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Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix 1 Immunogenic Detection Method

Detection Method of Neutralization Potency against Pseudovirus

The serum to be tested was inactivated at 56°C for 30 minutes, a 3-fold serial dilution starting from 20-fold was carried out in a 96-well cell culture plate, and the volume of each was 100μl. Then 0.5μl pseudovirus with a concentration of 1.3×104TCID50/ml after the dilution by DMEM complete medium was added to each of the well, and placed in a carbon dioxide incubator at 36.5℃±1℃ for one hour. After the neutralization, 100μl cell suspension with a concentration of 2.0×10^5 cells/ml was added to the 96-well plate, and placed in a carbon dioxide incubator at 36.5℃±1℃ for 20~28 hour. The 96-cell plate was taken out from the carbon dioxide incubator after the cultivation. A multichannel pipette was used to aspirate 150μl of supernatant from each well, 100μl luciferase detection reagent was added to the well. Subsequently, the 96-well plate was placed from light at room temperature for two minutes. After that, the liquid in the reaction well was pipette repeatedly for 6~8 times with a multichannel pipette to make the cells fully lysed. 150μl of liquid was taken from each well, and then was added to the corresponding 96-well chemiluminescence detection plate, which was placed in a chemiluminescence detector to read the luminescence value. Neutralization inhibition rate = [1-(average luminous intensity of the test product group-that of the blank control) / (average luminous intensity of negative group-that of blank control)] × 100%. ID50 was calculated by the Reed-Muench method by the neutralization inhibition rate.

Detection Method of Neutralization Potency against Live SARS-CoV-2

Micro cytopathic effect assay was adopted.

Serum treatment: all serum samples were inactivated at 56℃ in a water bath for 30 minutes.

Medium addition: the cell maintenance medium was added to the cell control group at 100μL/well, and 50 μL/well of maintenance medium was supplemented to the to-be-tested serum group, virus back titration group and positive control group from the second dilution.

Dilution of the serum sample: The serum was diluted four-fold (60 μL sample + 180 μL maintenance medium) with cell maintenance medium (2% newborn calf serum-199 (2% sodium hydrogen carbonate) cell maintenance medium). The diluted serum was added to the cell plate at 100 μL/well, and each sample was diluted to 2 wells in parallel. 50 μL of the mixture in the first dilution was pipetted into the next dilution, and the mixture was pipetted up and down for 8-10 times. The mixture was diluted to the appropriate dilution range by this method, and 50 μL of the last dilution was discarded, and 50 μL of the diluted sample was retained in each well.

Dilution of the virus for neutralization: the SAR-CoV-2 used for neutralization was diluted to 100CCID50/0.05ml by titer.

Neutralization: Serum of different dilutions was mixed with $100CCID_{50}$/0.05ml virus liquid in equal volume (50μL+50μL), respectively, and then incubated in an incubator at 36.5℃， 5%CO_2 for 2h.

Experimental control: Negative serum control, positive serum control, serum sample and cell control were set simultaneously.

Virus Back Titration: The virus suspension diluted to 100 CCID50/0.05 mL was diluted via ten-fold serial dilution, i.e. diluted to 10 CCID50/0.05 mL, 1 CCID50/0.05 mL and 0.1 CCID50/0.05 mL, and added to the 96-well cell plate respectively, 12 well per dilution and 50 μL per well, then 50 μL of cell maintenance medium was added to each well, and the plate was incubated in an incubator at 36.5°C, 5% CO2 for 5 days.

Cell Inoculation and Culture: After incubation, 100μL of Vero cell suspension (cell concentration: 1.0-2.0×105 cell/mL) was added to each well, and then incubated in an incubator at 36.5°C, 5% CO2 for 5 days.

Interpretation of the Results: It was observed for the cytopathic effect after cultured for 3-5 days, and the neutralizing antibody titer of the to-be-tested serum sample was determined according to the observation results of

the cytopathic effect (CPE). The reciprocal of the highest serum dilution without cytopathic effects the end titer. When 1 of the 2 wells of the highest dilution serum shows CPE, while the other does not, the reciprocal of the dilution should be the neutralizing antibody titre of the serum specimen; the reciprocal of the mean dilution of the two wells should be the neutralizing antibody titre of the serum specimen when the 2 wells with the highest dilution are completely pathological while the adjacent 2 wells with low dilution are not pathological completely; when 1 of two adjacent wells is pathological while the other not, the reciprocal of the average dilutions of 2 wells should be the neutralizing antibody titer of the serum specimen. For example, 2 wells with high dilution of 1:8 have a complete CPE, while the adjacent 2 wells with low dilution of 1:16 have no CPE; or in 2 adjacent wells with dilutions of 1:8 and 1:16, one has a CPE, while the other does not. In this case, the reciprocal 12 of the average dilutions of 2 wells is the neutralizing antibody titer of the serum.

Detection Method of specific RBD IgG

Coating: Dilute the recombinant RBD antigen with 0.01M PBS to a final concentration of 1μg/ml. Mix well and add to plate, 100μL per well. Incubate overnight (16-20 hours) at 2-8°C. Wash the plate for 3 times and dry the plate. **Blocking:** Prepare 0.01M blocking solution with 10% BSA, 200μL per well. Incubate for 60-120 minutes at 37°C. Store at 4°C and use within 7 days.

Sample loading: Perform dilution on serum samples with 0.01M PBS. Add one concentration (100μL) per well. Add same species negative blood to 8 wells as negative control. Take sample diluent as blank, add to 8 wells. Incubate at 37°C for 60 to 70 minutes. Wash with washing solution 3 times and dry the plate.

Add HRP conjugated antibody: Add 100μL HRP conjugated antibody (goat anti-human) per well, and incubate for 45-60 minutes at 37°C. Wash the plate for 5 times and dry the plate.

Color developing: Add 50μL color developing solution A and solution B onto the plate respectively, incubate for 15 minutes at room temperature.

Termination of reaction: Add 50μL stop solution to each well, read absorbance at 450nm (630nm as reference).

Result determination: Take 2.1 times of the absorbance of negative serum as the cut-off value, the antibody titer is determined as the highest dilution fold satisfy with OD>cut-off value. When OD is less than 0.05, take 0.05.

Evaluation: Take the maximum dilution ratio as the serum sample titer when the OD value is 2.1 times of the absorbance of negative serum at the same dilution ratio.

Detection Method of T Cell Immune Response

ELISpot Method was adopted to detect the protein-specific T cell response.

The peripheral blood mononuclear cells (PBMCs) of the vaccine recipients can produce the cytokines after in vitro cytotoxic T lymphocyte (CTL) epitope stimulation. Such cytokines can be captures by the specific monoclonal antibody coated on the ELISPOT plate. After cell decomposition, the captured cytokine will bind with the biotin-labelled secondary antibody, and then bind with the horseradish peroxidase-labelled avidin. After substrate incubation, clear and distinguishable spots will appear at the positions of the cells which secrete the cytokine. Count the spot using the ELISpot analysis system. One spot indicates 1 viable cell. Calculate the frequency of the cells which secrete the cytokine. The procedure is as followings:

Prepare ELISpot plate (aseptic conditions)

- Insert the plate strip into the plate frame, and wash 4 times with sterile PBS (200 μL/well).
- Add 200 μL of RPMI1640+1% double antibody +10% FBS medium, and allow to stand at room temperature for more than 30 minutes.

Culture of PBMCs in the ELISpot Plate (Aseptic Conditions)

Prepare the 2× peptide stimulation mixture, stimulation-free control and positive stimulant with RPMI1640+1% double antibody +10% FBS medium according to the test requirements,
According to the layout of the plate, add 50 μL of each of the peptide stimulation mixture, stimulation-free control or positive stimulants to each well. Then add 50 μL of PBMCs of the corresponding density so that each well of the peptide stimulation well and stimulation-free well will contain 1 × 105 cells, and each positive stimulation well will contain 1 × 104 cells.
Establish 3 peptide stimulation wells, 3 stimulation-free wells and 2 positive stimulation wells for each portion of sample. Each well of the peptide stimulation well contains 1 μg/mL of each S protein overlapping peptide. Other conditions except free of overlapping peptide library of the stimulation-free wells are all same as those of the peptide stimulation wells. The stimulants used for the positive stimulation wells are PMA and Ionomycin. The concentrations of the stimulants are PMA 50 ng/mL and Ionomycin 500 ng/mL.
Incubate cells in the 37°C, 5% CO2 cell incubator for 12 h to 24 h, and do not move ELISpot plate during the period.

Spot Detection

- Discard the cells in the plate, and wash the plate with PBS 5 times and 200 μL for each well.
- Dilute 7-B6-ALP with PBS+0.5 % FB according to 1:200, add 100 μL to each well on the ELISpot plate, and place at room temperature for 2 hours.
- Discard the liquid in the plate, and wash the plate with PBS 5 times and 200 μL for each well.
- Filter the substrate (BCIP/NBT-plus) through a 0.45 μm filter membrane, add 100 μL to each well, and react until obvious spot appears. Rinse with plenty of water to stop the reaction. Remove the plate frame from the plastic tray, and rinse the bottom surface of the membrane.
- After ELISpot plate is dry, use ELISA spot image analysis system to count and analyze the spots.

Appendix 2 List Study Endpoints

- **Study Endpoints of Phase 1**

Primary Endpoint

- Incidence of adverse reactions occur from the beginning of the vaccination to 28 days after the whole schedule vaccination.

Secondary Endpoints

- Incidence of adverse reactions within 7 days after each dose of vaccination;
- Incidence of abnormal laboratory index (blood routine test, blood chemistry test, and urine routine test) on the 3rd day after each dose of vaccination;
- Incidence of SAEs from the beginning of the vaccination to 6 months after the whole schedule vaccination;
- Seroconversion rate, seropositive rate, GMT and GMI of neutralizing antibody on the 7,14,21,28, and 42th day after the first dose vaccination (for the days 0 and 14 schedule);
- Seropositive rate of IgG and IgM antibody on the 7,14,21,28, and 42th day after the first dose vaccination (for the days 0 and 14 schedule);
- Seroconversion rate, seropositive rate, GMT and GMI of neutralizing antibody on the 28,35,42, and 56 th day after the first dose vaccination (for the days 0 and 28 schedule);
- Seropositive rate of IgG and IgM antibody on the 28, 35, 42, and 56th day after the first dose vaccination (for the days 0 and 28 schedule).

Exploratory Endpoints

- Positive rate of specific T cell response 14 days after the whole schedule vaccination (IFN-γ detection using Elispot);
- Serpositive rate and GMT 6 months after the whole schedule vaccination;
- Change of IL-6, IL-2 and TNF-α in serum on the 7th day after each dose vaccination.

- **Study Endpoints of Phase 2**

Primary Endpoints

- Seroconversion rate of neutralizing antibody on the 14th (for the days 0 and 14 schedule) or 28th (for the days 0 and 28 schedule) day after the whole schedule vaccination;
- Incidence of adverse reactions occur from the beginning of the vaccination to 28 days after the whole schedule vaccination.

Secondary Endpoints

- Seropositive rate, GMT, and GMI of the neutralizing antibody on the 14th (for the days 0 and 14 schedule) or 28th (for the days 0 and 28 schedule) day after the whole schedule vaccination;
- Seroconversion rate, seropositive rate, GMT, and GMI of the neutralizing antibody on the 28th day after the whole course vaccination for the days 0 and 14 schedule;
- Incidence of adverse reactions within 7 days after each dose vaccination;
- Incidence of SAEs from the beginning of the vaccination to 6 months after the whole schedule vaccination.

Exploratory Endpoints

- Seropositive rate and GMT of neutralizing antibody 6 months after the whole schedule vaccination.

Appendix 3 Adverse events

Table 3-1 Adverse Reactions Post Two Doses of 0/14 Schedule in the Phase 1 Clinical Trial.

Adverse reactions	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=24)	Total (N=72)	*P* value†
Total	7(29.2)	9(37.5)	2(8.3)	8(25.0)	0.0507
Grade 1	7(29.2)	9(37.5)	2(8.3)	18(25.0)	0.0507
Solicited	6(25.0)	9(37.5)	2(8.3)	17(23.6)	0.0695
Unsolicited	1(4.2)	2(8.3)	0(0.0)	3(4.2)	0.7682
Systemic reactions	3(12.5)	4(16.7)	1(4.2)	8(11.1)	0.5137
Fatigue	2(8.3)	3(12.5)	1(4.2)	6(8.3)	0.8654
Hypersensitivity	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000
Diarrhea	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000
Fever	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000
Abdominal pain	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000
Lower abdominal pain	1(4.2)	0(0.0)	0(0.0)	1(1.4)	1.0000
Injection-site reactions	4(16.7)	5(20.8)	1(4.2)	10(13.9)	0.3164
Pain	4(16.7)	5(20.8)	1(4.2)	10(13.9)	0.3164
Discolouration	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000

Note: data in the table were reported within 28 days post any of the two doses.
†P value of the comparison of incidence rate among three groups.

Table 3-2 Adverse Reactions Post Dose 1 or Dose 2 of 0/14 Schedule in the Phase 1 Clinical Trial.

Adverse reactions	Dose 1*					Dose 2¶				
	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=24)	Total (N=72)	*P* value†	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=24)	Total (N=72)	*P* value†
Total	7(29.2)	6(25.0)	2(8.3)	15(20.8)	0.1845	1(4.2)	5(20.8)	1(4.2)	7(9.7)	0.1991
Grade 1	7(29.2)	6(25.0)	2(8.3)	15(20.8)	0.1845	1(4.2)	5(20.8)	1(4.2)	7(9.7)	0.1991
Solicited	6(25.0)	6(25.0)	2(8.3)	14(19.4)	0.2728	1(4.2)	5(20.8)	1(4.2)	7(9.7)	0.1991
Unsolicited	1(4.2)	2(8.3)	0(0.0)	3(4.2)	0.7682	-	-	-	-	-
Systemic reactions	2(8.3)	2(8.3)	1(4.2)	5(6.9)	1.0000	0(0.0)	2(8.3)	1(4.2)	3(4.2)	0.7682
Fatigue	2(8.3)	1(4.2)	1(4.2)	4(5.6)	1.0000	0(0.0)	2(8.3)	1(4.2)	3(4.2)	0.7682
Hypersensitivity	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000	-	-	-	-	-
Diarrhea	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000	-	-	-	-	-
Fever	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000	-	-	-	-	-
Abdominal pain	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000	-	-	-	-	-
Lower abdominal pain	1(4.2)	0(0.0)	0(0.0)	1(1.4)	1.0000	-	-	-	-	-
Injection-site reactions	4(16.7)	4(16.7)	1(4.2)	9(12.5)	0.3700	1(4.2)	3(12.5)	0(0.0)	4(5.6)	0.3143
Pain	4(16.7)	4(16.7)	1(4.2)	9(12.5)	0.3700	1(4.2)	3(12.5)	0(0.0)	4(5.6)	0.3143
Discolouration	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000	-	-	-	-	-

Note：*Reported within 14 days post dose 1. ¶Reported within 28 days post dose 2. †P value of the comparison of incidence rate among three groups.

Table 3-3 Adverse Reactions Post Two Doses of 0/28 Schedule in the Phase 1 Clinical Trial.

Adverse reactions	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=23)	Total (N=71)	*P* value†
Total	3(12.5)	4(16.7)	3(13.0)	10(14.1)	1.0000
Grade 1	3(12.5)	4(16.7)	3(13.0)	10(14.1)	1.0000
Solicited	3(12.5)	4(16.7)	3(13.0)	10(14.1)	1.0000
Unsolicited	0(0.0)	0(0.0)	1(4.4)	1(1.4)	0.3239
Systemic reactions	2(8.3)	2(8.3)	1(4.4)	3(4.2)	0.5364
Fever	0(0.0)	1(4.2)	1(4.4)	2(2.8)	0.7682
Fatigue	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000
Diarrhea	1(4.2)	0(0.0)	0(0.0)	1(1.4)	1.0000
Cough	2(8.3)	0(0.0)	0(0.0)	2(2.8)	0.3239
Injection-site reactions	3(12.5)	3(12.5)	3(13.0)	9(12.7)	1.0000
Pain	3(12.5)	3(12.5)	3(13.0)	9(12.7)	1.0000
Discolouration	0(0.0)	0(0.0)	1(4.4)	1(1.4)	1.0000

Note: data in the table were reported within 28 days post any of the two doses.
†P value of the comparison of incidence rate among three groups.

Table 3-4 Adverse Reactions Post Dose 1 and Dose 2 of 0/28 Schedule in the Phase 1 Clinical Trial.

Adverse reactions	Dose 1*					Dose 2¶				
	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=23)	Total (N=71)	*P* value†	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=23)	Total (N=71)	*P* value†
Total	3(12.5)	3(12.5)	2(8.7)	8(11.3)	1.0000	2(8.3)	1(4.2)	1(4.4)	4(5.6)	1.0000
Grade 1	3(12.5)	3(12.5)	2(8.7)	8(11.3)	1.0000	2(8.3)	1(4.2)	1(4.4)	4(5.6)	1.0000
Solicited	3(12.5)	3(12.5)	2(8.7)	8(11.3)	1.0000	2(8.3)	1(4.2)	1(4.4)	4(5.6)	1.0000
Unsolicited	0(0.0)	0(0.0)	1(4.4)	1(1.4)	0.3239	-	-	-	-	-
Systemic reactions	1(4.2)	1(4.2)	1(4.4)	3(4.2)	1.0000	1(4.2)	1(4.2)	0(0.0)	2(2.8)	1.0000
Fever	0(0.0)	1(4.2)	1(4.4)	2(2.8)	0.7682	-	-	-	-	-
Fatigue	-	-	-	-	-	0(0.0)	1(4.2)	0(0.0)	1(1.4)	1.0000
Diarrhea	1(4.2)	0(0.0)	0(0.0)	1(1.4)	1.0000	-	-	-	-	-
Cough	1(4.2)	0(0.0)	0(0.0)	1(1.4)	1.0000	1(4.2)	0(0.0)	0(0.0)	1(1.4)	1.0000
Injection-site reactions	3(12.5)	3(12.5)	2(8.7)	8(11.3)	1.0000	1(4.2)	0(0.0)	1(4.4)	2(2.8)	0.7682
Pain	3(12.5)	3(12.5)	2(8.7)	8(11.3)	1.0000	1(4.2)	0(0.0)	1(4.4)	2(2.8)	0.7682
Discolouration	0(0.0)	0(0.0)	1(4.4)	1(1.4)	0.3239	-	-	-	-	-

Note：*Reported within 28 days post dose 1. ¶Reported within 28 days post dose 2. †P value of the comparison of incidence rate among three groups.

Table 3-5 Adverse Reactions Post Two Doses of 0/14 Schedule in the Phase 2 Clinical Trial

Adverse reactions	3 μg group (N=120)	6 μg group (N=120)	Placebo group (N=60)	Total (N=300)	*P* value†
Total	40(33.3)	42(35.0)	13(21.7)	95(31.7)	0.1626
Grade 1	39(32.5)	42(35.0)	13(21.7)	94(31.3)	0.1774
Solicited	39(32.5)	40(33.3)	13(21.7)	92(30.7)	0.2455
Unsolicited	3(2.5)	3(2.5)	0(0.0)	6(2.0)	0.6564
Systemic reactions	19(15.8)	16(13.3)	9(15.0)	44(14.7)	0.8695
Fatigue	4(3.3)	7(5.8)	6(10.0)	17(5.7)	0.1761
Fever	4(3.3)	1(0.8)	1(1.7)	6(2.0)	0.4505
Diarrhea	6(5.0)	1(0.8)	1(1.7)	8(2.7)	0.1577
Nausea	2(1.7)	3(2.5)	0(0.0)	5(1.7)	0.6373
Headache	2(1.7)	4(3.3)	1(1.7)	7(2.3)	0.7074
Muscle pain	3(2.5)	2(1.7)	1(1.7)	6(2.0)	1.0000
Cough	0(0.0)	2(1.7)	0(0.0)	2(0.7)	0.3579
Hypersensitivity	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000
Vomiting	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000
Chest pain	1(0.8)	1(0.8)	0(0.0)	2(0.7)	1.0000
Drowsiness	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000
Dizziness	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000
Decreased appetite	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000
Palpitations	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000
Injection-site reactions	28(23.3)	33(27.5)	6(10.0)	67(22.3)	0.0218
Pain	25(20.8)	31(25.8)	6(10.0)	62(20.7)	0.0427
Swelling	2(1.7)	3(2.5)	0(0.0)	5(1.7)	0.6373
Redness	1(0.8)	2(1.7)	0(0.0)	3(1.0)	0.8061
Hypoaesthesia	1(0.8)	1(0.8)	0(0.0)	2(0.7)	1.0000
Discolouration	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000
Pruritus	1(0.8)	1(0.8)	0(0.0)	2(0.7)	1.0000
Induration	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000

Note: data in the table were reported within 28 days post any of the two doses.
†P value of the comparison of incidence rate among three groups.

Table 3-6 Adverse Reactions Post Dose 1 and Dose 2 of 0/14 Schedule in the Phase 2 Clinical Trial

Adverse reactions	Dose 1*					Dose 2¶				
	3 μg group (N=120)	6 μg group (N=120)	Placebo group (N=60)	Total (N=300)	*P* value†	3 μg group (N=120)	6 μg group (N=119)	Placebo group (N=60)	Total (N=299)	*P* value†
Total	24(20.0)	29(24.2)	10(16.7)	63(21.0)	0.5182	20(16.7)	20(16.8)	6(10.0)	46(15.4)	0.4429
Grade 1	24(20.0)	29(24.2)	10(16.7)	63(21.0)	0.5182	19(15.8)	20(16.8)	6(10.0)	45(15.1)	0.5010
Solicited	23(19.2)	27(22.5)	10(16.7)	60(20.0)	0.6558	19(15.8)	20(16.8)	6(10.0)	45(15.1)	0.5010
Unsolicited	2(1.7)	3(2.5)	0(0.0)	5(1.7)	0.6373	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000
Systemic reactions	15(12.5)	13(10.8)	6(10.0)	34(11.3)	0.9135	5(4.2)	6(5.0)	4(6.7)	15(5.1)	0.6955
Fatigue	2(1.7)	6(5.0)	4(6.7)	12(4.0)	0.2059	2(1.7)	2(1.7)	3(5.0)	7(2.3)	0.3762
Fever	3(2.5)	1(0.8)	1(1.7)	5(1.7)	0.8438	2(1.7)	0(0.0)	0(0.0)	2(0.7)	0.5179
Diarrhea	5(4.2)	1(0.8)	0(0.0)	6(2.0)	0.1449	1(0.8)	0(0.0)	1(1.7)	2(0.7)	0.6795
Nausea	2(1.7)	2(1.7)	0(0.0)	4(1.3)	0.6892	0(0.0)	1(0.8)	0(0.0)	1(0.3)	0.5987
Headache	1(0.8)	1(0.8)	1(1.7)	3(1.0)	1.0000	1(0.8)	3(2.5)	0(0.0)	4(1.3)	0.4329
Muscle pain	3(2.5)	1(0.8)	1(1.7)	5(1.7)	0.8438	0(0.0)	2(1.7)	1(1.7)	3(1.0)	0.3249
Cough	0(0.0)	2(1.7)	0(0.0)	2(0.7)	0.3579	-	-	-	-	-
Hypersensitivity	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Vomiting	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Chest pain	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Drowsiness	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Dizziness	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Decreased appetite	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Palpitations	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Injection-site reactions	13(10.8)	21(17.5)	6(10.0)	40(13.3)	0.3661	17(14.2)	15(12.6)	2(3.3)	34(11.4)	0.0816
Pain	11(9.2)	20(16.7)	6(10.0)	37(12.3)	0.1945	16(13.3)	14(11.8)	2(3.3)	32(10.7)	0.0896
Swelling	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000	1(0.8)	3(2.5)	0(0.0)	4(1.3)	0.4329
Redness	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000	0(0.0)	2(1.7)	0(0.0)	2(0.7)	0.1973
Hypoaesthesia	1(0.8)	1(0.8)	0(0.0)	2(0.7)	1.0000	-	-	-	-	-
Discolouration	-	-	-	-	-	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000
Pruritus	-	-	-	-	-	1(0.8)	1(0.8)	0(0.0)	2(0.7)	1.0000
Induration	-	-	-	-	-	1(0.8)	1(0.8)	0(0.00)	2(0.7)	1.0000

Note：*Reported within 14 days post dose 1. ¶Reported within 28 days post dose 2. †P value of the comparison of incidence rate among three groups.

Table 3-7 Adverse Reactions Post Two Doses of 0/28 Schedule in the Phase 2 Clinical Trial

Adverse reactions	3 μg group (N=120)	6 μg group (N=120)	Placebo group (N=60)	Total (N=300)	*P* value†
Total	23(19.2)	23(19.2)	11(18.3)	57(19.0)	1.0000
Grade 1	23(19.2)	23(19.2)	11(18.3)	57(19.0)	1.0000
Solicited	23(19.2)	23(19.2)	10(16.7)	56(18.7)	0.9437
Unsolicited	0(0.0)	1(0.8)	1(1.7)	2(0.7)	0.6789
Systemic reactions	14(11.7)	12(10.0)	6(10.0)	32(10.7)	0.9135
Fatigue	10(8.3)	3(2.5)	2(3.3)	15(5.0)	0.1393
Fever	4(3.3)	4(3.3)	1(1.7)	9(3.0)	0.8300
Diarrhea	1(0.8)	3(2.5)	1(1.7)	5(1.7)	0.8438
Nausea	2(1.7)	0(0.0)	0(0.0)	2(0.7)	0.3579
Headache	3(2.5)	1(0.8)	0(0.0)	4(1.3)	0.5351
Muscle pain	2(1.7)	4(3.3)	3(5.0)	9(3.0)	0.4557
Hypersensitivity	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000
Decreased appetite	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000
Cough	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000
Injection-site reactions	12(10.0)	16(13.3)	7(11.7)	35(11.7)	0.7335
Pain	12(10.0)	13(10.8)	6(10.0)	31(10.3)	1.0000
Redness	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000
Discolouration	0(0.0)	1(0.8)	1(1.7)	2(0.7)	0.6789
Pruritus	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000
Swelling	0(0.0)	1(0.8)	1(1.7)	2(0.7)	0.6789

Note: data in the table were reported within 28 days post any of the two doses.
†P value of the comparison of incidence rate among three groups.

Table 3-8 Adverse Reactions Post Dose 1 and Dose 2 of 0/28 Schedule in the Phase 2 Clinical Trial

Adverse reactions	Dose 1*					Dose 2¶				
	3 μg group (N=120)	6 μg group (N=120)	Placebo group (N=60)	Total (N=300)	*P* value†	3 μg group (N=117)	6 μg group (N=118)	Placebo group (N=61)	Total (N=296)	*P* value†
Total	22(18.3)	21(17.5)	10(16.7)	53(17.7)	0.9803	7(6.0)	10(8.5)	2(3.3)	19(6.4)	0.4407

Adverse reactions	Dose 1*					Dose 2¶				
	3 μg group (N=120)	6 μg group (N=120)	Placebo group (N=60)	Total (N=300)	*P* value†	3 μg group (N=117)	6 μg group (N=118)	Placebo group (N=61)	Total (N=296)	*P* value†
Grade 1	22(18.3)	20(16.7)	10(16.7)	52(17.3)	0.9409	7(6.0)	10(8.5)	2(3.3)	19(6.4)	0.4407
Solicited	22(18.3)	21(17.5)	9(15.0)	52(17.3)	0.9025	7(6.0)	10(8.5)	2(3.3)	19(6.4)	0.4407
Unsolicited	0(0.0)	1(0.8)	1(1.7)	2(0.7)	0.6789	0(0.0)	0(0.0)	0(0.0)	0(0.0)	-
Systemic reactions	14(11.7)	10(8.3)	6(10.0)	30(10.0)	0.7019	4(3.4)	3(2.5)	0(0.0)	7(2.4)	0.4798
Fatigue	10(8.3)	2(1.7)	2(3.3)	14(4.7)	0.0454	3(2.6)	1(0.9)	0(0.0)	4(1.4)	0.4379
Fever	4(3.3)	3(2.5)	1(1.7)	8(2.7)	0.9057	0(0.0)	2(1.7)	0(0.0)	2(0.7)	0.3555
Diarrhea	1(0.8)	2(1.7)	1(1.7)	4(1.3)	1.0000	0(0.0)	1(0.9)	0(0.0)	1(0.3)	1.0000
Nausea	2(1.7)	0(0.0)	0(0.0)	2(0.7)	0.3579	1(0.9)	0(0.0)	0(0.0)	1(0.3)	0.6014
Headache	3(2.5)	1(0.8)	0(0.0)	4(1.3)	0.5351	2(1.7)	0(0.0)	0(0.0)	2(0.7)	0.1973
Muscle pain	2(1.7)	4(3.3)	3(5.0)	9(3.0)	0.4557	-	-	-	-	-
Hypersensitivity	1(0.8)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Decreased appetite	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Cough	-	-	-	-	-	1(0.9)	0(0.0)	0(0.0)	1(0.3)	0.6014
Injection-site reactions	9(7.5)	15(12.5)	5(8.3)	29(9.7)	0.4436	3(2.6)	8(6.8)	2(3.3)	13(4.4)	0.3245
Pain	9(7.5)	12(10.0)	4(6.7)	25(8.3)	0.7650	3(2.6)	7(5.9)	2(3.3)	12(4.1)	0.4786
Redness	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Discolouration	0(0.0)	1(0.8)	1(1.7)	2(0.7)	0.6789	-	-	-	-	-
Pruritus	0(0.0)	1(0.8)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Swelling	-	-	-	-	-	0(0.0)	1(0.9)	1(1.6)	2(0.7)	0.6838

Note：*Reported within 28 days post dose 1. ¶Reported within 28 days post dose 2. †P value of the comparison of incidence rate among three groups.

Table 3-9 Adverse Reactions Post Dose 1 and Dose 2 of 0/14 Schedule in the Phase 1&2 Clinical Trial

	3 μg group (N=144)	6 μg group (N=144)	Placebo group (N=84)	Total (N=372)	*P* value†
Total	47(32.6)	51(35.4)	15(17.9)	113(30.4)	0.0136
Grade 1	46(31.9)	51(35.4)	15(17.9)	112(30.1)	0.0144
Solicited	45(31.3)	49(34.0)	15(17.9)	109(29.3)	0.0256
Unsolicited	4(2.8)	5(3.5)	0(0.0)	9(2.4)	0.2609
Systemic reactions	22(15.3)	20(13.9)	10(11.9)	52(14.0)	0.8261
Fatigue	6(4.2)	10(6.9)	7(8.3)	23(6.2)	0.4038
Fever	4(2.8)	2(1.4)	1(1.2)	7(1.9)	0.7027
Diarrhea	6(4.2)	2(1.4)	1(1.2)	9(2.4)	0.3174
Nausea	2(1.4)	3(2.1)	0(0.0)	5(1.3)	0.4630
Headache	2(1.4)	4(2.8)	1(1.2)	7(1.9)	0.7027
Muscle pain	3(2.1)	2(1.4)	1(1.2)	6(1.6)	1.0000
Cough	0(0.0)	2(1.4)	0(0.0)	2(0.5)	0.3480
Hypersensitivity	0(0.0)	2(1.4)	0(0.0)	2(0.5)	0.3489
Vomiting	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000
Chest pain	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000
Abdominal pain	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000
Lower abdominal pain	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000
Drowsiness	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000
Dizziness	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000
Decreased appetite	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000
Palpitations	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000
Injection-site reactions	32(22.2)	38(26.4)	7(8.3)	77(20.7)	0.0025
Pain	29(20.1)	36(25.0)	7(8.3)	72(19.4)	0.0057
Swelling	2(1.4)	3(2.1)	0(0.0)	5(1.3)	0.4630
Redness	1(0.7)	2(1.4)	0(0.0)	3(0.8)	0.7953
Discolouration	1(0.7)	1(0.7)	0(0.0)	2(0.5)	1.0000
Pruritus	1(0.7)	1(0.7)	0(0.0)	2(0.5)	1.0000
Induration	1(0.7)	1(0.7)	0(0.0)	2(0.5)	1.0000
Hypoesthesia	1(0.7)	1(0.7)	0(0.0)	2(0.5)	1.0000

Note: data in the table were reported within 28 days post any of the two doses.
†P value of the comparison of incidence rate among three groups.

Table 3-10 Adverse Reactions Post Dose 1 and Dose 2 of 0/14 Schedule in the Phase 1&2 Clinical Trial

Adverse reactions	Dose 1*					Dose 2¶				
	3 μg group (N=144)	6 μg group (N=144)	Placebo group (N=84)	Total (N=372)	*P* value†	3 μg group (N=144)	6 μg group (N=143)	Placebo group (N=84)	Total (N=371)	*P* value†
Total	**31(21.5)**	**35(24.3)**	**12(14.3)**	**78(21.0)**	**0.1861**	**21(14.6)**	**25(17.5)**	**7(8.3)**	**53(14.3)**	**0.1519**
Grade 1	31(21.5)	35(24.3)	12(14.3)	78(21.0)	0.1861	20(13.9)	25(17.5)	7(8.3)	52(14.0)	0.1535
Solicited	**29(20.1)**	**33(22.9)**	**12(14.3)**	**74(19.9)**	**0.2909**	**20(13.9)**	**25(17.5)**	**7(8.3)**	**52(14.0)**	**0.1535**
Unsolicited	**3(2.1)**	**5(3.5)**	**0(0.0)**	**8(2.2)**	**0.2285**	**1(0.7)**	**0(0.0)**	**0(0.0)**	**1(0.3)**	**1.0000**
Systemic reactions	**18(12.5)**	**17(11.8)**	**7(8.3)**	**44(11.8)**	**0.8155**	**5(3.5)**	**8(5.6)**	**5(6.0)**	**18(5.0)**	**0.6132**
Fatigue	4(2.8)	7(4.9)	5(6.0)	16(4.3)	0.4606	2(1.4)	4(2.8)	4(4.8)	10(2.7)	0.2646
Fever	3(2.1)	2(1.4)	1(1.2)	6(1.6)	1.0000	2(1.4)	0(0.0)	0(0.0)	2(0.5)	0.3487
Diarrhea	5(3.5)	2(1.4)	0(0.0)	7(1.9)	0.1680	1(0.7)	0(0.0)	1(1.2)	2(0.5)	0.7000
Nausea	2(1.4)	2(1.4)	0(0.0)	4(1.1)	0.6827	0(0.0)	1(0.7)	0(0.0)	1(0.3)	0.6119
Headache	1(0.7)	1(0.7)	1(1.2)	3(0.8)	1.0000	1(0.7)	3(2.1)	0(0.0)	4(1.1)	0.3659
Muscle pain	3(2.1)	1(0.7)	1(1.2)	5(1.3)	0.8459	0(0.0)	2(1.4)	1(1.2)	3(0.8)	0.3451
Cough	0(0.0)	2(1.4)	0(0.0)	2(0.5)	0.3489	-	-	-	-	-
Hypersensitivity	0(0.0)	2(1.4)	0(0.0)	2(0.5)	0.3489	-	-	-	-	-
Vomiting	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Chest pain	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Abdominal pain	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Lower abdominal pain	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Drowsiness	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Dizziness	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Decrease appetite	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Palpitations	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Injection-site reactions	**18(12.5)**	**27(18.8)**	**7(8.3)**	**52(14.0)**	**0.2196**	**18(12.5)**	**18(12.6)**	**2(2.4)**	**38(10.2)**	**0.0157**
Pain	15(10.4)	24(16.7)	7(8.3)	46(12.4)	0.1364	17(11.8)	17(11.9)	2(2.4)	36(9.7)	0.0224
Swelling	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000	1(0.7)	3(2.1)	0(0.0)	4(1.1)	0.3659
Erythema	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000	0(0.0)	2(1.4)	0(0.0)	2(0.5)	0.1987
Discolouration	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000
Hypoesthesia	1(0.7)	1(0.7)	0(0.0)	2(0.5)	1.0000	-	-	-	-	-
Pruritus	-	-	-	-	-	1(0.7)	1(0.7)	0(0.0)	2(0.5)	1.0000
Induration	-	-	-	-	-	1(0.7)	1(0.7)	0(0.0)	2(0.5)	1.0000

Note：*Reported within 14 days post dose 1. ¶Reported within 28 days post dose 2. †P value of the comparison of incidence rate among three groups.

Table 3-11 Adverse Reactions Post Two doses of 0/28 Schedule in the Phase 1&2 Clinical Trial

	3 μg group (N=144)	6 μg group (N=144)	Placebo group (N=83)	Total (N=371)	*P* value†
Total	26(18.1)	27(18.8)	14(16.9)	67(18.1)	0.9546
Grade 1	26(18.1)	27(18.8)	14(16.9)	67(18.1)	0.9546
Solicited	26(18.1)	27(18.8)	13(15.7)	66(17.8)	0.8538
Unsolicited	0(0.0)	1(0.7)	2(2.4)	3(0.8)	0.2424
Systemic reactions	16(11.1)	14(9.7)	7(8.4)	37(10.0)	0.8152
Fatigue	10(6.9)	4(2.8)	2(2.4)	16(4.3)	0.1737
Fever	4(2.8)	5(3.5)	2(2.4)	11(3.0)	1.0000
Diarrhea	2(1.4)	3(2.1)	1(1.2)	6(1.6)	1.0000
Nausea	2(1.4)	0(0.0)	0(0.0)	2(0.5)	0.3496
Headache	3(2.1)	1(0.7)	0(0.0)	4(1.1)	0.4558
Cough	3(2.1)	0(0.0)	0(0.0)	3(0.8)	0.1263
Muscle pain	2(1.4)	4(2.8)	3(3.6)	9(2.4)	0.4713
Hypersensitivity	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000
Decrease appetite	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000
Injection-site reactions	15(10.4)	19(13.2)	10(12.1)	44(11.9)	0.7686
Pain	15(10.4)	16(11.1)	9(10.8)	40(10.8)	1.0000
Redness	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000
Discolouration	0(0.0)	1(0.7)	2(2.4)	3(0.8)	0.2424
Pruritus	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000
Swelling	0(0.0)	1(0.7)	1(1.2)	2(0.5)	0.6979

Note: data in the table were reported within 28 days post any of the two doses.
†P value of the comparison of incidence rate among three groups.

Table 3-12 Adverse Reactions Post Dose 1 and Dose 2 of 0/28 Schedule in the Phase 1&2 Clinical Trial

Adverse reactions	Dose 1*					Dose 2¶				
	3 μg group (N=144)	6 μg group (N=144)	Placebo group (N=83)	Total (N=371)	*P* value†	3 μg group (N=141)	6 μg group (N=142)	Placebo group (N=84)	Total (N=367)	*P* value†
Total	25(17.4)	24(16.7)	12(14.5)	61(16.4)	0.8744	9(6.4)	11(7.8)	3(3.6)	23(6.3)	0.5107
Grade 1	25(17.4)	23(16.0)	12(14.5)	60(16.2)	0.8727	9(6.4)	11(7.8)	3(3.6)	23(6.3)	0.5107
Solicited	25(17.4)	24(16.7)	11(13.3)	60(16.2)	0.7112	9(6.4)	11(7.8)	3(3.6)	23(6.3)	0.5107
Unsolicited	0(0.0)	1(0.7)	2(2.4)	3(0.8)	0.2424	0(0.0)	0(0.0)	0(0.0)	0(0.0)	-

Adverse reactions	Dose 1*					Dose 2¶				
	3 μg group (N=144)	6 μg group (N=144)	Placebo group (N=83)	Total (N=371)	*P* value†	3 μg group (N=141)	6 μg group (N=142)	Placebo group (N=84)	Total (N=367)	*P* value†
Systemic reactions	15(10.4)	11(7.6)	7(8.4)	33(8.9)	0.7130	5(3.6)	4(2.8)	0(0.0)	9(2.5)	0.2373
Fatigue	10(6.9)	2(1.4)	2(2.4)	14(3.8)	0.0392	3(2.1)	2(1.4)	0(0.0)	5(1.4)	0.3756
Fever	4(2.8)	4(2.8)	2(2.4)	10(2.7)	1.0000	0(0.0)	2(1.4)	0(0.0)	2(0.5)	0.3479
Diarrhea	2(1.4)	2(1.4)	1(1.2)	5(1.4)	1.0000	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000
Nausea	2(1.4)	0(0.0)	0(0.0)	2(0.5)	0.3496	1(0.7)	0(0.0)	0(0.0)	1(0.3)	0.6131
Headache	3(2.1)	1(0.7)	0(0.0)	4(1.1)	0.4558	2(1.4)	0(0.0)	0(0.0)	2(0.5)	0.1989
Cough	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000	2(1.4)	0(0.0)	0(0.0)	2(0.5)	0.1989
Muscle pain	2(1.4)	4(2.8)	3(3.6)	9(2.4)	0.4713	-	-	-	-	-
Hypersensitivity	1(0.7)	0(0.0)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Decrease appetite	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Injection-site reactions	12(8.3)	18(12.5)	8(9.6)	38(10.2)	0.5088	4(2.8)	8(5.6)	3(3.6)	15(4.1)	0.5301
Pain	12(8.3)	15(10.4)	6(7.2)	33(8.9)	0.7538	4(2.8)	7(4.9)	3(3.6)	14(3.8)	0.6543
Erythema	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Discolouration	0(0.0)	1(0.7)	2(2.4)	3(0.8)	0.2424	-	-	-	-	-
Pruritus	0(0.0)	1(0.7)	0(0.0)	1(0.3)	1.0000	-	-	-	-	-
Swelling	-	-	-	-	-	0(0.0)	1(0.7)	1(1.2)	2(0.5)	0.7019

Note：*Reported within 28 days post dose 1. ¶Reported within 28 days post dose 2. †P value of the comparison of incidence rate among three groups.

Appendix 4 Laboratory Abnormalities

Table 4-1 Clinically Significant Laboratory Abnormalities on Day 3 after vaccination in the Cohort of Day 0,14 Schedule in the Phase 1 Clinical Trial.

Dose	Laboratory measures	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=24)	Total (N=72)
Total	**Any Laboratory index**	**2(8·3)**	**2(8·3)**	**1(4·2)**	**5(7.0)**
	Garde 1	2(8·3)	1(4·2)	1(4·2)	4(5·6)
	Grade 3	-	1(4·2)	-	1(1·4)
	ALT				
	Grade 1	-	1(4·2)	-	1(1·4)
	AST				
	Grade 1	-	1(4·2)	-	1(1·4)
	Creatine phosphokinase				
	Grade 1	1(4·2)	-	-	1(1·4)
	Urine red cell				
	Grade 1	-	-	1(4·2)	1(1·4)
	Urine glucose				
	Grade 3	-	1(4·2)	-	1(1·4)
	Urine protein				
	Grade 1	1(4·2)	-	-	1(1·4)
First	**Laboratory index**	**1(4·2)**	**1(4·2)**	**1(4·2)**	**3(4·2)**
	Grade 1	1(4·2)	-	1(4·2)	2(2·8)
	Grade 3	-	1(4·2)	-	1(1·4)
	Creatine phosphokinase				
	Grade 1	1(4·2)	-	-	1(1·4)
	Urine red cell				
	Grade 1	-	-	1(4·2)	1(1·4)
	Urine glucose				
	Grade 3	-	1(4·2)	-	1(1·4)
Second	**Laboratory index**				
	Grade 1	1(4·2)	1(4·2)	-	2(2·8)
	ALT				
	Grade 1		1(4·2)		1(1·4)
	AST				
	Grade 1		1(4·2)		1(1·4)
	Urine protein				
	Grade 1	1(4·2)			1(1·4)

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase

Generally, we would assume that the laboratory abnormities occurred at day 3 were related to the vaccination because of the strong correlation in time.

Table 4-2 Clinically Significant Laboratory Abnormalities on Day 3 after vaccination in the Cohort of Day 0,28 Schedule in the Phase 1 Clinical Trial.

Dose	Laboratory measures	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=23)	Total (N=71)
Total	**Any laboratory index**	**2(8.3)**	**2(8.3)**	**1(4.4)**	**5(7.0)**
	Grade 1	2(8.3)	1 (4.2)	1(4.4)	4(5.6)
	Grade 2	1(4.2)	-	1(4.4)	2(2.8)
	Grade 3	-	1(4.2)	-	1(1.4)
	Total bilirubin	**1(4.2)**	**-**	**-**	**1(1.4)**
	Grade 1	1(4.2)	-	-	1(1.4)
	Grade 2	1(4.2)	-	-	1(1.4)
	Creatine phosphokinase				
	Grade 2	-	-	1(4.4)	1(1.4)
	Urine red cell	**1(4.2)**	**1(4.2)**	1 (4.4)	**3(4.2)**
	Grade 1	1(4.2)	1(4.2)		2(2.8)
	Grade 2	-	-	1(4.4)	1(4.3)
	Urine glucose	**-**	**1(4.2)**	**1(4.4)-**	**2(2.8)**
	Grade 1	-	-	1(4.4)	1(4.3)
	Grade 3	-	1(4.2)	-	1(4.3)
First	**Laboratory index**	**2(8.3)**	**1(4.2)**	**-**	**2(2.8)**
	Grade 1	1(4.2)	-	-	1(1.4)
	Grade 2	1(4.2)	-	-	1(1.4)
	Grade 3	-	1(4.2)	-	1(1.4)
	Total bilirubin				
	Grade 2	1(4.2)	-	-	1(1.4)
	Urine red cell				
	Grade 1	1(4.2)	-	-	1(1.4)
	Urine glucose				
	Grade 3	-	1(4.2)	-	1(1.4)
Second	**Laboratory index**	**1(4.2)**	**1 (4.2)**	**1 (4.4)**	**3(4.2)**
	Grade 1	1(4.2)	-	1 (4.4)	2 (2.8)
	Grade 2	-	1 (4.2)	1 (4.4)	2 (2.8)
	Total bilirubin				
	Grade 1	1(4.2)	-	-	1(1.4)
	Creatine phosphokinase				
	Grade 2	-	-	1(4.4)	1(1.4)
	Urine red cell				
	Grade 2	-	1 (4.2)	1 (4.4)	2(2.8)
	Urine glucose				
	Grade 1	-	-	1 (4.4)	1(1.4)

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase.

Generally, we would assume that the laboratory abnormities occurred at day 3 were related to the vaccination because of the strong correlation in time.

Appendix 5 Serum Inflammatory Factors

Table 5-1 Changes of Serum Inflammatory Factors on Day 7 after vaccination in the Cohort of Day 0,14 Schedule in the Phase 1 Clinical Trial.

Inflammatory factors	Time& Characteristics	First dose				Second dose			
		3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=24)	P†	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=23)	P†
IL-6	Before vaccination								
	Mean (SD)	9·1(14·1)	10·0(13·4)	7·7(10·3)	0·2607	4·7(6·4)	10·0(12·6)	6·1(6·7)	0·0073
	Median	2·5	5·2	4·3		1·7	5·4	3·5	
	7 days after first dose								
	Mean (SD)	9·1(12·8)	9·2(13·0)	7·6(9·7)	0·7130	6·6(10·9)	11·2(14·4)	7·5(11·5)	0·0077
	Median	2·8	4·4	4·3		2·1	5·8	3·0	
	Difference (After-Before)								
	Mean (SD)	0·0(2·9)	-0·8(2·6)	-0·1(2·5)	0·4729	1·9(6·6)	1·2(2·9)	1·4(5·6)	0·3558
	Median	0·8	-0·8	0·6		0·6	0·3	0.0	
	P *	0·9500	0·1568	0·8762		0·1705	0·0611	0·2415	
IL-2	Before vaccination								
	Mean (SD)	1·2(2·6)	0·6(0·8)	0·7(1·0)	0·5098	0·4(0·9)	1·6(2·0)	1.0 (1·2)	<0·0001
	Median	0·145	0·277	0·201		0·166	0·731	0·477	
	7 days after first dose								
	Mean (SD)	1·3(1·6)	1·5(2·2)	1·2(1·6)	0·8533	1·0(2·014)	0·8(1·1)	0·5(0·8)	0·6126
	Median	0·478	0·595	0·591		0·145	0·224	0·189	
	Difference (After-Before)								
	Mean (SD)	0·1(1·8)	0·9(2·5)	0·5(1·6)	0·5501	0·6(1·6)	-0·8(1·3)	-0·5(0·8)	<0·0001
	Median	0·3	0·2	0·4		0·0	-0·5	-0·3	
	P *	0·7621	0·0949	0·1178		0·0662	**0·0102**	**0·0053**	
TNF-α	Before vaccination								
	Mean (SD)	19·7(33·5)	5·3(9·1)	9·2(12·2)	0·0145	14·5(17·3)	5·2(8·1)	11·8(12·9)	0·0017
	Median	6·7	1·3	6·1		8·9	2·3	8·7	
	7 days after first dose								
	Mean (SD)	17·7(26·7)	12·2(15·6)	14·3(13·2)	0·5115	22·5(27·294)	7·1(9·654)	15·1(16·6)	0·0004
	Median	10·0	7·9	8·2		14·4	3·8	12·4	
	Difference (After-Before)								
	Mean (SD)	-1·9(11·8)	6·9(8·4)	5·1(5·6)	0·0041	8·0(22·4)	1·8(3·0)	3·3(8·2)	0·1374
	Median	1.0	6·2	4·4		4·1	1·7	3·1	
	P *	0·4351	0·0006	0·0002		0·0917	**0·0060**	0·0623	

* Paired t test. †P value of the comparison among three groups.

Table 5-2 Changes of Serum Inflammatory Factors on Day 7 after Vaccination in the Cohort of Day 0,28 Schedule.

Inflammatory factors	Time& Characteristics	First dose				Second dose			
		3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=24)	P†	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=23)	P†
IL-6	Before vaccination								
	Mean (SD)	6·1 (9·8)	7·9 (7·7)	8·8(14·8)	0·0610	12·2 (33·6)	5·8 (7·9)	6·4 (11·2)	0·3873
	Median	2·9	5·2	2·7		3·4	2·7	12·0	
	7 days after first dose								
	Mean (SD)	6·4 (11·2)	7·9 (8·2)	8·8 (14·0)	0·0362	6·8 (10·9)	5·1 (8·0)	6·6 (11·5)	0·4455
	Median	3.0	5·0	3·1		3·3	2·7	1·8	
	Difference (After-Before)								
	Mean (SD)	0·3 (2·3)	-0·1 (1·8)	-0·1 (1·6)	0·9620	-5·4 (26·2)	-0·7 (2·1)	0·2 (2·5)	0·9155
	Median	0·0	-0·1	-0·2		-0·3	-0·4	-0·3	
	P *	0·4955	0·8151	0·8130		0·3189	0·1448	0·7644	
IL-2	Before vaccination								
	Mean (SD)	0·8(1·8)	1·0(1·3)	1·2 (2·8)	0·0061	0·9 (1·4)	1·4 (2·3)	1·0 (1·9)	0·7493
	Median	0·1	0·6	0·3		0·427	0·413	0·430	
	7 days after first dose								
	Mean (SD)	0·7 (1·5)	0·9 (1·2)	1·2 (2·2)	0·0197	0·9 (1·8)	0·4 (0·9)	0·9 (2·1)	0·0093
	Median	0·2	0·5	0·3		0·331	0·118	0·183	
	Difference (After-Before)								
	Mean (SD)	-0·1 (0·8)	-0·1 (0·3)	-0·145 (0·925)	0·4280	0·1 (0·7)	-1·0 (2·6)	-0·1 (2·6)	0·0233
	Median	0·1	0·0	0·1		-0·1	-0·2	-0·1	
	P *	0·6294	0·1779	0·4597		0·6010	0·0603	0·8761	
TNF-α	Before vaccination								
	Mean (SD)	5·3 (9·1)	8·3 (9·6)	7·8 (13·9)	0·0535	8·2 (13·3)	10·1 (8·9)	10·3 (18·3)	0·0797
	Median	2·2	4·2	0·7		3·806	8·248	4·422	
	7 days after first dose								
	Mean (SD)	6·2 (7·9)	8·5 (8·7)	7·3 (14·0)	0·2779	7·6 (9·6)	4·6 (7·9)	6·9 (10·7)	0·2420
	Median	4·0	5·9	2·1		4·559	3·221	3·144	
	Difference (After-Before)								
	Mean (SD)	0·9 (8·3)	0·2 (5·7)	-0·6 (6·8)	0·2864	-0·6 (8·1)	-5·5 (5·3)	-3·4 (11·4)	0·0296

Inflammatory factors	Time& Characteristics	First dose				Second dose			
		3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=24)	P†	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=23)	P†
	Median	2·3	-0·1	0·4		-0·5	-4·7	-3·2	
	P *	0·5117	0·1646	0·4009		0·6988	**<0·0001**	0·1662	

* Paired t test. †P value of the comparison among three groups.

Appendix 6 Supplementary Data of Different Categories of Antibodies

Table 6-1 GMTs of neutralizing antibodies to live SARS-CoV-2 and RBD-specific IgG Induced by Two doses of CoronaVac Administrated at Day 0,14 and Day 0,28 schedule in the phase 1& 2 Clinical Trial.

Phase	Schedule, Antibody categories	Time*	3 μg group	6 μg group	Placebo group	P value[1]	P value[2]
Phase 1	**Day 0,14 schedule**						
	Neutralizing antibodies¶	Baseline	2·0 (2·0,2·0)	2·1 (1·9,2·2)	2·0 (2·0,2·0)	0·3731	0·3225
		14 days	5·6 (3·6,8·7)	7·7 (5·2,11·5)	2·0 (2·0,2·0)	<0·0001	0·2744
		28 days	5·4 (3·6,8·1)	15·2 (11·2,20·7)	2·0 (2·0,2·0)	<0·0001	0·0001
	RBD-IgG	Baseline	80·0 (80·0,80·0)	80·0 (80·0,80·0)	80·0 (80·0,80·0)	-	-
		14 days	465·8 (277·6,781·7)	987·0 (647·8,1504·0)	84·8 (78·0,92·1)	<0·0001	0·0244
		28 days	465·8 (288·1,753·1)	1395·9 (955·2,2039·7)	89·8 (76·1,105·9)	<0·0001	0·0006
	Day 0,28 schedule						
	Neutralizing antibodies¶	Baseline	2·0 (2·0,2·0)	2·0 (2·0,2·0)	2·0 (2·0,2·0)	-	-
		14 days	16·0 (10·4,24·7)	25·9 (14·6,46·1)	2·0 (2·0,2·0)	<0·0001	0·1736
		28 days	19·0 (13·2,27·4)	29·6 (17·9,48·9)	2·2 (1·8,2·8)	<0·0001	0·1467
	RBD-IgG	Baseline	82·3 (77·6,87·4)	82·3 (77·6,87·4)	80·0 (80·0,80·0)	0·6216	1.0000
		14 days	1356·1 (881·4,2086·4)	2152·7 (1446·1,3204·6)	80·0 (80·0,80·0)	<0·0001	0·1099
		28 days	1045·7 (721·6,1515·5)	1917·9 (1344·8,2735·2)	80·0 (80·0,80·0)	<0·0001	0·0184
Phase 2	**Day 0,14 schedule**						
	Neutralizing antibodies¶	Baseline	2·0 (2·0,2·0)	2·0 (2·0,2·0)	2·0 (2·0,2·0)	-	-
		14 days	27·6 (22·7,33·5)	34·5 (28·5,41·8)	2·3 (2·0,2·5)	<0·0001	0·1051
		28 days	23·8 (20·5,27·7)	30·1 (26·1,34·7)	2·0 (2·0,2·0)	<0·0001	0·0267
	RBD-IgG	Baseline	81·5 (79·8,83·2)	81·4 (79·8,83·1)	81·0 (79·0,83·0)	0·9423	0·9746
		14 days	1094·3 (936·7,1278·4)	1365·4 (1160·4,1606·7)	81·0 (79·0,83·0)	<0·0001	0·0528
		28 days	1053·7 (911·7,1217·7)	1318·2 (1156·9,1501·9)	80·0 (80·0,80·0)	<0·0001	0·0235
	Day 0,28 schedule						
	Neutralizing antibodies¶	Baseline	2·0 (2·0,2·0)	2·0 (2·0,2·0)	2·0 (2·0,2·0)	-	-
		28 days	44·1 (37,2,52·2)	65·4 (56·4,75·9)	2·0 (2·0,2·1)	<0·0001	0·0006
	RBD-IgG	Baseline	81·0 (79·6,82·3)	80·5 (79·5,81·4)	81·0 (79·1,82·9)	0·8297	0·5631
		28 days	1783·6 (1519·3,2093·8)	2287·5 (2038·2,2567·3)	87·9 (79·7,96·9)	<0·0001	0·0133

*Days post the dose 2.

P value[1] indicate the P value of comparison among three groups;

P value[2] indicate the P value of comparison between 3μg and 6μg group

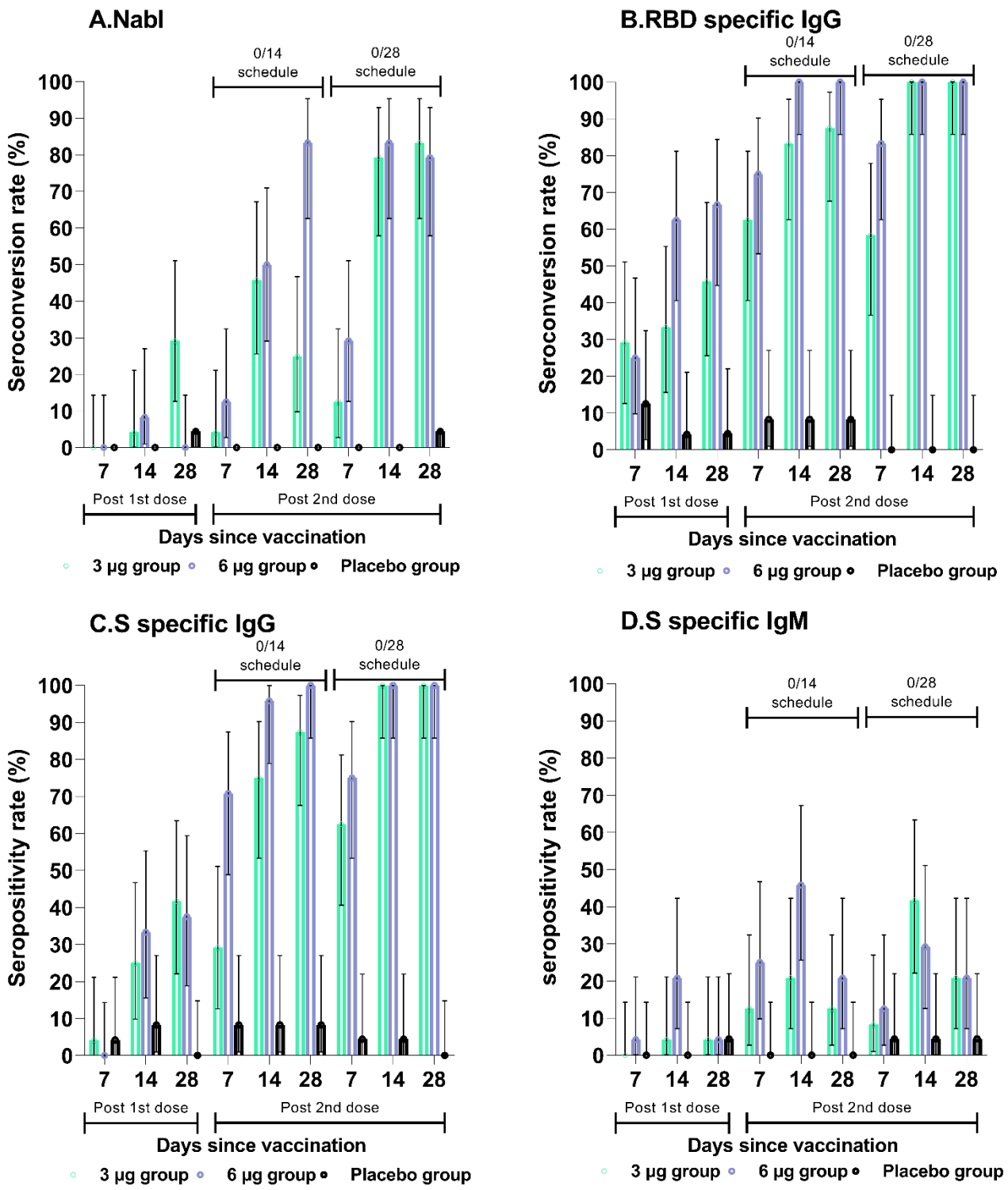

Figure 6-1 Seroconversion Rates (95%CI) of neutralizing antibodies, IgG and IgM against SARS-CoV-2 after Two Doses of CoronaVac Administrated Following Two Different Schedule in the Phase I Clinical Trial

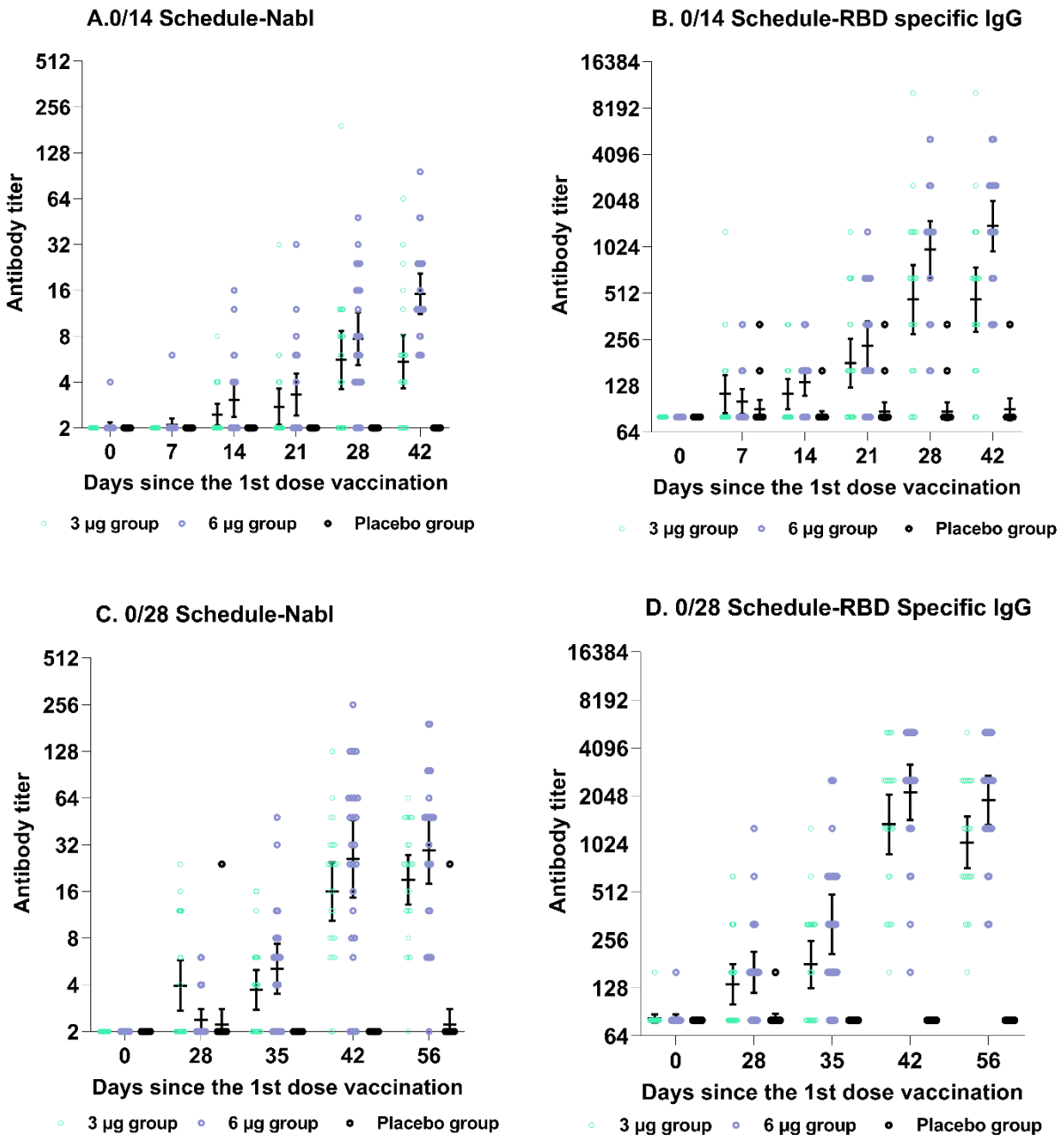

Figure 6-2 GMT (95%CI) of the neutralizing antibodies and RBD Specific IgG after Two Doses of CoronaVac Administrated Following Two Different Schedule in the Phase I Clinical Trial.

Table 6-2 Kinetic of Different Categories of Antibody Induced by Two Doses of CoronaVac Administrated at Day 0,14 or Day 0,28 Schedule in the Phase 1 Clinical Trial.

Antibody Categories	Group	Indicators	Day 0, 14 Schedule					Day 0,28 Schedule			
			Post dose 1		Post dose 2			Post dose 1	Post dose 2		
			Day7	Day14	Day 7	Day 14	Day 28	Day 28	Day 7	Day 14	Day 28
Neutralizing antibodies¶	3μg	Seroconversion n (%) (95%CI)	0(0·0) (0·0,14·3)	1(4·2) (0·1,21·1)	1(4·2) (0·1,21·1)	11(45·8) (25·6,67·2)	6(25·0) (9·8,46·7)	7(29·2) (12·6,51·1)	3(12·5) (2·7,32·4)	19(79·2) (57·9,92·9)	20(83·3) (62·6,95·3)
		GMT (95%CI)	2·0 (2·0,2·0)	2·4 (2·1,2·9)	2·8 (2·1,3·6)	5·6 (3·6,8·7)	5·4 (3·6,8·1)	4·0 (2·7,5·8)	3·7 (2·8,5·0)	16·0 (10·4,24·7)	19·0 (13·2,27·4)
	6μg	Seroconversion n (%) (95%CI)	0(0·0) (0·0,14·3)	2(8·3) (1·0,27·0)	3(12·5) (2·7,32·4)	12(50·0) (29·1,70·9)	20(83·3) (62·6,95·3)	0(0·0) (0,14·3)	7(29·2) (12·6,51·1)	20(83·3) (62·6,95·3)	19(79·2) (57·9,92·9)
		GMT (95%CI)	2·1 (1·9,2·3)	3·1 (2·4,4·0)	3·3 (2·4,4·6)	7·7 (5·2,11·5)	15·2 (11·2,20·7)	2·4 (2·0,2·8)	5·1 (3·5,7·4)	25·9 (14·6,46·1)	29·6 (17·9,48·9)
	Placebo	Seroconversion n (%) (95%CI)	0(0·0) (0·0,14·3)	0(0·0) (0·0·14·3)	0(0·0) (0,14·3)	0(0·0) (0,14·3)	0(0·0) (0,14·3)	1(4·4) (0·1,22·0)	0(0·0) (0,14·8)	0(0·0) (0,14·8)	1(4·4) (0·1,22·0)
		GMT (95%CI)	2·0 (2·0, 2·0)	2·0 (2·0, 2·0)	2·0 (2·0, 2·0)	2·0 (2·0,2·0)	2·0 (2·0,2·0)	2·2 (1·8,2·8)	2·0 (2·0,2·0)	2·0 (2·0,2·0)	2·2 (1·8,2·8)
		P value*	1·000	0·7682	0·3143	0·0002	<0·0001	0·0028	0·0128	<0·0001	<0·0001
		P value†	0·3731	**0·0029**	0·0114	<0·0001	<0·0001	0·0045	<0·0001	<0·0001	<0·0001
IgG-RBD	3μg	Seroconversion n (%) (95%CI)	7(29·2) (12·6,51·1)	8(33·3) (15·6,55·3)	15(62·5) (40·6,81·2)	20(83·3) (62·6,95·3)	21(87·5) (67·6,97·3)	11(45·8) (25·6,67·2)	14(58·3) (36·6,77·9)	24(100) (85·8,100)	24(100) (85·8,100)
		GMT (95%CI)	113·1 (85·0,150·6)	113·1 (90·0,142·2)	179·6 (125·0,258·1)	465·8 (277·6,781·7)	465·8 (288·1,753·1)	134·5 (100·7,179·7)	179·6 (127·6,252·7)	1356·1 (881·4,2086·4)	1045·7 (721·6,1515·5)
	6μg	Seroconversion n (%) (95%CI)	6(25·0) (9·8,46·7)	15(62·5) (40·6,81·2)	18(75·0) (53·3,90·2)	24(100) (85·8,100)	24(100) (85·8,100)	16(66·7) (44·7,84·4)	20(83·3) (62·6,95·3)	24(100) (85·8,100)	24(100) (85·8,100)
		GMT (95%CI)	100·8 (83·6,121·5)	134·5 (110·4,164·0)	232·9 (161·5,335·8)	987·0 (647·8,1504·0)	1395·9 (955·2,2039·7)	160·0 (118·7,215·8)	320·0 (207·84,492·7)	2152·7 (1446·1,3204·6)	1917·9 (1344·8,2735·2)
	Placebo	Seroconversion n (%) (95%CI)	3(12·5) (2·7,32·4)	1(4·2) (0·1,21·1)	2(8·3) (1·0,27·0)	2(8·3) (1·0,27·0)	2(8·3) (1·0,27·0)	1(4·4) (0·1,22·0)	0(0·0) (0,14·8)	0(0·0) (0,14·8)	0(0·0) (0,14·8)
		GMT (95%CI)	89·80 (78·0,103·4)	82·3 (77·6,87·4)	87·2 (76·5,99·5)	84·8 (78·0,92·1)	89·8 (76·1,105·9)	82·5 (77·5,87·8)	80·0 (80·0,80·0)	80·0 (80·0,80·0)	80·0 (80·0,80·0)
		P value*	0·3518	0·0001	<0·0001	<0·0001	<0·0001	0·0001	<0·0001	<0·0001	<0·0001
		P value†	0·2916	0·0005	<0·0001	<0·0001	<0·0001	0·0006	<0·0001	<0·0001	<0·0001
IgG-S	3μg	Seropositivity n (%) (95%CI)	1(4·2) (0·1,21·1)	6(25·0) (9·8,46·7)	7(29·2) (12·6,51·1)	18(75·0) (53·3,90·2)	21(87·5) (53·3,90·2)	10(41·7) (22·1,63·4)	15(62·5) (40·6,81·2)	24(100·0) (85·8,100·0)	24(100·0) (85·8,100·0)
	6μg	Seropositivity n (%) (95%CI)	0(0·0) (0,14·3)	8(33·3) (15·6,55·3)	17(70·8) (48·9,87·4)	23(95·8) (78·9,99·9)	24(100·0) (85·8,100·0)	9(37·5) (18·8,59·4)	18(75·0) (53·3,90·2)	24(100·0) (85·8,100·0)	24(100·0) (85·8,100·0)
	Placebo	Seropositivity	1(4·2)	2(8·3)	2(8·3)	2(8·3)	2(8·3)	0(0·0)	1(4·4)	1(4·4)	0(0·0)

Antibody Categories	Group	Indicators	Day 0, 14 Schedule					Day 0,28 Schedule			
			Post dose 1		Post dose 2			Post dose 1	Post dose 2		
			Day7	Day14	Day 7	Day 14	Day 28	Day 28	Day 7	Day 14	Day 28
		n (%) (95%CI)	(0·1,21·1)	(1·0,27·0)	(1·0,27·0)	(1·0,27·0)	(1·0,27·0)	(0,14·8)	(0·1,22·0)	(0·1,22·0)	(0,14·8)
		P value*	1·000	0·1054	<0·0001	<0·0001	<0·0001	0·0019	<0·0001	<0·0001	<0·0001
IgM	3μg	Seropositivity	0(0·0)	1(4·2)	3(12·5)	5(20·8)	3(12·5)	1(4·2)	2(8·3)	10(41·7)	5(20·8)
		n (%) (95%CI)	(0,14·3)	(0·1,21·1)	(2·7,32·4)	(7·1,42·2)	(2·7,32·4)	(0·1,21·1)	(1·0,27·0)	(22·1,63·4)	(7·1,42·2)
	6μg	Seropositivity	1(4·2)	5(20·8)	6(25·0)	11(45·8)	5(20·8)	1(4·2)	3(12·5)	7(29·2)	5(20·8)
		n (%) (95%CI)	(0·1,21·1)	(7·1,42·2)	(9·8,46·7)	(25·6,67·2)	(7·1,42·2)	(0·1,21·1)	(2·7,32·4)	(12·6,51·1)	(7·1,42·2)
	Placebo	Seropositivity	0(0·0)	0(0·0)	0(0·0)	0(0·0)	0(0·0)	1(4·4)	1(4·4)	1(4·4)	1(4·4)
		n (%) (95%CI)	(0,14·3)	(0,14·3)	(0·14·3)	(0,14·3)	(0,14·3)	(0·1,22·0)	(0·1,22·0)	(0·1,22·0)	(0·1,22·0)
		P value*	1·000	0·0418	0·0343	0·0007	0·0855	1·000	0·8654	0·0116	0·2036

*P value of the comparison of seroconversion/seropositivity rates among three groups; † P value of the comparison of GMTs among the three groups

Table 6-3 Neutralizing Antibody to Pseudovirus Induced by Two Doses of CoronaVac Administrated at the Day 0,14 Schedule in the Phase 1 and 2 Clinical Trial.

Group	Indicators	Phase 1				Phase 2
		Post 1st dose		Post 2nd dose		After 2nd dose
		Day 7	Day 14	Day 7	Day 14	Day 14
3μg	Seroconversion	2(8·3)	7(29·2)	3(12·5)	10(41·7)	94(79·7)
	n (%) (95%CI)	(1·0,27·0)	(12·6,51·1)	(2·7,32·4)	(22·1,63·4)	(71·3,86·5)
	GMT	15·2	15·8	11·2	22·4	84·9
	(95%CI)	(12·0,19·2)	(11·3,22·1)	(7·7,16·3)	(13·6,36·9)	(72·9,98·7)
6μg	Seroconversion	1(4·2)	5(20·8)	7(29·2)	18(75·0)	103(86·6)
	n (%) (95%CI)	(0·1,21·1)	(7·1,42·2)	(12·6,51·1)	(53·3,90·2)	(79·1,92·1)
	GMT	5·6	15·1	20·2	45·4	95·6
	(95%CI)	(4·4,7·1)	(8·9,25·5)	(12·7,32·0)	(27·0,76·4)	(82·4,110·9)
Placebo	Seroconversion	2(8·3)	0(0·0)	0(0·0)	0(0·0)	3(5·0)
	n (%) (95%CI)	(1·0,27·0)	(0,14·3)	(0,14·3)	(0,14·3)	(1·0,13·9)
	GMT	9·2	5·8	5·7	6·0	14·8
	(95%CI)	(6·7,12·7)	(4·9,7·0)	(4·9,6·5)	(5·0,7·1)	(12·6,17·5)
	P value*(three groups)	1·000	0·0137	0·0128	<0·0001	<0·0001
	P value*, 3μg vs 6μg	1·000	0·5050	0·1551	0·0192	0·1566
	P value†（three groups）	<0·0001	0·0002	<0·0001	<0·0001	<0·0001
	P value†, 3μg vs 6μg	<0·0001	0·8685	0·0465	0·0483	0·2671

*P value of the comparison of the seroconversion rates; † P value of the comparison of the GMTs.

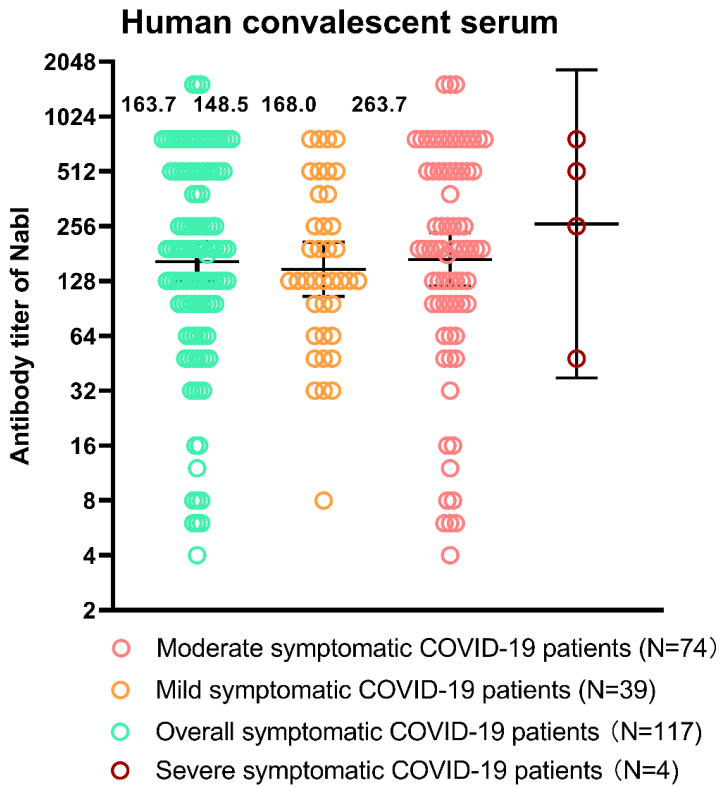

Figure 6-3 Neutralizing antibody to live SARS-CoV-2 (Nabl) in serum of symptomatic COVID-19 patients.

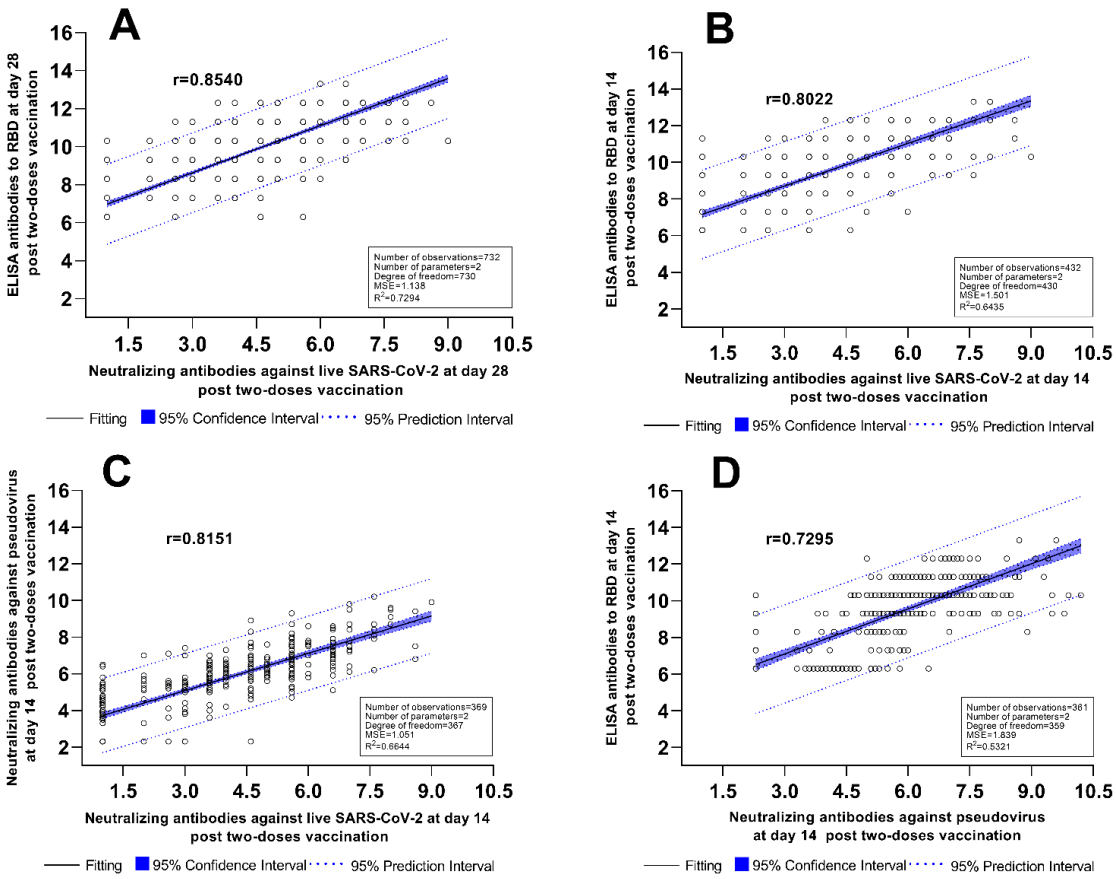

Figure 6-4 The Association between Different Categories of Antibodies.
Note: the correlation analysis was conducted after $\log_2$ transformation of the raw data, based on the pooled data of phase 1

and 2 trial (with two vaccination schedule cohorts pooled).

Appendix 7 T Cell Response

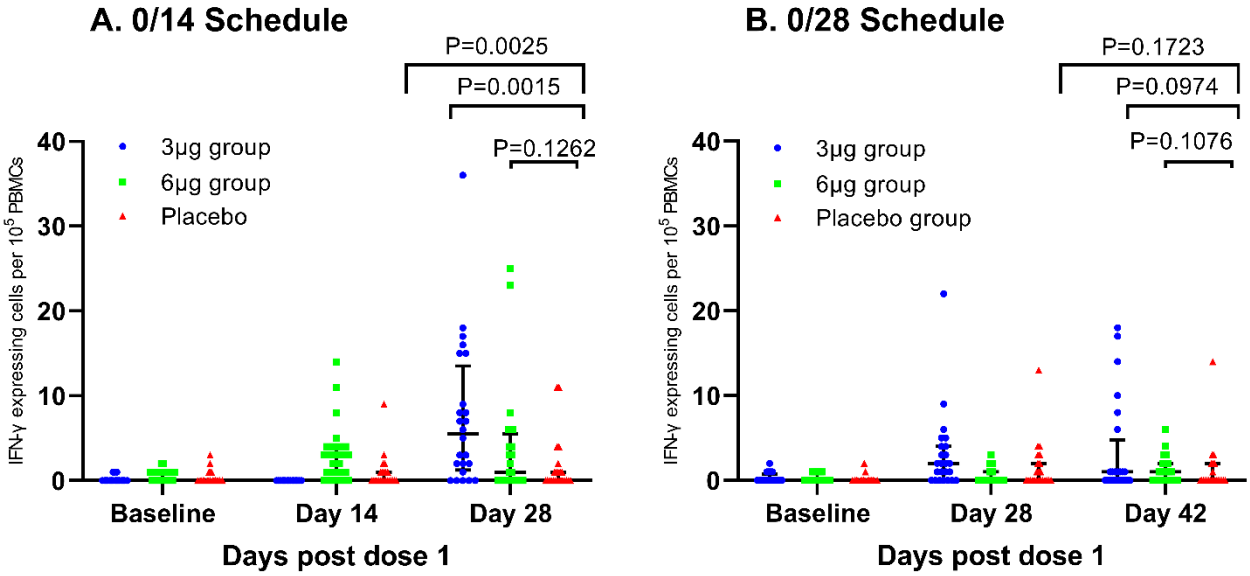

Figure 7-1 The T Cell Response (IFN-γ detection) in the Phase 1 Clinical Trial.

Table 7-1 The T Cell Responses (IFN-γ detection) for of 0/14 Schedule in the Phase 1 Clinical Trial

Time	Indicators	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=24)	Total (N=72)	*P* (Three groups)	*P* (3 μg vs 6 μg)
Baseline	**Mean number of spot-forming units**						
	Mean (SD)	0.2 (0.3)	0.6 (0.6)	0.3 (0.8)	0.4 (0.6)	0.0052	0.0039
	95%CI	0.0, 0.3	0.4, 0.9	0.0, 0.7	-0.2, 1.0		
	Median	0.0	0.7	0.3	0.0		
	Min, Max	0.0, 1.3	0.0, 2.3	0.0, 3.3	0.0, 3.3		
	Proportion of positive responders						
	N (%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1.0000	1.0000
	95%*CI*	0.0, 14.3	0.0, 14.3	0.0, 14.3	0.0, 5.0		
14 days post dose 1	**Mean number of spot-forming units**						
	Mean (SD)	0.0(0.0)	3.2 (3.6)	0.9 (1.8)	1.4 (2.6)	<0.0001	<0.0001
	95%CI	(0.0, 0.0)	1.7, 4.7	0.1,1.7	-2.8, 5.5		
	Median	0.0	2.7	0.3	0.3		
	Min, Max	0.0, 0.3	0.0, 14.3	0.0, 8.7	0.0, 14.3		
	Proportion of positive responders						
	N (%)	0 (0.0)	3 (12.5)	1 (4.2)	4 (5.6)	0.3143	0.2340
	95%*CI*	0.0, 14.3	2.7, 32.4	0.1, 21.1	1.5, 13.6		
14 days post dose 2	**Mean number of spot-forming units**						
	Mean (SD)	7.4 (8.5)	3.9 (6.7)	1.5 (3.1)	4.3 (6.8)	0.0025	0.0461
	95%CI	3.9,11.1	1.0, 6.7	0.2,2.9	-3.2, 11.8		
	Median	5.5	1.0	0.0	1.3		
	Min, Max	0.0, 35.7	0.0, 25.0	0.0, 11.0	0.0, 35.7		
	Proportion of positive responders						
	N (%)	11 (45.8)	5 (20.8)	2 (8.3)	18 (25.0)	0.0094	0.0662
	95%*CI*	25.6, 67.2	7.1, 42.2	1.0, 27.0	15.5, 36.6		

Table 7-2 The T Cell Responses (IFN-γ detection) for of 0/28 Schedule in the Phase 1 Clinical Trial

Time	Indicators	3 μg group (N=24)	6 μg group (N=24)	Placebo group (N=23)	Total (N=71)	*P* (Three groups)	*P* (3 μg vs 6 μg)
Baseline	**Mean number of spot-forming units**						
	Mean (SD)	0.3(0.5)	0.3(0.4)	0.3(0.6)	0.3(0.5)	0.4501	0.8130
	95%CI	0.1, 0.5	0.1, 0.5	0.0, 0.5	0.2, 0.3		
	Median	0.2	0.0	0.0	0.0		
	Min, Max	0.0,2.0	0.0,1.3	0.0,2.3	0.0,2.3		
	Proportion of positive responders						
	N (%)	0 (0.0)	0(0.0)	0(0.0)	0(0.0)	1.0000	1.0000
	95%*CI*	0.0,14.3	0.0,14.3	0.0,14.8	0.0, 5.1		
14 days post dose 1	**Mean number of spot-forming units**						
	Mean (SD)	3.1(4.6)	0.6(0.9)	1.5(2.8)	1.7(3.3)	0.0045	0.0014
	95%CI	1.1, 5.0	0.1, 0.9	0.2, 2.7	-1.5, 4.9		
	Median	2.0	0.0	0.3	0.3		
	Min, Max	0.0, 22.0	0.0, 3.0	0.0, 13.0	0.0, 22.0		
	Proportion of positive responders						
	N (%)	1(4.2)	0(0.0)	1(4.4)	2(2.8)	0.7682	1.0000
	95%*CI*	0.1, 21.1	0.0, 14.3	0.1, 22.0	0.3, 9.8		
14 days post dose 2	**Mean number of spot-forming units**						
	Mean (SD)	3.4(5.7)	1.2(1.5)	1.2(3.0)	1.9(3.9)	0.1723	0.7838
	95%CI	0.9, 5.7	0.5, 1.8	-0.1, 2.5	-1.2,5.0		
	Median	0.7	0.7	0.0	0.3		
	Min, Max	0.0, 18.3	0.0, 6.0	0.0, 14.0	0.0, 18.3		
	Proportion of positive responders						
	N (%)	5 (20.8)	0 (0.0)	1 (4.4)	6 (8.5)	0.0275	0.0496
	95%*CI*	7.1, 42.2	0.0, 14.3	0.1, 22.0	3.2, 17.5		

Appendix 8 The proportion of Spikes in CoronaVac

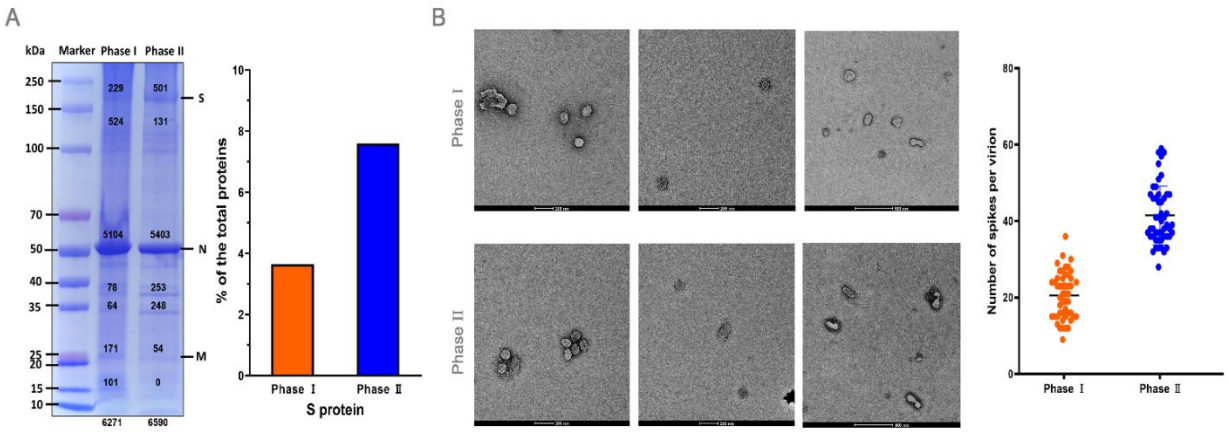

Figure 8-1 The proportion of Spikes in CoronaVac used for phase 1 and 2 vaccine evaluation.
(A) Protein composition analysis of CoronaVac samples from phase 1 and 2 by a NuPAGE 4-12% Bis-Tris gel, followed by whole-gel protein staining using Coomassie Blue gel staining reagent (45% methanol, 10% glacial acetic acid, 0·25% Coomassie Blue R-250). The viral protein bands of vaccine strain used for phase I and II were quantified by densitometry using ImageJ software with values depicted in the gel. The proportions of spikes to the total proteins in each gel lane in CoronaVac samples used forof phase 1 and 2 were calculated separately. (B) Representative negative staining images of the CoronaVac samples used in phase 1 and 2 trials. Three images were randomly selected for each phase. Grouped scatter plot showing the numbers of Spikes on two-dimensional projections of randomly selected 50 virions of CoronaVac samples used for phase 1 (left) and phase 2 (right), respectively.

Appendix 9 Baseline Characteristics in Phase 1 and Phase 2 Clinical Trial.

Characteristics	3μg group	6μg group	Placebo group	Overall
Phase 1, day 0,14 schedule				
N	24	24	24	72
Male, no·%	13(54·2)	10(41·7)	15(62·5)	38(52·8)
Han nationality, no·%	24(100·0)	24(100·0)	24(100·0)	72(100)
Age (years), Mean±sd	44·6±9·9	45·0±9·2	39·5±10·8	43·0±10·2
BMI (kg/m^2), Mean±sd	25·8±4·0	25·5±2·4	24·5±2·9	25·3±3·2
Phase 1, day 0,28 schedule				
N	24	24	23	71
Male, no·%	6(25·0)	11(45·8)	8(34·8)	25(35·2)
Han nationality, no·%	24(100)	24(100)	13(100)	71(100)
Age (years), Mean±sd	43·1±8·1	44·5±11·3	43·5±10·9	43·7±10·1
BMI (kg/m^2), Mean±sd	25·6±2·8	24·6±3·8	25·9±3·8	25·3±3·5
Phase 2, day 0,14 schedule				
N	120	120	60	300
Male, no·%	54(45·0)	48(40·0)	25(41·7)	127(42·3)
Han nationality, no·%	120(100)	120(100)	60(100)	300(100)
Age (years), Mean±sd	42·0±10·2	42·4±9·0	43·6±7·6	42·5(9·3)
BMI (kg/m^2), Mean±sd	24·9±3·6	25·5±3·2	25·5±3·0	25·2(3·35)
Phase 2, day 0,28 schedule				
N	120	120	60	300
Male, no·%	63(52·5)	63(52·5)	30(50·0)	
Han nationality, no·%	120(100)	120(100)	60(100)	300(100)
Age (years), Mean±sd	41·5±9·6	40·6±9·9	44·3±8·4	41·7±9·6
BMI (kg/m^2), Mean±sd	25·2±3·1	25·2±3·3	26·1±3·1	25·4±3·2

Appendix 10 Multivariate Logistic Model Analysis

Table 10-1 Logistic regression analysis of seroconversion rate of neutralizing antibodies to live SARS-CoV-2 at 28days after the two-doses vaccination in the phase 1 clinical trial.

Parameter	Estimates	P value	OR	
			Point estimates	Wald 95%CI
Univariate analysis				
Vaccination schedule	-0·0159	0·9249		
(day 0,14 VS day 0,28)			0·969	(0·501, 1·875)
3μg	1·4363	0·0009		
6 μg	2·1691	<·0001		
(3μg VS 6μg)			0·481	(0·162, 1·427)
(3μg VS placebo)			154·727	(19·092, >999·999)
(6μg VS placebo)			322·000	(37·212, >999·999)
Age	0·00611	0·7150	1·006	(0·974, 1·040)
Sex	-0·1869	0·2717		
(Male VS female)			0·688	(0·353,1·340)
Multivariable analysis				
Interpret	1·8925	0·2053		
Vaccination schedule	0·0677	0·8031		
(day 0,14 VS day 0,28)			1·145	(0·395, 3·321)
3μg	1·4788	0·0008		
6 μg	2·3245	<·0001		
(3μg VS 6μg)			0·429	(0·140, 1·316)
(3μg VS placebo)			196·777	(22·353, >999·999)
(6μg VS placebo)			458·443	(46·735, >999·999)
Age	-0·0490	0·1391	0·952	(0·892, 1·016)
Sex	-0·2533	0·3537		
(Male VS female)			0·602	(0·206, 1·758)

Table 10-2 Logistic regression analysis of seroconversion rate of neutralizing antibodies to live SARS-CoV-2 at 28days after the two-doses vaccination in the phase 2 clinical trial.

Parameter	Estimates	P value	OR	
			Point estimates	Wald 95%CI
Univariate analysis				
Vaccination schedule	-0·00585	0·9537		
(day 0,14 VS day 0,28)			0·988	(0·666, 1·467)
3μg	2·6812	0·9723		
6 μg	13·7377	0·8872		
(3μg VS 6μg)			<0·001	(<0·001, >999·999)
(3μg VS placebo)			>999·999	(<0·001, >999·999)
(6μg VS placebo)			>999·999	(<0·001, >999·999)
Age	-0·0268	0·0194	0·974	(0·952, 0·996)
Sex	-0·00517	0·9591		
(Male VS female)			0·990	(0·667, 1·470)
Multivariable analysis				
Interpret	1·6534	0·9893		
Vaccination schedule	-0·0373	0·9290		
(day 0,14 VS day 0,28)			0·928	(0·179, 4·799)
3μg	2·9081	0·9812		
6 μg	14·8514	0·9236		
(3μg VS 6μg)			<0·001	(<0·001, >999·999)
(3μg VS placebo)			>999·999	(<0·001, >999·999)
(6μg VS placebo)			>999·999	(<0·001, >999·999)
Age	-0·0147	0·7506	0·985	(0·900, 1·079)
Sex	-0·8028	0·1508		

(Male VS female)			0·201	(0·022, 1·795)

Table 10-3 Logistic regression analysis of seroconversion rate of neutralizing antibodies to live SARS-CoV-2 at 28days after the two-doses vaccination (phase 1&2 pooled).

Parameter	Estimates	P value	OR	
			Point estimates	Wald 95%CI
Univariate analysis				
Vaccination schedule	-0·00880	0·9171		
(day 0,14 VS day 0,28)			0·983	(0·705, 1·369)
3μg	2·2569	<·0001		
6 μg	3·3424	<·0001		
(3μg VS 6μg)			0·338	(0·131, 0·870)
(3μg VS placebo)			>999·999	(340·396, >999·999)
(6μg VS placebo)			>999·999	(912·378, >999·999)
Age	-0·0188	0·0420	0·981	(0·964, 0·999)
Sex	-0·0361	0·6701		
(Male VS female)			0·930	(0·668, 1·297)
Multivariable analysis				
Interpret	2·8314	0·0179		
Vaccination schedule	0·0222	0·9163		
(day 0,14 VS day 0,28)			1·045	0·457, 2·390
3μg	2·3324	<·0001		
6 μg	3·4060	<·0001		
(3μg VS 6μg)			0·342	(0·132, 0·884)
(3μg VS placebo)			>999·999	(404·294, >999·999)
(6μg VS placebo)			>999·999	(>999·999, >999·999)
Age	-0·0542	0·0377	0·947	(0·900, 0·997)
Sex	-0·1767	0·4085		
(Male VS female)			0·702	(0·304, 1·624)