Article

Title Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: The PROFISCOV study

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Abstract

Background

Vaccines are urgently needed to tackle the unprecedented morbidity and mortality of COVID-19. Administration of inactivated viruses are the common and mature platform of developing new vaccines. CoronaVac is an inactivated vaccine that has undergone preclinical tests and phase I/II clinical trials.

Methods

We conducted a randomised, double-blind, placebo-controlled phase 3 clinical trial with CoronaVac among healthy healthcare professionals in 16 centres in Brazil. Participants received two doses of vaccine (3 μg in 0.5 mL) vaccine or placebo at day 0 and 14. The primary efficacy endpoint was the number of symptomatic COVID-19 cases confirmed by RT-PCR 14 days after the second dose of the vaccine. Prevention of disease severity was a major secondary efficacy endpoint, and adverse events incidence up to seven days after immunization was the primary safety outcome. The trial was registered at ClinicalTrials.gov, NCT04456595.

Findings

Between July 21 and Dec 16, 2020, 12 396 participants were enrolled and received at least one vaccine or placebo dose. There were 9,823 participants who received the two doses and were followed for at least 14 days and had, therefore, reached the final efficacy analysis. There were 253 confirmed COVID-19 cases in the cohort: 85 cases (11.0/100 person-year) among 4,953 participants in the vaccine group, and 168 cases (22·3/100 person-year) among 4,870 participants in the placebo group. The primary efficacy against symptomatic COVID-19 was 50·7% (95%CI 36·0-62·0). The

secondary efficacy against cases requiring assistance (score ≥3) and moderate and severe cases (score ≥4) were 83·7% (95%CI 58·0-93.7) and 100% (95%CI 56·4-100.0) respectively. All 6 cases of severe COVID-19 occurred in the placebo group. The incidence of adverse reactions, which was mainly pain at the administration site, was higher in the vaccine group (77·1%) than in the placebo group (66·4%). There were 67 serious adverse events reported by 64 participants and all were determined to be unrelated to vaccination, including two fatal cases. In a subset of participants, neutralizing antibody assays showed similar seroconversion and geometric mean titres against B.1.128, P.1, and P.2 variants.

Interpretation

A phase 3 clinical trial conducted in healthcare professionals in Brazil demonstrated that the inactivated CoronaVac vaccine has a good safety profile and is efficacious against any symptomatic SARS-CoV-2 infections and highly protective against moderate and severe COVID-19.

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Introduction

Three coronaviruses (SARS-CoV-1, MERS, and SARS-CoV-2) have been identified as the cause of severe acute respiratory disease in humans this century. An inactivated vaccine was developed for the first of these diseases, SARS, but its development was discontinued in phase I clinical trial because the transmission receded. [1] After the emergence of COVID-19, the same group updated this development using a SARS-CoV-2 strain isolated in January 2020. The new product, later named CoronaVac (Sinovac Life Sciences, Beijing, China), had promising performance in non-clinical studies, as shown by the reduction of disease in non-human primate challenge experiments.[2] Safety and immunogenicity results in phase I/II clinical trials, in younger [3] and older adults [4], prompted the conduction of this phase III clinical trial.

Our study focused on healthcare professionals directly caring for or in close contact with COVID-19 patients. The obtention of results in a timely fashion is significant for vaccine development in a pandemic of such proportion and a a major common challenge for all COVID-19 vaccine developers. Brazil has been one of the countries most affected by the COVID-19 pandemic and overall incidence rates have reached high levels, especially in healthcare professionals caring for COVID-19 patients. Therefore, a focus on the latter group was proposed to provide a rapid means to determine the potential efficacy of a vaccine candidate.[5] This population has been shown to have higher incidence of disease in epidemiological surveys [6,7] and could, in principle, adhere better to study case surveillance. Therefore, the objective of the present phase III clinical trial was to assess the efficacy and safety of an inactivated COVID-19 vaccine in healthcare professionals. The greater number of presumed

cases and a high degree of adherence to the protocol were expected to rapidly meet the research objectives and eventual Emergency Use Authorization for CoronaVac.

Methods

Study design and participants

This is a phase III multicentre endpoint-driven, randomized, placebo-controlled clinical trial to assess the safety and efficacy of a two-dose schedule of an inactivated COVID-19 vaccine (CoronaVac, Sinovac Life Sciences, Beijing, China) containing aluminium hydroxide adjuvant in healthcare professionals ddirectly dealing with COVID-19 patients. Volunteers were recruited in sixteen clinical sites in Brazil, with 1:1 allocation ratio between vaccine and placebo. Initially, the study included only participants aged 18-59 years without previous SARS-CoV-2 infection. After phase I/II data in the elderly population became available,[4] those with 60 years of age or above were also enrolled, and a study amendment dropped any restriction of prior infection. The primary efficacy objective considered the whole study population regardless of age group and previous infection. The sample size for efficacy was calculated considering an attack rate of 2.5% and one interim analysis. The required number of cases was 61 for the interim analysis and 151 for the primary outcome analysis with estimated recruitment of 13,060 participants. The primary safety objective was incidence of adverse events by age group with up to 11800 participants in the 18-59 years group and up to 1260 in the group of 60 years or older.

Participants needed to be 18 years of age or older and work as healthcare professionals caring for COVID-19 patients and had to agree to participate by signing the informed consent form. The main exclusion criteria were pregnant or lactating

women, unstable chronic disease, previous use of any COVID-19 vaccines, and acute disease symptoms including COVID-19 in the previous 72 hours. The full protocol has been published previously.[8]

The study complied with ICH Good Clinical Practices and Brazilian ethical and regulatory guidelines, and was approved by the Brazilian National Research Ethics Council - CONEP - (CAAE 34634620.1.1001.0068) and the Brazilian National Regulatory Agency - ANVISA - (CE 47/2020) and is registered in the ClinicalTrials.gov platform (NCT0445659).

Randomization and masking

Two permuted block randomization lists were created according to age group, 18-59 years, and 60 years or older. Vaccine and placebo were randomized at a 1:1 ratio and all sites accessed the same randomization lists through an IWRS provided by Cenduit (Durham, NC, USA). Study vaccines and placebos were provided in prefilled syringes with similar characteristics. An unblinded pharmacist at each clinical site prepared the vaccine or placebo. The pharmacist only received a coded request for an experimental product and delivered the randomized product without any contact with the study participant or her/his identification information in a concealed syringe to a blind research staff. Participants and all other study staff as well as monitors, lab technicians, and data management team remained unaware of the product allocation.

Procedures

CoronaVac is an inactivated vaccine candidate against COVID-19 derived from the CN02 strain of SARS-CoV-2 grown in African green monkey kidney cells (Vero cells). At the end of the incubation period, the virus was harvested, inactivated with β-

propiolactone, concentrated, purified, and finally absorbed by aluminium hydroxide. The placebo was aluminium hydroxide diluent with no virus. Both the vaccine and placebo were prepared in a GMP-accredited facility. Vaccine (3 μg in 0.5ml) and placebo were provided in a ready-to-use syringe and administered intramuscularly following the two-dose schedule of 0,14 (+14) days. The selected vaccine doses have been proven to be sufficient for protection against SARS-CoV-2 challenge in macaques.[2]

This study was carried out in 16 clinical research centres in Brazil. All participants who provided the informed consent were enrolled after baseline assessment of inclusion and exclusion criteria, medical history, physical examination, vital signs, pregnant test, and blood tests. At screening, blood samples and a throat swab were collected for laboratory detection of SARS-CoV-2.

CoronaVac or placebo preparation was performed by the unblinded pharmacist at each site and then administered by nurses in a blinded fashion. After vaccination, safety evaluation was conducted by investigators who were unaware of treatment assignments onsite for 60 minutes. Follow-up contacts were allocated to each participant to verify the occurrence of adverse events and COVID-19 symptoms. These contacts could be made electronically, by telephone, or in-person, at the discretion of the study team and the participant informed the team about the means of contact they preferred. Contacts were made between the third and fifth day after each vaccination and thereafter every week for the first 13 weeks after vaccination and every two weeks for the remainder of the study. Once fever or other symptoms related to COVID-19 was reported, the participants were asked to seek assistance from the study team to collect a throat swab to diagnose COVID-19. All possible cases were

followed up to the resolution of all symptoms and the duration and severity of each of the signs and symptoms documented.

An independent data and safety monitoring committee was established prior to the study initiation. Safety data were assessed and reviewed by the committee to ensure safety.

Outcomes

The primary endpoint was the efficacy of CoronaVac against confirmed symptomatic COVID-19 with onset at least 14 days after the second injection in the *per protocol* population. All the cases were judged by a blind independent clinical endpoint adjudication committee. Confirmed COVID-19 cases were defined as: 1) at least two consecutive days with one or more specific symptoms (cough, newly developed taste or smell disorders, shortness of breath or dyspnea); or 2) with two or more non-specific symptoms (fever [axillary temperature ≥37·5°C], chills, sore throat, fatigue, nasal congestion or runny nose, body pain, muscle pain, headache, nausea or vomiting, diarrhoea; or 3) imaging features of COVID-19; and 4) detection of SARS-CoV-2 nucleic acid in respiratory swab by RT-PCR. A case definition based on the U.S. Food and Drug Administration (FDA) criteria was also used as a sensitivity analysis.[9]. Following the latter criteria, a positive case was considered as anyone who presented at least one of the following symptoms for two days or more, with a positive SARS-CoV-2 RT-PCR result: fever or chills, cough, shortness of breath or difficulty in breathing, fatigue, muscle or body pain, headache, sore throat, nasal congestion or runny nose, nausea or vomiting, and diarrhoea. The primary efficacy was also evaluated in distinct subgroups, including age groups, race, and ethnic group, with or without underlying medical conditions, different vaccination intervals

between two doses (<21 days or ≥21 days), and severity of COVID-19 according to WHO Clinical Progression Scale.[10] A modified intention-to treat analysis was also performed to verify the exploratory aim of evaluating the efficacy after a single dose. All the cases included for efficacy analysis had symptoms initiating up to December 16, 2020.

The primary safety endpoint was incidence of adverse reactions within 7 days after injection. The safety profile was assessed based on the safety set (SS), consisting of all the participants who received at least one dose vaccination. The events included in this analysis were those initiating up to December 16, 2020 and corresponded to a median follow-up of two months after the second dose.

Serum samples from a subset of the first participants per age group of the coordinating clinical site were analysed to determine neutralization titres by cytopathic effect-based virus neutralization test (CPE - VNT)using SARS-CoV-2 wild-type variants: B.1.128 (SARS-CoV-2 / human / BRA / SP02 / 2020 strain (MT126808.1), SARS-CoV-2-P.1 (MAN 87201 strain) and SARS-CoV-2-P.2 (LMM 38019 strain) in 96-well plates containing 5E+04 cells / mL of Vero cells (ATCC CCL-81). All procedures related to VNT were performed in a level 3 biosafety laboratory, from the Institute of Biomedical Sciences of the University of São Paulo, following WHO recommendations.

Statistical analysis

The primary efficacy analysis of was a -modified *per protocol* analysis calculated with all virologically confirmed cases of COVID-19 occurring in the period from the beginning of vaccination to two weeks after the second dose, using Cox proportional hazards regression model. This model calculates the estimated vaccine efficacy (1 -

hazard ratio), and the Wald test based on the Cox model compared to the p-values described above, and 95% confidence interval according to the appropriate alpha level was similarly transformed and presented. Cumulative incidence charts were also created with this model. The hypothesis test of the primary efficacy endpoint in the *per protocol* population was based on the on each analysis' alpha spent levels and followed up with the corresponding confidence intervals. Interim efficacy analysis was set to be triggered upon collection of at least 61 primary endpoint cases. The safety analysis included all participants who received at least one dose of CoronaVac or placebo. For neutralization assays, seroconversion was defined as a person with a post-vaccination titre ≥20 with a baseline negative result. The Geometric Mean Titres (GMT) were also calculated for those that seroconverted in each group. The Pearson Chi-square test or Fisher's exact test was adopted for the analysis of categorical outcomes. The 95% confidence intervals (95%CIs) of categorical outcomes were computed with the Clopper-Pearson method. Hypothesis testing was two-sided and P-values<0.05 was considered statistically significant.

Role of the funding sources

Employees of Fundação Butantan and Instituto Butantan participated in the study design, data collection, data analysis, data interpretation, and the report writing. Those organizations are non-profit. All the authors have full access to all the data in the study and the corresponding authors had final responsibility for the decision to submit for publication.

Results

From July 21 to December 16, 2020, 12,842 participants were screened, and 12,408 were randomized at 16 study sites in Brazil. A total of 12,396 participants received at least one dose of CoronaVac or placebo (Figure 1), 6,195 in the vaccine group and 6,201 in the placebo group.

Among those 12,396 participants, 5·1% were elderly participants aged 60 years or older, 64·2% were female, and most participants self-identified themselves as white (75·3%). More than half of the participants (55·9%) had underlying diseases, 22·5% of them were obese (BMI ≥30 kg/m²). The average age and BMI of participants were 39·5 years and 26·8 kg/m^2, respectively (Table 1).

All 12,396 participants were involved in the safety set (SS) and monitored for adverse events from the beginning of vaccination up until 12 months after the first dose vaccination. By the cut-off date, the incidence of adverse events and adverse reactions were 78·8% and 71·7%, respectively, by the cut-off date (Appendix p6). Generally, the vaccine group reported more adverse reactions than the placebo group (77·1% *vs*. 66·4%; p<0001), and most adverse reactions were solicited (73·1% *vs*. 60·0%, p<0·0001) (Figure 2A).

Among solicited adverse reactions, the incidence of local adverse reactions was 61·5% in the vaccine group, and this was higher than the 34·6% in the placebo group (p<0·0001). Local adverse reactions were mainly driven by pain at the injection site (60·3% *vs*. 32·5%, p<0·0001). All solicited local reactions were more frequently in the vaccine group, and the incidences were less than 6% in the vaccine group, except pain at the injection site (Figure 2B). Systemic adverse reactions were similar in the vaccine and placebo groups (48·4% *vs*. 47·6%, p=0·3882), including headache and

fatigue, the most common systemic symptom collected in this trial. Myalgia was more frequent in the vaccine group (11·7% *vs.* 10·5%, p=0·0257). Fever (≥37.8°C) was rare and only reported by 0·2% and 0·1% (p=0·2666) participants in the vaccine and placebo groups, respectively (Figure 2C). Unsolicited ARs were reported by 36·8% in the vaccine and 35·8% in the placebo groups (p=0·2177, Figure 2A). Only tremor, flushing and local reactions in the administration site (reported in an unsolicited period) showed higher incidence in the vaccine group. No difference was found for other unsolicited symptoms (Appendix p7-10).

In this study, 67 serious adverse events were reported by 64 participants, 33 in the vaccine group and 31 in the placebo group (Appendix p20-23). The overall incidence of SAE was 0·5%. All SAEs were determined as unrelated to the vaccine. Two deaths were reported in this trial: one case of cardiopulmonary arrest (placebo group), and one case of medication overdose (vaccine group); all of them unrelated to the vaccine. One additional death due to COVID-19 (placebo group) occurred as outcome on an ongoing case by the data cut time.

Among 9,823 participants in the *per protocol* analysis, 253 cases of symptomatic COVID-19 were reported during the primary efficacy analysis period (Table 2). There were 85 cases (11.0/100 person-year) among 4,953 participants in the vaccine group, and 168 cases (22·3/100 person-year) among 4,870 participants in the placebo group. The efficacy to prevent symptomatic COVID-19 was 50·7% (95%CI 35·9-62·0). Considering the α spending in the interim analysis, the corrected efficacy was 50.7% (95.4%CI 35·7-62·2). Sensitivity analysis of primary efficacy was conducted based on other case definitions, and the efficacy results ranged from 51·2% to 54·1% (Appendix p24).

A key secondary endpoint was to evaluate the efficacy to prevent COVID-19 disease at different clinical severities. There were 35 cases scored 3 and above, 10 cases scored 4 and above, 6 severe cases (including one fatal case) reported among the 9823 participants. For cases scored 3 and above, 5 cases were in the vaccine group, 30 were in the placebo group, resulting in a vaccine efficacy of 83·7% (95%CI 58·0-93·7). All cases scored 4 and above were in the placebo group, resulting in 100% vaccine efficacy against moderate and sever cases (95%CI 56·4-100·0).

Subgroup analyses were also conducted by the interval between two doses, the exposure status to SARS-CoV-2 pre-vaccination, age group, and underlying disease. Participants with two doses interval of fewer than 21 days showed similar efficacy (49·1%; 95%CI 33·0-61·4) as the primary efficacy analysis. For the small portion of participants who received two doses of vaccine or placebo with an interval of 21 days or more, the efficacy was calculated at 62·3% (95%CI 13·9-83·5). The efficacy was similar between different exposure status to SARS-CoV-2 pre-vaccination (Unexposed: 50·5%; Exposed: 49·5%), and between other age groups (18 to 59 years: 50·7%; ≥60 years: 51·1%). For participants with underlying diseases, a total of 130 cases were reported in this population, resulting in 48·9% efficacy (95%CI 26·6-64·5). For participants with cardiovascular disease, diabetes, and obesity, the efficacy was 39·5% (95%CI -66·4-78·0), 48·6% (95%CI -115·3-87·7) and 74·9% (95%CI 53·7-86·4), respectively. Two-hundred and fifty participants of Asian ethnicity reported 4 cases, of which 1 in the vaccine group and 3 in the placebo group, resulted in 66·0% efficacy (95%CI -226·8-96·5).

After the first dose or 14 days after the first dose, secondary efficacy endpoints were analysed using the intention-to-treat (ITT) approach. Among the 12,396 participants,

378 cases were reported after the first dose, of which 126 were in the vaccine group and 252 were in the placebo group, resulting in an efficacy of 50·8% (95%CI 39·0-60·3) after the first dose, similar to the calculated efficacy with the complete vaccination schedule. For 14 days after the first dose, 313 cases were collected among 11,431 participants, 94 were in the vaccine group and 219 were in the placebo group, resulting in an efficacy of 57·9% (95%CI 46·4-66·9) (Figure 3).

One hundred and nine participants had samples processed for neutralization assay before vaccination and two weeks after the second dose. Six of them had positive pre-vaccination samples (four for the vaccine and two for the placebo groups) and were not included in the seroconversion assessment. Two of four vaccinated participants with previous antibody titres had a 4-fold increase or higher for all tested variants. Three participants (5.2%) out of 58 in the placebo arm seroconverted for the variant B.1.1.28, but not to the other variants. Thirty-two (71.1%; GMT 64.4) of the 45 participants vaccine arm seroconverted for B.1.1.28, 31 (68.9%; GMT 46.8) for P.1, and 36 (80.0% GMT 45.8) for P.2. There were no significant differences in GMT against the B.1.128 variant as compared to P.1 GMT (p=0.34) and P.2 GMT (p=0.72).

In vaccinated individuals who seroconverted, 21 of 22 (95.5%; GMT 72.8) adults aged 18 to 59 years, 21 had seroconversion for B.1.1.28, 17 of 22 (77.3%; GMT 60.9) for P.1 and 21 of 22 (95.5%; GMT 50.4)) for P.2. Of the 23 samples analysed from participants aged 60 years or more, 11 (47.8%; GMT 58.1) evidenced seroconversion for B.1.1.28, 14 (60.9%; GMT 34.5) for P.1, and 15 (65.2%; GMT 40.0) for P.2. When the different age groups are compared, there were significant in seroconversion rates for B.1.1.28 (p<0.001) and P.2 (p=0,022) variants, but not for the P.1 variant (p=0.337). The differences in GMT between age groups were not significantly

different for the B.1.1.28 variant (p=0.086) nor the P.2 variant (p=0.174) but was different for the P.1. variant (p=0.029).

Discussion

The PROFISCOV study was designed to test CoronaVac in a group exposed to SARS-CoV-2 more often and at potentially higher infectious doses than in a community exposure. Using a smaller sample size compared to other large Phase III clinical trials with vaccine candidates, we were able to demonstrate that this vaccine was safe, well-tolerated, and efficacious. Efficacy to prevent any symptomatic COVID-19 started at 50.7% and became more extensive as disease severity increased. Of note, the case definition and professional profile of the study population allowed highly sensitive surveillance and the study was able to detect even the mildest cases of COVID-19. The conditions of this trial should be considered when the results are extrapolated to other populations or comparisons with other trials are suggested.

The vaccine performance met the requirements for Emergency Use Authorization in 32 countries and regions allowing a fast response to an ongoing public health emergency at a speed similar to other vaccine candidates receiving heavy subsidies from governments and international organizations.

One of the factors that might have affected the study's overall efficacy was the interval between two doses of 14 days. Although there were a limited number of participants in this study having doses with an interval of 21 days or higher, there was a trend to higher efficacy. Furthermore, previous neutralization data in adults were lower with a 14-days interval[3] , and, in this study, participants aged 60 years or more had a lower response than adults with the same 14-days schedule. These results contrast with previous studies where the immune responses in adults and elderly

populations with a 28-days interval schedule were comparable [3,4]. Taken together, these data suggests that it is advisable to encourage longer intervals between doses, i.e., 28 days, in the vaccine implementation. The study cannot make a clear assumption of efficacy with a single dose due to the limited number of outcomes and the odds of having more participants infected around the time of first injection in the vaccine arm (Figure 3). However, it must be noticed that the efficacy of CoronaVac was already present after the second week of the first dose.

The study was not designed to provide subgroup efficacy analysis by previous SARS-CoV-2 exposure, age group, or underlying medical conditions. Nonetheless, the efficacy found in participants with obesity is promising because this condition has been associated with lower immune response in other inactivated vaccines.[11]

There is international concern that the emergency of SARS-CoV-2 variants may alter vaccine efficacy. Two variants haveemerged in Brazil after this trial started, the so-called P.2 and P.1 Out of them, only the P.2 variant was circulating on the study centres during the period covered by this analysis. Although these variants have several mutations that are key to the function of many antibodies, there was a consistent neutralization of all these variants by serum of participants given the inactivated vaccine. This is expected as the vaccine contains the whole virus.

The observed safety and tolerability profiles were outstanding. As it was observed with other COVID-19 vaccines, no vaccine-enhanced disease effect was documented, besides post-implementation surveillance is advisable.[12] Local pain was the most frequent adverse reaction. Differences in adverse event rates between experimental and control products became an issue in several COVID-19 vaccine developments, as study blinding could be compromised leading to changes in participant behaviour.

Since CoronaVac showed similar reactogenicity to placebo, such concern was not an issue in this trial.

This pivotal trial for CoronaVac was able to demonstrate the safety and efficacy of a new COVID-19 vaccine with one of the most efficient approaches among first-wave developers maintaining the highest standards in science and ethics. After the results of this study were initially released on January 12, 2021, Butantan have delivered 38,2 million doses to the Brazilian Public Health System and Sinovac distributed additional 180 million doses in around 30 low-and-middle-income countries up to April 07, 2021. The deployment rate of this vaccine was higher and more opportune for those countries than other initiatives [13] demonstrating the success of the Sinovac-Butantan co-development and confirming that the use of traditional inactivated virus vaccine strategies cannot be ruled out as a platform of rapid public health response to epidemics or pandemics caused by emerging pathogens, such as SARS-CoV-2.

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Figure legends

Figure 1: Study Profile.

All participants enrolled from Jul. 21 to Dec. 16, 2020, were shown in the diagram.

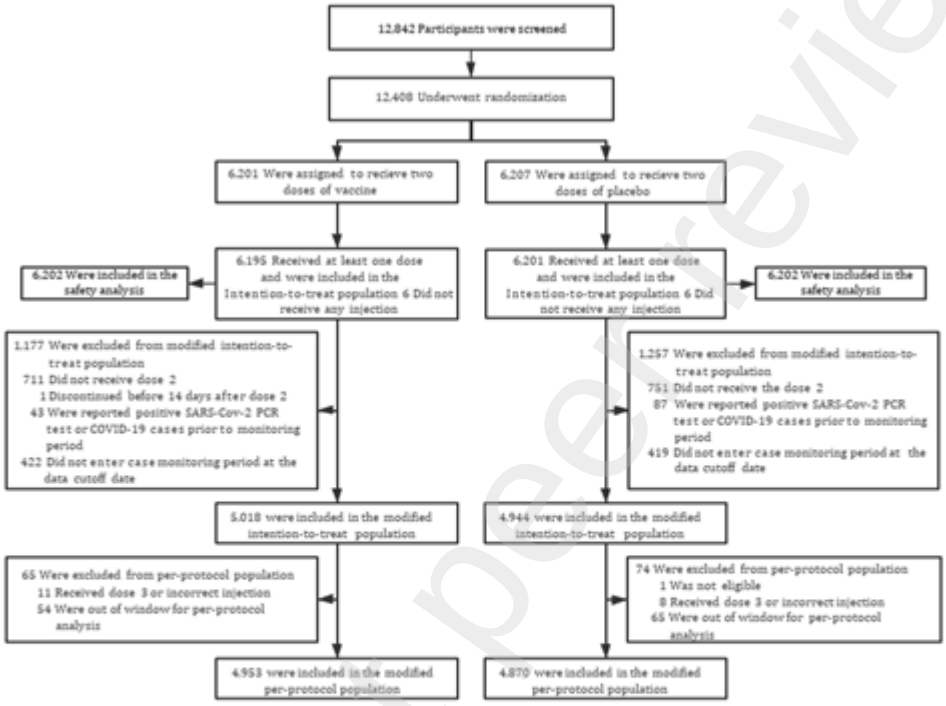


Figure 2: Overview of Adverse Reactions and Solicited Local/Systemic Adverse Reactions.

The percentage of participants who had adverse reactions after any administration of vaccine or placebo was shown. (A) The overview of the percentage of participants who had any adverse reactions; (B) The percentage of participants who had local solicited adverse reactions by different symptoms; (C) The percentage of participants who had systematic solicited adverse reactions by different symptoms.

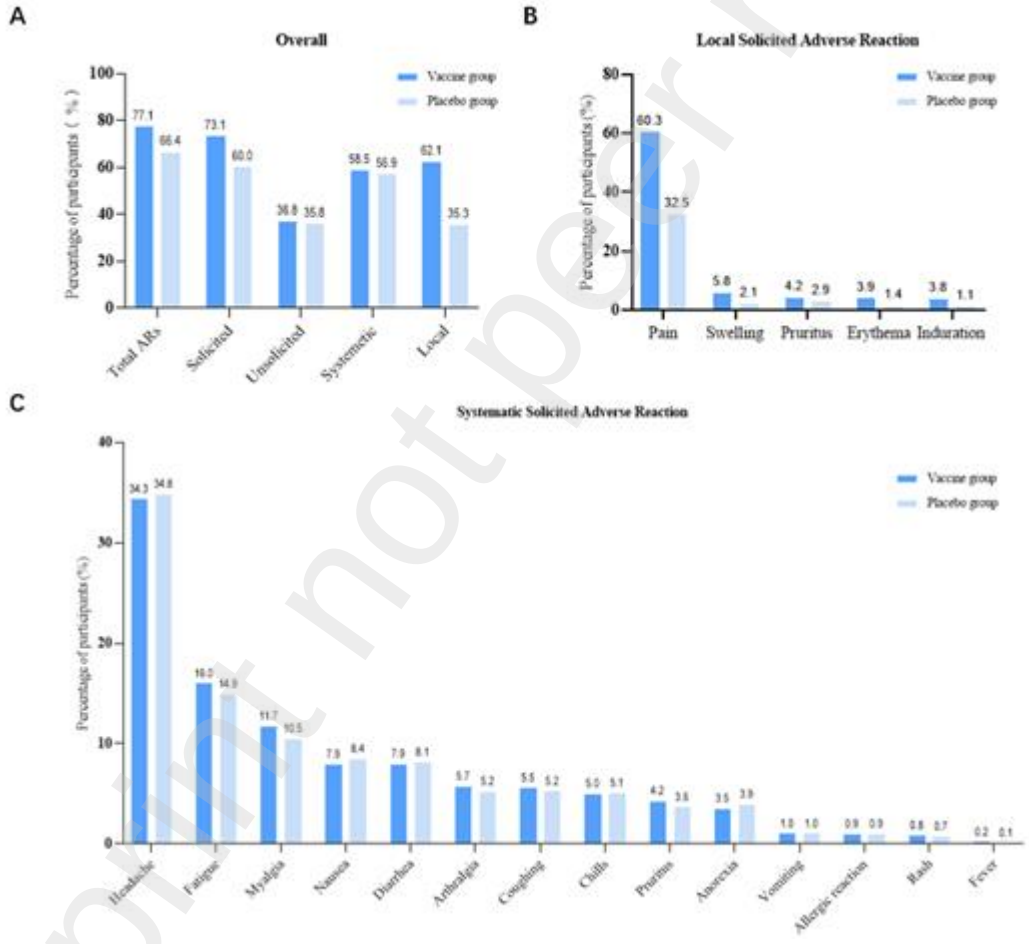
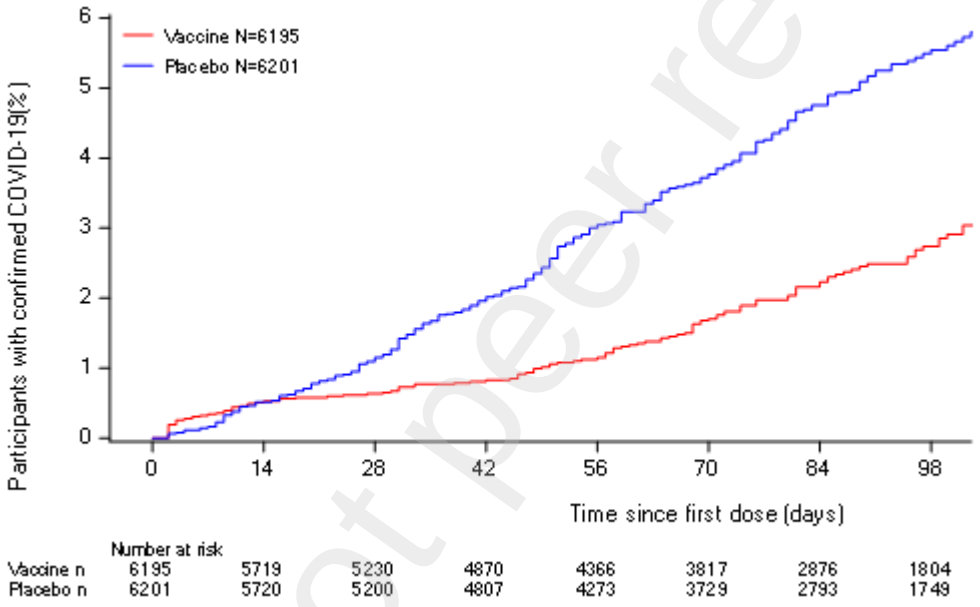


Figure 3. Efficacy of vaccine against COVID-19 cases after the 1st dose and the Kaplan-Meier cumulative incidence curves

(A) The Kaplan-Meier cumulative incidence curves of symptomatic Covid-19 cases after the 1st dose of vaccination. (B) The number of cases collected, incidence density, and efficacy of 14 days after the 1st dose and 2nd dose. Analysis was based on the intention-to-treat population; Incidence density: per 100 person-years.

A



B

Time	No. of cases	Vaccine n/N(incidence density)	Placebo n/N(incidence density per 100 person-year)	Efficacy (95%CI)
14 days after 1st dose	313	94/5717(8·0)	219/5714(19·0)	57·9 (46·4, 66·9)
14 days after 2nd dose	253	85/4953(11·0)	168/4870(22·3)	50·7 (35·9, 62·0)

Tables

Table 1: Baseline characteristics of participants who received at least one dose of vaccine or placebo

	Vaccine (N=6195)	Placebo (N=6201)	Total (N=12396)
Age Group			
18~59 years	5879 (94·9%)	5885 (94·9%)	11764 (94·9%)
≥60 years	316 (5·1%)	316 (5·1%)	632 (5·1%)
Gender			
Male	2270 (36·6%)	2171 (35·0%)	4441 (35·8%)
Female	3925 (63·4%)	4030 (65·0%)	7955 (64·2%)
Ethnic			
White	4685 (75·8%)	4633 (74·8%)	9318 (75·3%)
Multiracial	1012 (16·4%)	1065 (17·2%)	2077 (16·8%)
Black or African American	329 (5·3%)	319 (5·2%)	648 (5·2%)
Asian	148 (2·4%)	163 (2·6%)	311 (2·5%)
American Indian or Alaska Native	11 (0·2%)	13 (0·2%)	24 (0·2%)

	Vaccine (N=6195)	Placebo (N=6201)	Total (N=12396)
Underlying Disease	3441 (55·5%)	3484 (56·2%)	6925 (55·9%)
Cardiovascular disease	792 (12·8%)	773 (12·5%)	1565 (12·6%)
Diabetes	218 (3·5%)	197 (3·2%)	415 (3·4%)
Obesity	1386 (22·4%)	1403 (22·6%)	2789 (22·5%)
Age, years	39·42 (10·7)	39·59 (10·8)	39·50 (10·8)
BMI, kg/m^2	26·841 (5·1)	26·792 (5·3)	26·817 (5·2)

1 Data are n (%) and mean (SD).

2

3

Table 2. Efficacy against COVID-19 cases 14 days after the 2nd dose

	Total No. of cases	Vaccine	Placebo	Vaccine Efficacy (95%CI)
		n/N(incidence density)	n/N(incidence density per 100 person-year)	
Overall	253	85/4953(11·0)	168/4870(22·3)	50·7 (35·9, 62·0) [1]
Severity				
Score 3 and above	35	5/4953(0·7)	30/4870 (4·1)	83·7(58·0, 93·7)
Score 4 and above	10	0/4953 (0·0)	10/4870 (1·4)	100·0(56·4, 100·0) [2]
Severe	6	0/4953 (0·0)	6/4870 (0·8)	100·0(16·9, 100·0) [2]
Interval between two doses				
<21 days	226	77/4184(11·6)	149/4148(22·7)	49·1(33·0, 61·4)
≥21 days	27	8/769(8·6)	19/722(23·1)	62·3(13·9, 83·5)

	Total No. of cases	Vaccine	Placebo	Vaccine Efficacy (95%CI)
		n/N(incidence density)	n/N(incidence density per 100 person-year)	
Exposure to SARS-Cov-2 pre-vaccination				
Unexposed	200	67/3637(13·3)	133/3587(26·8)	50·5(33·6, 63·1)
Exposed	9	3/401(5·9)	6/408(11·7)	49·5(-101·8, 87·4)
Age group				
18~59 years	247	83/4741 (11·3)	164/4663 (22·8)	50·7(35·8, 62·1)
≥60 years	6	2/212 (10·8)	4/207 (21·9)	51·1(-166·9, 91·0)
Underlying Disease				
No	123	41/2222(13·2)	82/2140(27·8)	52·4(30·8, 67·3)
Yes	130	44/2731(10·6)	86/2730(20·8)	48·9(26·6, 64·5)

	Total No. of cases	Vaccine	Placebo	Vaccine Efficacy (95%CI)
		n/N(incidence density)	n/N(incidence density per 100 person-year)	
Cardiovascular disease	16	6/621(7·1)	10/608(11·6)	39·5(-66·4, 78·0)
Diabetes	8	3/175(11·2)	5/159(21·1)	48·6(-115·3, 87·7)
Obesity	63	13/1099(5·8)	50/1112(23·0)	74·9(53·7, 86·4)
Asian	4	1/125(5.38)	3/125(15.54)	66.02(-226.82, 96.47)

[1] The efficacy corrected based on the α spending in the interim analysis was 50.7% (95.4%CI: 35.7, 62.2).

[2] Calculated based on Poisson regression model

Appendix 1 Protocol violation

Table 1-1. Data set division of each protocol violation

No.	Protocol Violations	Efficacy Evaluation			Safety Evaluation		
		PPS	ITT	mITT	SS	SS1	SS2
1	Not vaccinated after randomisation	N	N	N	N	N	N
2	Received 1 dose vaccination	N	Y	N	Y	Y	N
3	Withdraw before 14 days after the second dose vaccination	N	Y	N	NA	NA	NA
4	Received 3 doses vaccination	N	Y	Y	Y	Y	Y
5	Participated in any COVID-19 vaccine clinical trial or vaccinated COVID-19 vaccine in the past	N	Y	Y	NA	NA	NA
6	Received the second dose vaccination beyond the window period	N	Y	Y	Y	Y	Y
7	Received wrong vaccine*	N	Y	Y	NA	NA	NA
8	The time of data analysis was before 14 days after the second dose vaccination	N	Y	N	NA	NA	NA
9	PCR positive between the first dose vaccination to the 14 days after the second dose vaccination	N	Y	Y	NA	NA	NA
10	Diagnosed COVID-19 between the first dose vaccination to the 14 days after the second dose vaccination	N	Y	Y	NA	NA	NA

*Details see Table 1-2.

Table 1-2. List of wrong vaccinations*

No. of subject	Wrong dose vaccination	No. of vaccine	Date of wrong dose vaccination	Describe of protocol violation
111451	1	111454	2020/8/6	
111577	2	111571	2020/8/25	
112384	1	112386	2020/8/20	
112538	2	114579	2020/9/4	
112828	2	111828	2020/9/8	
113046	2	113007	2020/9/9	
115170	2	115191	2020/9/23	
115191	2	115170	2020/9/23	
116623	1	116593	2020/9/17	
116737	2	wrong arm**	2020/10/1	Due to the error of the unblinded pharmacist, subject 116737 was assigned the wrong vaccine in V2.
116811	1	wrong arm**	2020/9/18	Due to the error of the unblinded pharmacist, subject 116811 was assigned the wrong vaccine in V1.
116881	1	wrong arm**	2020/9/18	Due to lack of supervision, the unblinded pharmacist assigned the wrong vaccine to subject 116881 in V1.
117927	2	118063	2020/10/9	
118339	1	wrong arm**	2020/9/26	Due to the error of the unblinded staff, an error occurred in the allocation of vaccine to subject 118339. Date of occurrence of PD: 2020-09-26
119167	2	119538	2020/10/20	
119278	1	wrong arm**	2020/10/3	Due to the absence of double review, subject 119278 was assigned the wrong vaccine in V1.

120446	1	120426	2020/11/6	
120579	1	Unknown**	2020/10/19	The unblinded monitor confirmed that subject 120579 was vaccinated on October 19, 2020, but the IWRS indicated that this assignment did not occur on that day. Therefore, it is unknown which vaccine the subject has been assigned.

*From the protocol deviation list provided by the monitor

**In the overall and corresponding dose safety analysis, from a conservative perspective, subjects with “wrong arm” and “unknown” are analyzed by vaccine group.

Appendix 2 Study sites

Table 2. Information of study sites

Code.	Study Site	Address	Principal Investigator
SAO06	Instituto de Infectologia Emílio Ribas	Sao Paulo, SP, Brazil, 01246-900	Luiz Carlos Pereira Júnior, MD, PhD
CWB01	Hospital das Clínicas da Universidade Federal do Paraná	Curitiba, PR, Brazil, 80060-900	Sonia Mara Raboni, MD, PhD
POA01	Hospital São Lucas da Pontificia Universidade Catolica do Rio Grande do Sul	Porto Alegre, RS, Brazil, 90619-900	Fabiano Ramos, MD, PhD
BHZ01	Universidade Federal de Minas Gerais	Belo Horizonte, MG, Brazil, 30750-140	Mauro Martins Teixeira, MD, PhD
BSB01	Universidade de Brasília	Brasilia, DF, Brazil, 71691-082	Gustavo Adolfo Sierra Romero, MD, PhD
SCS01	Universidade Municipal de São Caetano do Sul	São Caetano do Sul, SP, Brazil, 09521-160	Fábio Eudes Leal, MD, PhD
SAO06	Instituto Israelita de Ensino e Pesquisa Albert Einstein	Sao Paulo, SP, Brazil, 05652-900	Luis Fernando Aranha Camargo, MD, PhD
VCP01	Hospital das Clínicas da UNICAMP	Campinas, SP, Brazil, 13083-888	Francisco Hideo Aoki, MD, PhD
RAO01	Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo	Ribeirao Preto, SP, Brazil, 14015-069	Eduardo Barbosa Coelho, MD, PhD
SAO01	Centro de Pesquisas Clínicas do Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo	Sao Paulo, SP, Brazil, 05403-000	Esper Georges Kallás, MD,PhD
PET01	Universidade Federal de Pelotas, Faculdade de Medicina. Departamento de Clínica Médica	Pelotas, RS, Brasil, 96030-002	Danise Senna Oliveira, MD, PhD
SJP01	Faculdade de Medicina de São José do Rio Preto - FAMERP	São José Do Rio Preto, SP, Brazil, 15090-000	Maurício Lacerda Nogueira, MD, PhD
CWB01	Universidade Federal de Mato Grosso, Faculdade de Ciências Médicas, Hospital Univeristário Júlio Müller.	Cuiabá, MT – Brasil, 78048-902	Cor Jesus Fernandes Fontes, MD, PhD
BAT01	Hospital de Amor	Barretos, SP, Brazil 14780-000	Gecilmara Cristina Salviato Pileggi, MD, PhD
CGR01	Hospital Universitário Maria Aparecida Pedrossian, Universidade Federal de Mato Grosso do Sul	Campo Grande, MS, Brazil, 79080-190	Ana Lúcia Lyrio de Oliveira, MD, PhD

RIO01	Instituto de Infectologia Evandro Chagas - Fiocruz	Rio De Janeiro, Brazil, 21710-232	André Machado de Siqueira, MD, PhD

Appendix 3 Adverse Events

Table 3-1. Overview of adverse events in subjects after vaccination

Category	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Total AEs	29041	5096(82·2%)	25619	4670(75·4%)	54660	9766(78·8%)	<0·0001
AEs related to vaccine	21162	4782(77·1%)	17270	4111(66·4%)	38432	8893(71·7%)	<0·0001
Solicited AEs	14949	4536(73·1%)	11119	3714(60·0%)	26068	8250(66·6%)	<0·0001
Unsolicited AEs	6213	2284(36·8%)	6151	2215(35·8%)	12364	4499(36·3%)	0·2177
Systemic AEs	14164	3625(58·5%)	14056	3525(56·9%)	28220	7150(57·7%)	0·0842
Local AEs	6998	3854(62·1%)	3213	2188(35·3%)	10211	6042(48·7%)	<0·0001
AEs within 60 min	611	460(7·4%)	525	413(6·7%)	1136	873(7·0%)	0·1064
AEs within 0-7 days	16583	4613(74·4%)	12625	3823(61·7%)	29208	8436(68·1%)	<0·0001
AEs in 8-28 days	4046	1619(26·1%)	4132	1615(26·1%)	8178	3234(26·1%)	0·9837
Grade 1 Adverse Event	17693	4652(75·0%)	13889	3901(63·0%)	31582	8553(69·0%)	<0·0001
Grade 2 Adverse Event	3306	1648(26·6%)	3158	1546(25·0%)	6464	3194(25·8%)	0·042
Grade 3 Adverse Event	144	98(1·6%)	205	128(2·1%)	349	226(1·8%)	0·0441
AEs unrelated to vaccine	7813	2398(38·7%)	8295	2442(39·4%)	16108	4840(39·0%)	0·3869

Table 3-2. Adverse reactions reported within 28 days after whole-schedule vaccination

Category	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Total adverse reactions	21162	4782(77·1%)	17270	4111(66·4%)	38432	8893(71·7%)	<0·0001
Solicited adverse reactions	14949	4536(73·1%)	11119	3714(60·0%)	26068	8250(66·6%)	<0·0001
Local adverse reactions	6767	3815(61·5%)	3074	2143(34·6%)	9841	5958(48·1%)	<0·0001
Vaccination site pain	5508	3742(60·3%)	2555	2014(32·5%)	8063	5756(46·4%)	<0·0001
Swelling	434	359(5·8%)	147	130(2·1%)	581	489(3·9%)	<0·0001
Pruritus	306	263(4·2%)	207	181(2·9%)	513	444(3·6%)	<0·0001
Redness	264	241(3·9%)	93	89(1·4%)	357	330(2·7%)	<0·0001
Induration	255	235(3·8%)	72	67(1·1%)	327	302(2·4%)	<0·0001
Systemic adverse reactions	8182	2999(48·4%)	8045	2947(47·6%)	16227	5946(48·0%)	0·3882
Headache	3034	2128(34·3%)	3098	2157(34·8%)	6132	4285(34·6%)	0·5583
Fatigue	1209	989(16·0%)	1164	922(14·9%)	2373	1911(15·4%)	0·1059
Myalgia	879	727(11·7%)	771	648(10·5%)	1650	1375(11·1%)	0·0257
Nausea	573	490(7·9%)	629	522(8·4%)	1202	1012(8·2%)	0·2939
Diarrhea	576	492(7·9%)	576	501(8·1%)	1152	993(8·0%)	0·7659
Arthralgia	411	353(5·7%)	369	321(5·2%)	780	674(5·4%)	0·2195
Cough	392	343(5·5%)	369	322(5·2%)	761	665(5·4%)	0·4254

Category	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Chills	359	309(5·0%)	350	313(5·1%)	709	622(5·0%)	0·8693
Pruritus	315	263(4·2%)	266	225(3·6%)	581	488(3·9%)	0·0874
Appetite impaired	241	217(3·5%)	268	243(3·9%)	509	460(3·7%)	0·2169
Vomiting	64	61(1·0%)	66	61(1·0%)	130	122(1·0%)	1·0000
Hypersensitivity	66	58(0·9%)	68	58(0·9%)	134	116(0·9%)	1·0000
Rash	53	49(0·8%)	47	42(0·7%)	100	91(0·7%)	0·5281
Fever	10	9(0·2%)	4	4(0·1%)	14	13(0·1%)	0·2666
Unsolicited adverse reactions	6213	2284(36·8%)	6151	2215(35·8%)	12364	4499(36·3%)	0·2177
Tremor	10	10(0·2%)	1	1(0·0%)	11	11(0·1%)	0·0117
Complex local pain syndrome	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Wheezing	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Vaccination site pain	133	124(2·0%)	70	65(1·1%)	203	189(1·5%)	<0·0001
Vaccination site redness	19	17(0·3%)	10	10(0·2%)	29	27(0·2%)	0·2473
Vaccination site swelling	16	15(0·2%)	6	6(0·1%)	22	21(0·2%)	0·0781
Oedema	14	14(0·2%)	6	6(0·1%)	20	20(0·2%)	0·1150
Vaccination site induration	18	17(0·3%)	3	3(0·1%)	21	20(0·2%)	0·0026
Vaccination site warmth	10	10(0·2%)	5	5(0·1%)	15	15(0·1%)	0·3015

Category	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Oedema peripheral	4	4(0·1%)	1	1(0·0%)	5	5(0·0%)	0·3749
Intestinal angina	5	5(0·1%)	3	3(0·1%)	8	8(0·1%)	0·7265
Paraesthesia oral	6	6(0·1%)	1	1(0·0%)	7	7(0·1%)	0·1249
Gastritis	4	4(0·1%)	2	2(0·0%)	6	6(0·1%)	0·6874
Abdominal pain lower	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Gastroesophageal reflux disease	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Muscular weakness	5	5(0·1%)	3	3(0·1%)	8	8(0·1%)	0·7265
Joint swelling	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Ecchymosis	5	5(0·1%)	2	2(0·0%)	7	7(0·1%)	0·4530
Petechiae	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Alopecia	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Sinusitis	7	7(0·1%)	4	4(0·1%)	11	11(0·1%)	0·5486
Flushing	39	37(0·6%)	20	18(0·3%)	59	55(0·4%)	0·0142
Hyperaemia	13	13(0·2%)	10	8(0·1%)	23	21(0·2%)	0·3829
Hypoacusis	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Photophobia	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Anxiety disorder	5	4(0·1%)	2	2(0·0%)	7	6(0·1%)	0·6874

Category	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Tachycardia	7	7(0·1%)	4	4(0·1%)	11	11(0·1%)	0·5486
Palpitations	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000

Table 3-3. Adverse reactions reported within 14 days after first dose vaccination

Category	Vaccine group (N=6196)		Placebo group (N=6200)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Total adverse reactions	11658	4058(65·5%)	9964	3438(55·5%)	21622	7496(60·5%)	<0·0001
Local adverse reactions							
Vaccination site pain	2890	2750(44·4%)	1442	1387(22·4%)	4332	4137(33·4%)	<0·0001
Induration	90	88(1·4%)	35	34(0·6%)	125	122(1·0%)	<0·0001
Swelling	185	162(2·6%)	77	72(1·2%)	262	234(2·0%)	<0·0001
Redness	97	95(1·5%)	52	48(0·8%)	149	143(1·2%)	<0·0001
Pruritus	154	147(2·4%)	133	126(2·0%)	287	273(2·2%)	0·1993
Warmth	6	6(0·1%)	2	2(0·0%)	8	8(0·1%)	0·1794
Rash	5	4(0·1%)	2	2(0·0%)	7	6(0·1%)	0·4529
Systemic adverse reactions							
Fever	8	7(0·1%)	8	8(0·1%)	16	15(0·1%)	1·0000
Hypersensitivity	53	47(0·8%)	50	44(0·7%)	103	91(0·7%)	0·7537
Rash	42	36(0·6%)	32	30(0·5%)	74	66(0·5%)	0·4625
Diarrhea	502	451(7·3%)	512	454(7·3%)	1014	905(7·3%)	0·9450
Appetite impaired	208	188(3·0%)	231	213(3·4%)	439	401(3·2%)	0·2230

Category	Vaccine group (N=6196)		Placebo group (N=6200)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Vomiting	48	47(0·8%)	51	49(0·8%)	99	96(0·8%)	0·9185
Nausea	464	423(6·8%)	521	445(7·2%)	985	868(7·0%)	0·4599
Myalgia	686	604(9·8%)	631	545(8·8%)	1317	1149(9·3%)	0·0677
Headache	2615	1944(31·4%)	2726	1996(32·2%)	5341	3940(31·8%)	0·3348
Cough	380	337(5·4%)	364	318(5·1%)	744	655(5·3%)	0·4458
Fatigue	1016	860(13·9%)	943	798(12·9%)	1959	1658(13·4%)	0·1018
Arthralgia	331	293(4·7%)	308	276(4·5%)	639	569(4·6%)	0·4659
Chills	274	252(4·1%)	285	266(4·3%)	559	518(4·2%)	0·5596
Pruritus	243	213(3·4%)	226	194(3·1%)	469	407(3·3%)	0·3387
Oedema	8	8(0·1%)	3	3(0·1%)	11	11(0·1%)	0·1457
Chest pain	7	7(0·1%)	4	4(0·1%)	11	11(0·1%)	0·3873
Warm at the vaccination site	6	6(0·1%)	2	2(0·0%)	8	8(0·1%)	0·1794
Rash at the vaccination site	5	4(0·1%)	2	2(0·0%)	7	6(0·1%)	0·4529
Tremor	8	8(0·1%)	1	1(0·0%)	9	9(0·1%)	0·0214
Paraesthesia oral	5	5(0·1%)	1	1(0·0%)	6	6(0·1%)	0·1248
Lower abdominal pain	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	0·6248

Category	Vaccine group (N=6196)		Placebo group (N=6200)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Gastritis	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	0·6248
Back pain	26	26(0·4%)	19	17(0·3%)	45	43(0·4%)	0·1733
Muscle spasms	4	4(0·1%)	2	2(0·0%)	6	6(0·1%)	0·4529
Muscular weakness	3	3(0·1%)	1	1(0·0%)	4	4(0·0%)	0·3748
Hyperhidrosis	12	12(0·2%)	7	7(0·1%)	19	19(0·2%)	0·2627
Ecchymosis	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	0·6248
Alopecia	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	0·6248
Oral herpes	16	16(0·3%)	10	9(0·2%)	26	25(0·2%)	0·1681
Rhinitis	5	5(0·1%)	3	3(0·1%)	8	8(0·1%)	0·5075
Conjunctivitis	4	4(0·1%)	2	2(0·0%)	6	6(0·1%)	0·4529
Sinusitis	4	4(0·1%)	1	1(0·0%)	5	5(0·0%)	0·2185
Amygdalitis	2	2(0·0%)	2	1(0·0%)	4	3(0·0%)	0·6248
Flushing	18	18(0·3%)	13	12(0·2%)	31	30(0·2%)	0·2803
Palpitation	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	0·6248

Table 3-4. Adverse reactions reported within 28 days after second-dose vaccination

Category	Vaccine group (N=5453)		Placebo group (N=5481)		Total (N=10934)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Total adverse reactions	9481	3294(60·1%)	7329	2418(44·3%)	16810	5712(52·2%)	<0·0001
Local adverse reactions							
Vaccination site pain	2746	2520(46·0%)	1188	1079(19·8%)	3934	3599(32·9%)	**<0·0001**
Induration	180	174(3·2%)	40	39(0·7%)	220	213(2·0%)	**<0·0001**
Swelling	265	235(4·3%)	76	70(1·3%)	341	305(2·8%)	**<0·0001**
Redness	186	174(3·2%)	51	51(0·9%)	237	225(2·1%)	**<0·0001**
Pruritus	174	154(2·9%)	109	89(1·6%)	283	243(2·2%)	**<0·0001**
Sclerosis at the vaccination site	2	2(0·0%)	0	0(0·0%)	2	2(0·0%)	0·5000
Epidermis exfoliation at the vaccination site	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Pustules at the vaccination site	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Systemic adverse reactions							
Fever	3	3(0·1%)	4	4(0·1%)	7	7(0·1%)	0·7258
Hypersensitivity	37	32(0·6%)	43	37(0·7%)	80	69(0·6%)	0·5482
Rash	25	25(0·5%)	25	23(0·4%)	50	48(0·4%)	0·8852
Diarrhea	335	300(5·5%)	340	296(5·4%)	675	596(5·5%)	0·9329

Category	Vaccine group (N=5453)		Placebo group (N=5481)		Total (N=10934)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Appetite impaired	126	110(2·0%)	143	131(2·4%)	269	241(2·2%)	0·1714
Vomiting	50	50(0·9%)	48	45(0·8%)	98	95(0·9%)	0·6805
Nausea	304	263(4·8%)	311	266(4·9%)	615	529(4·8%)	0·8586
Myalgia	526	439(8·0%)	478	403(7·4%)	1004	842(7·7%)	0·2365
Headache	1957	1354(24·7%)	1922	1317(24·2%)	3879	2671(24·4%)	0·5044
Cough	283	247(4·5%)	282	245(4·5%)	565	492(4·5%)	1·0000
Fatigue	593	496(9·1%)	636	538(9·9%)	1229	1034(9·5%)	0·1504
Arthralgia	229	187(3·4%)	202	178(3·3%)	431	365(3·3%)	0·6706
Chills	185	164(3·0%)	200	186(3·4%)	385	350(3·2%)	0·232
Pruritus	155	129(2·4%)	117	100(1·8%)	272	229(2·1%)	0·0615
Oedema	6	6(0·1%)	3	3(0·1%)	9	9(0·1%)	0·5076
Complex local pain syndrome	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Intestinal angina	3	3(0·1%)	1	1(0·0%)	4	4(0·0%)	0·6249
Gastritis	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Pain in limb	29	25(0·5%)	18	15(0·3%)	47	40(0·4%)	0·1532
Neck pain	11	11(0·2%)	5	5(0·1%)	16	16(0·2%)	0·2098

Category	Vaccine group (N=5453)		Placebo group (N=5481)		Total (N=10934)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Dyspnea	19	18(0·3%)	10	10(0·2%)	29	28(0·3%)	0·1844
Rhinallergosis	8	8(0·2%)	5	5(0·1%)	13	13(0·1%)	0·5808
Erythema	36	35(0·6%)	25	23(0·4%)	61	58(0·5%)	0·1470
Ecchymosis	3	3(0·1%)	1	1(0·0%)	4	4(0·0%)	0·6249
Skin warm	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Pharyngitis	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Flushing	21	20(0·4%)	7	7(0·1%)	28	27(0·3%)	0·0190
Hyperaemia	6	6(0·1%)	5	4(0·1%)	11	10(0·1%)	0·7538
Eye irritation	4	4(0·1%)	3	2(0·0%)	7	6(0·1%)	0·6874
Anxiety disorder	5	4(0·1%)	1	1(0·0%)	6	5(0·1%)	0·3749
Tachycardia	5	5(0·1%)	2	2(0·0%)	7	7(0·1%)	0·4530

Table 3-5. Adverse events in subjects with concomitant diseases

Concomitant disease	Vaccine group (N=3447)		Placebo group (N=3478)		Total (N=6925)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Cardiovascular disease	2553	560/794(70·5%)	2083	480/771(62·3%)	4636	1040/1565(66·5%)	0·0006
Diabetes	802	150/219(68·5%)	554	123/196(62·8%)	1356	273/415(65·8%)	0·2543
Obesity	5147	1058/1388(76·2%)	4171	933/1401(66·6%)	9318	1991/2789(71·4%)	<0·0001
Chronic lung disease	7	4/5(80·0%)	2	1/4(25·0%)	9	5/9(55·6%)	0·2063
Malignant disease	85	19/27(70·4%)	87	18/25(72·0%)	172	37/52(71·2%)	1·0000

Table 3-6. Adverse reactions in subjects with concomitant diseases

Category	Vaccine group (N=3447)		Placebo group (N=3478)		Total (N=6925)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Total adverse reactions	12974	2701(78·4%)	10961	2413(69·4%)	23935	5114(73·9%)	<0·0001
Solicited adverse reactions	9046	2562(74·3%)	6962	2176(62·6%)	16008	4738(68·4%)	<0·0001
Local adverse reactions	3935	2134(61·9%)	1836	1235(35·5%)	5771	3369(48·7%)	<0·0001
Vaccination site pain	3143	2096(60·8%)	1512	1156(33·2%)	4655	3252(47·0%)	<0·0001
Swelling	277	225(6·5%)	96	84(2·4%)	373	309(4·5%)	<0·0001
Redness	156	141(4·1%)	55	52(1·5%)	211	193(2·8%)	<0·0001
Induration	162	147(4·3%)	43	38(1·1%)	205	185(2·7%)	<0·0001
Vaccination site pruritus	197	163(4·7%)	130	113(3·3%)	327	276(4·0%)	0·0017
Systemic adverse reactions	5111	1764(51·2%)	5126	1761(50·6%)	10237	3525(50·9%)	0·6653
Headache	1813	1241(36·0%)	1927	1297(37·3%)	3740	2538(36·7%)	0·2725
Fatigue	784	620(18·0%)	752	588(16·9%)	1536	1208(17·5%)	0·2414
Myalgia	552	448(13·0%)	502	417(12·0%)	1054	865(12·5%)	0·2165
Nausea	343	294(8·5%)	410	337(9·7%)	753	631(9·1%)	0·0950
Diarrhea	370	312(9·1%)	352	306(8·8%)	722	618(8·9%)	0·7360
Arthralgia	270	225(6·5%)	255	221(6·4%)	525	446(6·4%)	0·7693
Pruritus	210	167(4·8%)	174	145(4·2%)	384	312(4·5%)	0·1829

Category	Vaccine group (N=3447)		Placebo group (N=3478)		Total (N=6925)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Cough	263	226(6·6%)	236	202(5·8%)	499	428(6·2%)	0·2121
Chills	233	197(5·7%)	216	189(5·4%)	449	386(5·6%)	0·6374
Appetite impaired	150	132(3·8%)	171	154(4·4%)	321	286(4·1%)	0·2271
Rash	31	28(0·8%)	36	32(0·9%)	67	60(0·9%)	0·6978
Hypersensitivity	47	41(1·2%)	50	40(1·2%)	97	81(1·2%)	0·9113
Vomiting	40	38(1·1%)	44	39(1·1%)	84	77(1·1%)	1·0000
Fever	5	5(0·2%)	1	1(0·0%)	6	6(0·1%)	0·1232
Unsolicited adverse reactions	3928	1396(40·5%)	3999	1364(39·2%)	7927	2760(39·9%)	0·2802

Appendix 4 Serious Adverse Events

Table 4. Serious Adverse Events by System Organ Class/Preferred Term

SAE	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Overall SAE	34	33(0·5%)	33	31(0·5%)	67	64(0·5%)	0·9004
Infection and infestations	13	13(0·2%)	14	13(0·2%)	27	26(0·2%)	1·0000
COVID-19	2	2(0·0%)	9	9(0·2%)	11	11(0·1%)	0·0384
Appendicitis	5	5(0·1%)	1	1(0·0%)	6	6(0·1%)	0·2186
Pyelonephritis	2	2(0·0%)	2	2(0·0%)	4	4(0·0%)	1·0000
Severe acute respiratory syndrome (SARS)	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Vestibular neuronitis	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Urinary tract infection	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Diverticulitis	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Pelvic inflammatory disease	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Nasal abscess	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Injury, poisoning and procedural complications	4	4(0·1%)	5	5(0·1%)	9	9(0·1%)	0·7537
Road traffic accident	1	1(0·0%)	2	2(0·0%)	3	3(0·0%)	0·6247
Limb injury	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000

SAE	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Foot fracture	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Fall	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Ankle fracture	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Fracture	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Sacroiliac fracture	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Psychiatric disorders	3	3(0·1%)	2	2(0·0%)	5	5(0·0%)	1·0000
Suicidal ideation	2	2(0·0%)	0	0(0·0%)	2	2(0·0%)	0·5000
Bipolar disorder	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Suicide attempt	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Alcohol abuse	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Pregnancy, puerperium and perinatal conditions	1	1(0·0%)	3	3(0·1%)	4	4(0·0%)	0·3746
Abortion	1	1(0·0%)	2	2(0·0%)	3	3(0·0%)	0·6247
Foetal death	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
General disorders and administration site conditions	3	3(0·1%)	0	0(0·0%)	3	3(0·0%)	0·2499
Systemic inflammatory response syndrome	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Death	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000

SAE	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Chest pain	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Musculoskeletal and connective tissue disorders	2	2(0·0%)	1	1(0·0%)	3	3(0·0%)	1·0000
Arthralgia	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Intervertebral disc disorder	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Intervertebral disc protrusion	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Respiratory, thoracic and mediastinal disorders	3	3(0·1%)	0	0(0·0%)	3	3(0·0%)	0·2499
Dyspnea	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Asthma	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Acute pulmonary oedema	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Nervous system disorders	1	1(0·0%)	1	1(0·0%)	2	2(0·0%)	1·0000
Syncope	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Transient ischaemic attack	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Renal and urinary disorders	0	0(0·0%)	2	2(0·0%)	2	2(0·0%)	0·2497
Nephrolithiasis	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Obstructive nephropathy	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Gastrointestinal disorders	1	1(0·0%)	1	1(0·0%)	2	2(0·0%)	1·0000

SAE	Vaccine group (N=6202)		Placebo group (N=6194)		Total (N=12396)		*P* value
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	
Abdominal pain	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Haemorrhoids thrombosed	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Vascular disorders	2	2(0·0%)	0	0(0·0%)	2	2(0·0%)	0·5000
Deep vein thrombosis	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Hypertension	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Metabolism and nutrition disorders	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Hypokalaemia	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Cardiac disorders	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Cardio-respiratory arrest	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Reproductive system and breast disorders	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Endometriosis	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Skin and subcutaneous tissue disorders	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Rash	1	1(0·0%)	0	0(0·0%)	1	1(0·0%)	1·0000
Hepatobiliary disorders	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997
Cholelithiasis	0	0(0·0%)	1	1(0·0%)	1	1(0·0%)	0·4997

Appendix 5 Efficacy Analysis

Table 5-1. Efficacy analysis by case definitions

Case definition	Total No. of cases	Vaccine	Placebo	Vaccine Efficacy (95%CI)
		n/N(incidence density)	n/N(incidence density per 100 person-year)	
Case definition 1	253	85/4953(11·0)	168/4870(22·3)	50·7 (35·9, 62·0)
Case definition 2	261	87/4953(11·1)	174/4870(22·8)	51·2(36·9, 62·3)
Case definition 3	250	80/4953(10·4)	170/4870(22·7)	54·1 (40·1, 64·8)
Case definition 4	243	79/4953(10·5)	164/4870(22·2)	53·0(38·6, 64·1)

Table 5-2. Efficacy analysis by follow-up time after first-dose vaccination

Follow-up time (after first-dose vaccination)	Total No. of cases	Vaccine	Placebo	Vaccine Efficacy (95%CI)
		n/N(incidence density)	n/N(incidence density per 100 person-year)	
Within 14 days	63	32/6195(11·4)	31/6201(11·0)	-3·3(-4·8, -1·9)
Within 28 days	104	38/6195(5·7)	66/6201(9·8)	42·5(32·9,50·7)
Within 42 days	158	48/6195(8·1)	110/6201(18·5)	56·5(49·6,62·5)
Within 56 days	221	63/6195(7·6)	158/6201(19·1)	60·4(56·5,63·9)
Within 70 days	274	86/6195(8·0)	188/6201(17·7)	54·7(53·2,56·1)
Within 84 days	326	104/6195(8·2)	222/6201(17·7)	53·7(52·7,54·7)
Within 98 days	357	116/6195(8·4)	241/6201(17·6)	52·5(51·9,53·1)
14-28 days after 1 dose*	18	1/5709 (1·3)	17/5697 (21·6)	94·0 (55·1, 99·2)

*For participants who received only single dose vaccination.

Table 5-3. Efficacy analysis by exposure history to SARS-CoV-2

Exposure to SARS-Cov-2 pre-vaccination	Total No. of cases	Vaccine	Placebo	Vaccine Efficacy (95%CI)
		n/N(incidence density)	n/N(incidence density per 100 person-year)	
Unexposed				
Score 2 and above	200	67/3637(13·3)	133/3587(26·8)	50·5(33·6, 63·1)
Score 3 and above	27	2/3637(0·4)	25/3587(4·5)	92·1(66·7, 98·1)
Score 4 and above	10	0/3637(0·0)	10/3587(1·8)	100·0(56·0, 100·0)
Severe	6	0/3637(0·0)	6/3587(1·1)	100·0(16·3, 100·0)
Exposed				
Score 2 and above	9	3/401(5·9)	6/408(11·7)	49·5(-101·8, 87·4)
Score 3 and above	0	0/401(0·0)	0/408(0·0)	NE
Score 4 and above	0	0/401(0·0)	0/408(0·0)	NE
Severe	0	0/401(0·0)	0/408(0·0)	NE

Appendix 6 PROFISCOV Study Group

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