for Participation

Participants will be provided a stipend according to local practice to compensate for their time and travel required for each visit to the study site.

13.10 Adverse Event Compensation and Insurance

In the occurrence of an adverse event, the participant will be evaluated and treated by the investigators in accordance with local regulations. No additional form of compensation is available.

13.11 Publication Policy

Study result manuscripts will be prepared by the Global Principal Investigator and reviewed by all co-investigators and the study sponsor CanSino Biologics and submitted to peer-reviewed journals and scientific meetings within 24 months of the last participant contact.

14. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

14.1 Data Entry Instructions

Clinical data management will be performed at each enrollment site, following SOP standards and data cleaning procedures and under the supervision of the appointed Data Manager. Data entry will be performed by each of the study sites.

Completed ECDs are reviewed by the external Monitor at the study site. When omissions or inconsistencies are detected by ECD review, clarification or correction of the ECD may be necessary, following approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

14.2 Monitoring

It is the responsibility of monitors to:

- Verify that all participants have been enrolled according to the protocol and that informed consent has been obtained prior to any study procedure.
- Verify that data is authentic, accurate, and complete.
- Review all EDC prior to data entry
- Verify that study files, the participant files, source documents, EDCs, any SAE forms, product logs, and laboratory records are completed properly to ensure that the study is being conducted according to the protocol and GCP.
- Safety and rights of participants are being protected throughout the study.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

There will be a blinded monitor that will review all blinded data. There will be an unblinded monitor that will review the unblinded records.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The investigators and the head of the medical institutions (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigators must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigators or site staff, as appropriate, in accordance with applicable regulations, GCP, and CCfV procedures.

14.3 Record Retention

Following closure of the study, the investigators must maintain all site's study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigators must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigators must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

The investigators/institutions should seek the written approval of the Sponsor before proceeding with the disposal of these records after the indicated time period for record retention. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, standards/procedures; otherwise, the minimum retention period will default to 25 years.

The investigators/institutions must notify the Sponsor of any changes in the archival arrangements, including, but not limited to, archiving at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

14.4 Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection

of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigators and institutions agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

14.5 Posting of information on publicly available clinical trial registers

Study information from this protocol will be publicly available on clinicaltrials.gov before enrolment of participants begins.

14.6 Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will have access to statistical tables, figures, and relevant reports, and will have the opportunity to review the complete study results at a site or other mutually agreeable location.
The investigator is encouraged to share the summary results with the study participants, as appropriate.

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Version Change Log (Version 1.4→Version 1.5)

Section	Category	Description
Study synopsis and 2.2 Secondary Objectives	Rationale	The symptoms (or signs) that trigger laboratory testing are refined based on the WHO case definition.
	Was	This will be evaluated by weekly participant contact to assess for any signs or symptoms consistent with the WHO case definition.
	Changed to	This will be evaluated by weekly participant contact to assess for any signs or symptoms of COVID 19.
Efficacy participant contacts and throughout	Rationale	The symptoms (or signs) that trigger laboratory testing are refined based on the WHO case definition.
	Was	Any possible COVID-19 relevant symptoms (e.g. fever, cough, shortness of breath, etc. as per WHO case definitions, see Section 3.8) will trigger laboratory testing for SARS-CoV-2 infection.
	Changed to	Any possible COVID-19 relevant symptoms will trigger laboratory testing for SARS-CoV-2 infection.
Illness participant contact visits (Confirmed or suspected infection during study)	Rationale	The typical symptoms of COVID-19 are listed first.
	Was	Symptoms of interest include cough, fever, diarrhea, prolonged fatigue, respiratory symptoms, pneumonia, difficulty swallowing, loss of sense of smell and taste, and neurological events.
	Changed to	Symptoms of interest include fever, cough, dyspnoea & difficulty breathing, diarrhea, nausea, vomiting, prolonged fatigue, chills, myalgia, sore throat, headache, congested/runny nose, pneumonia, difficulty swallowing, anosmia/ageusia, loss of sense of smell and taste, and neurological events.
Illness participant contact visits (Confirmed or suspected infection during study)	Rationale	Since it is too difficult for some subjects to do the test every two days, especially when they were quarantined as required by the local policy. However, best efforts will be tried to make sure the sample will be taken every 2 days.
	Was	4. If the PCR is positive, repeat nasal/throat swabs will be taken every 2 days and tested for COVID-19 by PCR until a negative sample is obtained.
	Changed to	4. If the PCR is positive, all attempts to repeat nasal/throat swabs will be taken every 2 days and tested for COVID-19 by PCR until a negative sample is obtained.

3.8 Efficacy participant contacts	Rationale	Modification was made to clarify the procedure.
	Was	Any reported COVID-19 relevant symptoms (e.g. fever, cough, shortness of breath, etc. as per WHO case definitions (see below) will trigger laboratory testing for SARS-CoV-2 infection. The SARS-CoV-2 nucleic acid test is performed with a throat or nasal swab and repeated 3 days later if the result is negative. PCR SARS-CoV-2 tests will be done at local laboratories or at study site laboratories. Every effort will be made to verify positive PCR tests in a national or regional reference laboratory. Participants with a positive nasal/throat PCR will have it repeated at the local laboratory every two days until negative.
	Changed to	Any reported COVID-19 relevant symptoms will trigger laboratory testing for SARS-CoV-2 infection. The SARS-CoV-2 nucleic acid test is performed with a throat or nasal swab and repeated within 3 days if the result is negative. PCR SARS-CoV-2 tests will be done at local laboratories or at study site laboratories. Every effort will be made to repeat positive PCR tests in a national or regional reference laboratory. Participants with a positive nasal/throat PCR will have it repeated at the local laboratory every two days until negative (if possible).
3.8 Efficacy participant contacts	Rationale	The symptoms (or signs) that trigger laboratory testing are refined based on the WHO case definition.
	Was	**WHO Case definitions for surveillance：** **Suspect case** 1. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR 2. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset; OR 3. A patient with severe acute respiratory illness (fever and at least

		one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.
	Changed to	**Case definitions for surveillance：** **Suspect case** Subject with any of the following symptoms (or signs) is reported as suspected case： Fever, cough, dyspnoea & difficulty breathing, anosmia/ageusia, chills, myalgia, sore throat, prolonged fatigue, diarrhea, nausea, vomiting, headache, congested/runny nose, pneumonia, difficulty swallowing, loss of sense of smell and taste, and neurological events.
3.8 Efficacy participant contacts	Rationale	To clarify the definition of confirmed case and endpoint case.
	Was	**Confirmed case** A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms
	Changed to	**Confirmed case** A suspect case with laboratory confirmation of COVID-19 infection (including PCR positive result OR 4 folds 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: the participant with the clinical symptom(s) occurred not less than 28 days post-vaccination and the PCR test is positive. Secondary endpoint: the participant with the clinical symptom(s) occurred not less than 14 days post-vaccination and the PCR test is positive; or 4 folds 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.
Efficacy participant contacts (Confirmed or suspected infection during study) and throughout	Rationale	Simplified the redundant description in text.
	Was	Symptoms of interest include cough, fever, diarrhea, prolonged fatigue, respiratory symptoms, pneumonia, difficulty swallowing, loss of sense of smell, and neurological events.
	Changed to	Symptoms of interest please refer to 3.8 efficacy participate contact.
Efficacy participant contacts (Confirmed or suspected infection during study) and throughout	Rationale	It is too difficult for some subjects to do the test every two days, especially when they were quarantined as required by the local policy. However, best efforts will be tried to make sure the sample will be taken every 2 days.
	Was	Repeat nasal/throat swabs will be taken every 2 days until a negative sample is obtained.
	Changed to	Repeat nasal/throat swabs will be taken every 2 days until a negative sample is obtained (if possible).
9.4.4 Immunogenicity Analysis	Rationale	Mistake correction, ELISA is not the method for detecting the neutralizing antibody.
	Was	4. Seroconversion rate of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination by ELISA. 5. GMT of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination by ELISA. 6. GMI of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination by ELISA.
	Changed to	4. Seroconversion rate of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination. 5. GMT of pseudo-virus neutralizing antibody on Day 28, Week 24 and 52 after vaccination. 6. GMI of pseudo-virus neutralizing antibody on Day 28, Week 24

		and 52 after vaccination.
12.3 Endpoint Review Committee	Rationale	Clarified that the endpoint case including both primary and secondary endpoint cases.
	Was	The Endpoint Review Committee (ERC) will be blinded to the treatment assignments. Each endpoint case will be reviewed independently by two ERC members;
	Changed to	The Endpoint Review Committee (ERC) will be blinded to the treatment assignments. Each endpoint case (including primary and secondary endpoint case) will be reviewed independently by two ERC members;