SINOVAC

COVID-19 Vaccine (Vero cell), Inactivated

CoronaVac®

March, 2021

科兴控股生物技术有限公司
SINOVAC BIOTECH LTD.

克尔来福™
CoronaVac™
新型冠状病毒灭活疫苗

1 Platform description of vaccine

CoronaVac® information

- 【NAME】
  - Trade Name: CoronaVac®
  - Name: COVID-19 Vaccine (Vero Cell), Inactivated
- 【COMPOSITION】
  - Active ingredient: Inactivated SARS-CoV-2 Virus (CZ02 s train)
  - Adjuvant: Aluminum hydroxide
  - Excipients: disodium hydrogen phosphate dodecahydra te, sodium dihydrogen phosphate monohydrate, sodium chloride
- 【DESCRIPTION】
  - CoronaVac® is a milky-white suspension. Stratified precipitate may form which can be dispersed by shaking.
- 【TARGET GROUPS FOR VACCINATION】
  - Susceptible people aged 18 and above.
- 【PRESENTATION】
  - Each vial (syringe) contains 0.5 mL with 600SU of inactivated SARS-CoV-2 virus as antigen.

CoronaVac® information

- 【ADMINISTRATION AND SCHEDULE】
  - Two doses should be administered for primary immunization. The second dose is preferably given 14-28 days after the first dose.
  - CoronaVac should be administered by intramuscular injection in the deltoid region of the upper arm.
  - It has not been determined whether this product requires booster immunization.
- 【SHELF LIFE】
  - 24 months
- 【PACKAGE】
  - Vial or pre-filled syringe. One vial or syringe per box.
- 【STORAGE】
  - Store and transport between +2-8℃, and protect from light.

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2 Pre-clinical Study

PRECLINICAL STUDIES-safety

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Summary of the studies

Studies performed by GLP compliant labs, results presented in the following slides.

	Item	Animal
Efficacy	Immunogenicity	Mice, Rat
	Virus Challenge*	Macaca Rhesus
	Cross-protection test	Mice, Guinea Pig, Rabbit, Rat, Sheep
Safety	Singe dose Toxicity/ Acute Toxicity	Rat
	Active Systemic Anaphylaxis	Guinea Pig
	Repeat Doses Toxicity (inc. local irritation)	Rat, Macaca Fascicularis
	Reproductive toxicity	Rat

*. *An animal model which has been successfully developed for COVID-19 vaccine evaluation, including hCAE2 mice and Rhesus is employed*
https://www.biorxiv.org/content/10.1101/2020.02.07.939389v3

GLP compliance

Virus Challenge test:
Institute of Laboratory Animal Sciences, Chinese Academy of Medical Sciences
- National Institution

Other safety tests:
JOINN Laboratories (Beijing)
- CFDA GLP Certified
- U.S.FDA GLP Inspected
- AAALAC Accredited
- OECD GLP Certified
- Korean MFDS GLP Inspected
- http://www.joinn-lab.com/

PRECLINICAL STUDIES-summary safety results

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Single dose and repeated dose toxicity

➢No abnormal changes related to vaccination in those animals when given high dosage vaccine was administered alone to otherwise healthy control animals.

Active Systemic Anaphylaxis

➢No allergic reaction was observed after the guinea pigs was injected with high dosage vaccine intended for clinical use.

Reproductive toxicity

➢There was no effect on the fertility of parental female and male rats, no toxicity and teratogenicity of embryo fetus, and no effect on the growth and development of F1 generation pups.

PRECLINICAL STUDIES-virus challenge

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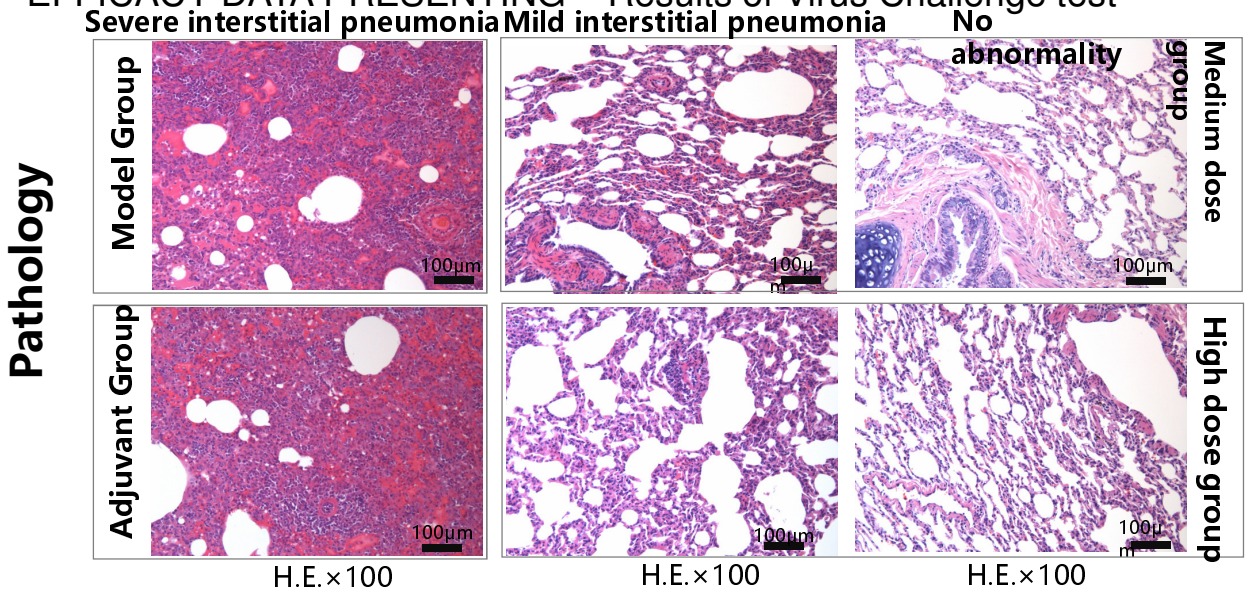
EFFICACY DATA PRESENTING – Results of Virus Challenge test



Significant protective effect observed for medium dose vaccination

Significant protective effect observed for high dose vaccination

- **Model:** 2 cases (2/2) showed severe interstitial pneumonia with Vascular and peribronhial inflammatory cells infiltrate
- **Adjuvant:** 1 case (1/2) showed mild interstitial pneumonia; 1 case (1/2) showed Severe interstitial pneumonia with Vascular and peribronchial inflammatory cells infiltrate

- **High dose group:** 4 cases (4/4) showed mild interstitial pneumonia; Compare with model group and adjuvant group, the pulmonary pathological change of vaccine groups has been siganificantely reduced.

- **Medium dose group:** 4 cases (4/4) showed mild interstitial pneumonia; Compare with model group and adjuvant group, the pulmonary pathological change of vaccine groups has been siganificantely reduced.

PRECLINICAL STUDIES

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EFFICACY DATA PRESENTING – Results of Virus Challenge test

3 dose schedule(0,7,14)

Group/day	Animal code	0d	7d	14d	21d
Medium dose group	K5	<8	<8	6	64
	K6	<8	<8	4	24
	K7	<8	<8	48	384
	K8	<8	<8	6	24
GMT	/	/	/	9.1	61.3
High dose group	K1	<8	<8	12	48
	K2	<8	<8	16	64
	K3	<8	<8	6	32
	K4	<8	<8	6	64
GMT	/	/	/	9.1	50.1

2 dose schedule(0,14)

Group/day	Animal code	0d	7d	14d	21d
Medium dose group	K21	<8	<8	4	64
	K22	<8	<8	4	128
	K23	<8	<8	6	48
	K24	<8	<8	32	64
GMT		/	/	7.4	70.8
High dose group	K17	<8	<8	16	128
	K18	<8	<8	16	256
	K19	<8	<8	4	96
	K20	<8	<8	<4	64
GMT				6.7	119.1

Virus challenge on D21-D23 →

Significant protection effect is shown for neutralizing antibody no lower than 1:24

Results and conclusion

- High virus load in pulmonary tissue of model group after virus challenge.
- Compare with model group, Virus was not detected in pulmonary tissue of medium dose group 7 days after virus challenge.
- Compare with model group, Virus was not detected in pulmonary tissue of high dose group 7 days after virus challenge.
- Pathological examination of pulmonary tissue is still ongoing.

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3 Clinical Study

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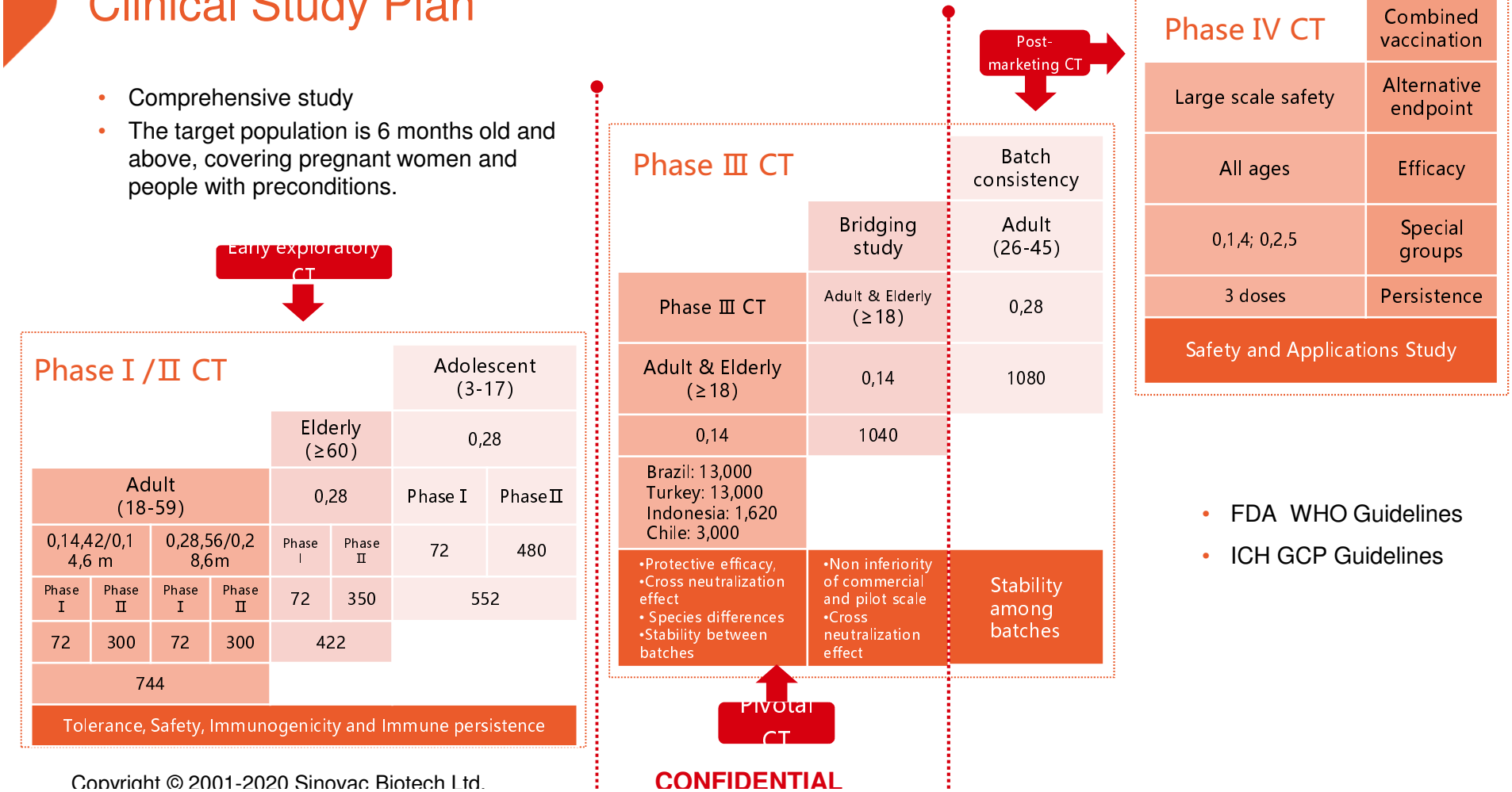
3.1 Phase I/II Clinical Trial

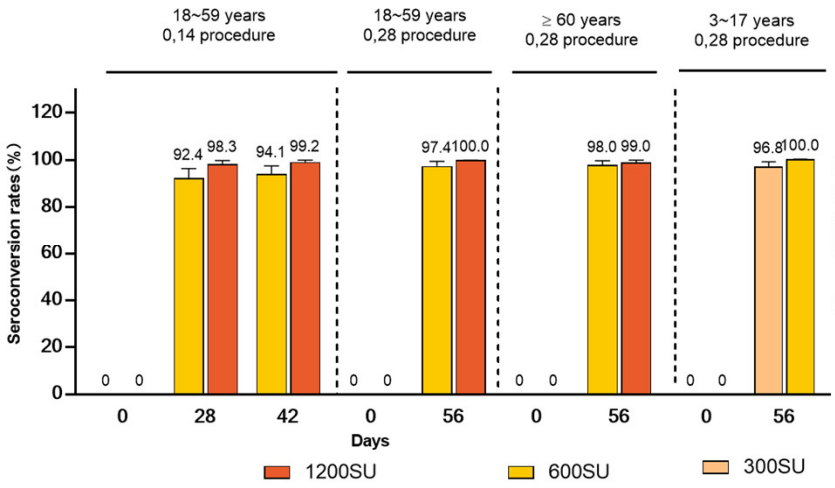
Clinical Study Plan

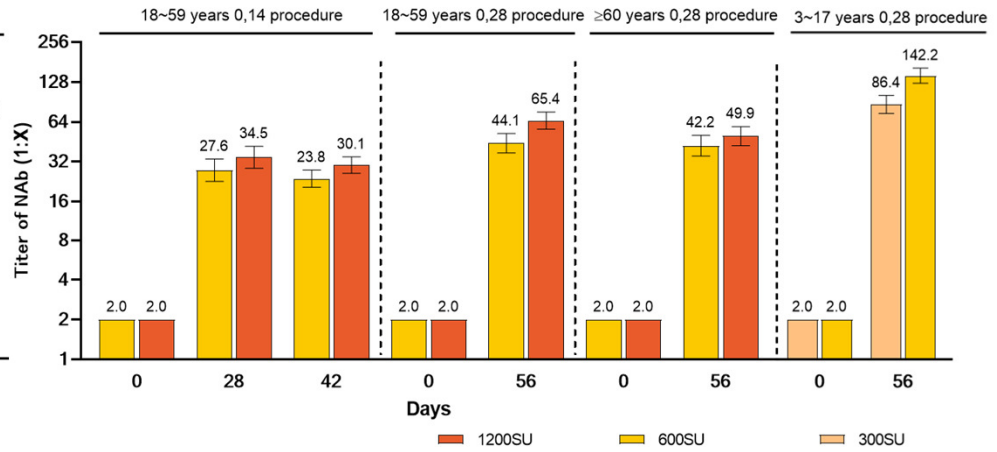
- Comprehensive study
- The target population is 6 months old and above, covering pregnant women and people with preconditions.



- FDA WHO Guidelines
- ICH GCP Guidelines

Phase I/II CT Data – Immunogenicity (Neutralizing antibody of Wild Virus)





- On the 28th day after immunization with different doses of vaccine by 0,14 and 0,28 procedures, the effective neutralizing antibody seroconversion reached ***more than 94%*** in different age groups;
- The neutralizing antibody titers ***were higher in children and adolescents*** aged 3-17 years than those in adults aged 18-59 years and elderly aged ≥60 years.

Summary of Phase I/II Clinical Trial

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- The preliminary data of phase I and II studies among the adults, the elderly and the adolescents and children had been obtained.
- The results showed that the participants vaccinated with medium dose (600SU) and high dose (1200SU) vaccines for 28 days, and then the positive seroconversion rate reached to over 94.1%.

The above studies showed that the medium dose, high dose and 0,14 and 0,28 procedures can produce a certain level of protective antibodies. Considering the urgency of the current pandemic emergency vaccination, the medium dose (600 SU) with the 0,14 procedure was selected to enter the phase III clinical trial to explore the basic data of the body protection effect in a short time.

NMPA conducted on-site inspections of the phase I/II clinical trials between November 24 and 30, 2020, and authenticity complied.

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3 3.2 Phase III Clinical Trial (Pivotal Study)

Study Design of Phase III Clinical Trial

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The same batch of vaccine (20200412) was carried out in different regions according to the same immunization procedure (0,14 procedure), which confirmed each other.

Turkey: start from Sept. 16th 2020

Subjects: Medical staff + General population （1:10）

Size: 13000，18-59 years old

Consideration of clinical trial site selection

- ☐Serious pandemic
- ☐Populous
- ☐Possible differences of epidemic strains in different regions

Brazil: start from July 21st 2020

Subjects: Medical staff

Size: 13,060，≥18 years old

Indonesia: start from August 11th, 2020

Subjects: General population

Size: 1620， 18-59 years old

Chile: start from November 27th, 2020

Subjects: Medical staff + General population （1:10）

Size: 3000，≥18 years old

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3.3 Phase III Clinical Trial-Efficacy Data

Demographics characteristics of participants in Brazil

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	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%)
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)

Study Plan of Phase III Clinical Trial

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Primary endpoint

•**To evaluate the efficacy of whole course immunization for COVID-19 patients with clinical symptoms and confirmed by RT-PCR after two weeks.**

•To evaluate the safety of the vaccine within 7 days after each dose.

Secondary endpoint

- To evaluate the efficacy on COVID-19 patients with clinical symptoms and confirmed by RT-PCR two weeks after the first dose of immunization
- To evaluate the efficacy on severe COVID-19 cases after two weeks of full-course vaccination.
- To evaluate the safety of 28 days after vaccination.
- To evaluate the efficacy on previously infected subjects after two weeks of full-course vaccination.
- To evaluate the incidence of severe cases (evaluation of the possibility of VED)

COVID-19 Case Definition

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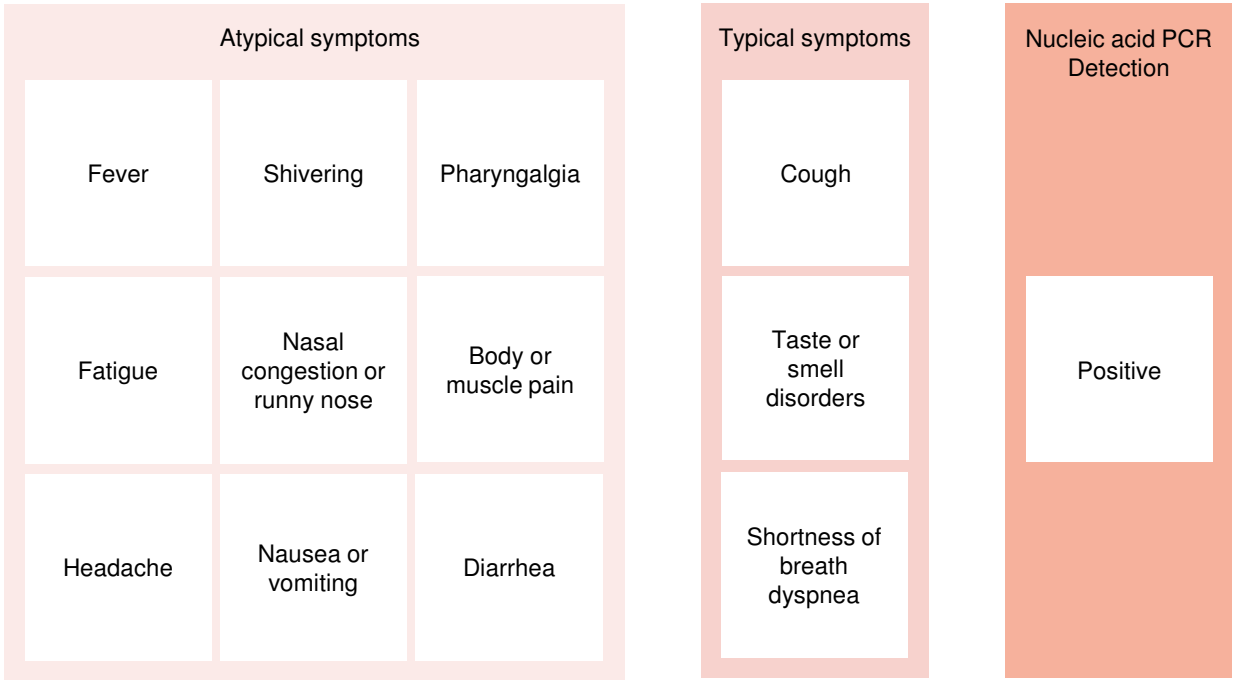

NMPA recommended definition: *two atypical symptoms or one typical symptom lasting for more than two days or COVID-19 imaging features + PCR positive = COVID-19 confirmed cases;*

Protocol definition: *any symptoms lasting for more than two days + PCR positive = COVID-19 confirmed cases*

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Definition of moderate and above cases of COVID-19

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WHO clinical progression scale

Patient State	Descriptor	Score
Uninfected	RNA Uninfected; noviral RNA detected	0
Ambulatory mild disease	Asymptonmatic; viral RNA detected	1
	Symptomatic; independent	2
	Symtomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation,$p0_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $p0_2/FiO_2 < 150$（$SpO_2/FiO_2 < 200$）or vasopressors	8
	Mechanical ventilation $P0_2/FiO_2 < 150$ （$SpO_2/FiO2 < 200$）and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

WHO Working Group on the Clinical Characterization and Management of COVID-19 infection. Lancet Infect Dis 2020 Aug;20(8):E192-E197

Efficacy on the confirmed cases (Brazilian health care workers)

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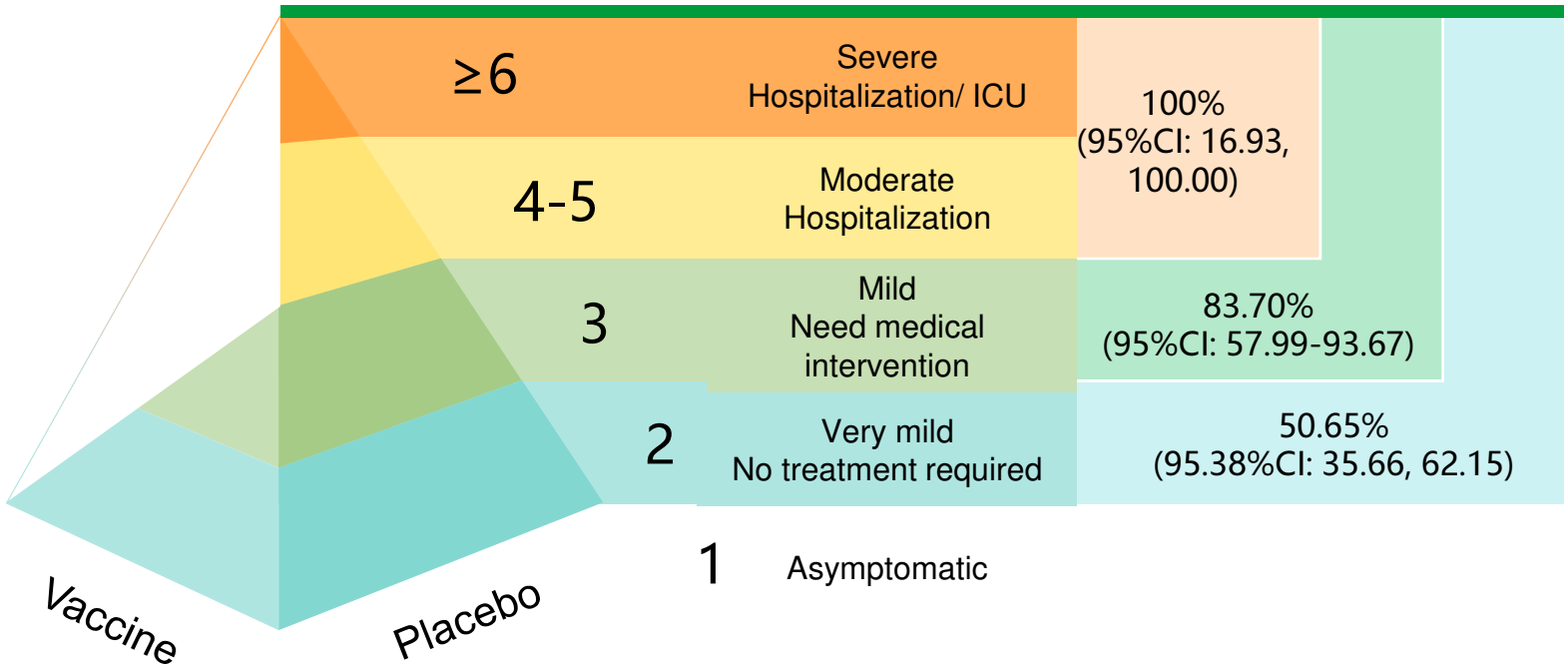
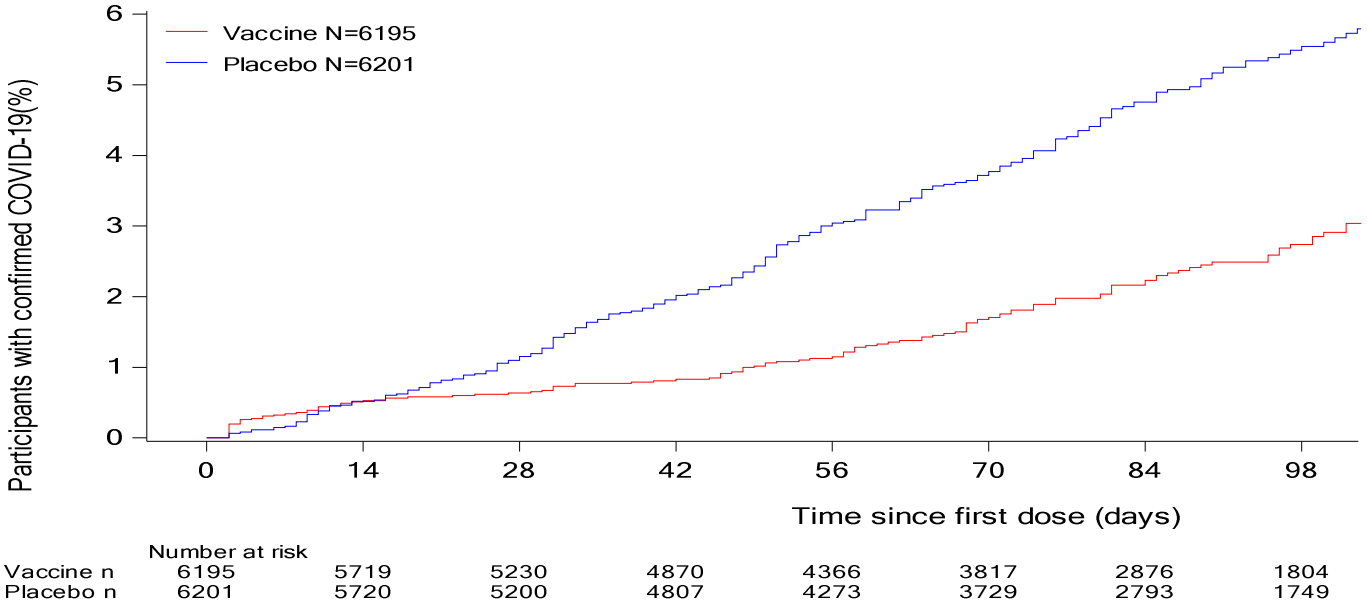
Efficacy: Grade 6 and above cases (10934 subjects completed two injections and 9823 subjects entered the monitoring period)



Efficacy on the confirmed cases in Brazil



As of 16th Dec 2020, the average follow-up time after the 2nd dose was **70.3 ± 25.6** days, and the median follow-up duration was **73.0** days.

Case definition	Number of Cases n (Incidence density/100 persons, year)		Efficacy (%) (95%CI)
	Vaccine	Placebo	
NMPA definition	85/4953(11.0)	168/4870(22.3)	50.7 (35.9, 62.0)
Protocol definition	80/4953(10.4)	170/4870(22.7)	54.1 (40.1, 64.8)

Efficacy on different subgroups

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Subgroups		Cases (n) / Monitored number (N)		Efficacy (95%CI)
		Vaccine	Placebo	
Age group	18~59 years old	83 / 4741	164 / 4663	50.66% (35.75%, 62.11%)
	60 years old and above	2 / 212	4/207	51.11% (-166.93%, 91.04%)
Interval between two doses	<21 days	77 / 4184	149 / 4148	49.12% (33.01%, 61.36%)
	21-28 days	8 / 769	19/722	62.32% (13.91%, 83.51%)

Efficacy on the population with precondition

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Precondition	Vaccine		Placebo		Efficacy %(95%CI)
	N	n(Incidence density)	N	n (Incidence density)	
No precondition	2222	41(13.21)	2140	82(27.81)	52.40(30.75, 67.28)
Precondition	2731	44(10.64)	2730	86(20.84)	48.93(26.57, 64.49)
Obesity	1099	13(5.78)	1112	50(23.02)	74.86(53.73, 86.35)
Cardiovascular disease	621	6(7.05)	608	10(11.64)	39.54(-66.38, 78.03)
Diabetes	175	3(11.21)	159	5(21.05)	48.59(-115.33, 87.72)

- Precondition had no significant effect on the Efficacy;
- The sample size of some patients is small, which needs further study.

Efficacy against COVID-19 cases* in Turkey

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Treatment Arm	Number of symptomatic COVID-19 Cases	Total Subject Number**	%	Person year exposure	Incidance rate (/100 person year)
CoronaVac	9	6559	0.14%	283.89	3.17
Placebo	32	3471	0.92%	166.53	19.22
Total	41	10030			

Vaccine Efficacy ***	83.50% CI_{95} (65.42-92.12)

Treatment Arm	Number of hospitalized COVID-19 Cases	Total Subject Number**	%	Person year exposure	Incidance rate (/100 person year)
CoronaVac	0	6550	0.00%	283.69	0.00
Placebo	6	3445	0.17%	166.51	3.63
Total	6	9995			

Vaccine Efficacy ***	100.00% CI_{95} (20.33-100.00)

* Based on symptomatic and RT-PCR positive COVID-19 cases after 14 days and more after the 2nd dose

** Number of subjects after 14 days and more after the 2nd dose

*** Based on calculation person x year in the follow up period

Efficacy against symptomatic COVID-19 cases in Indonesia

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A total of 1603 subjects in the Indonesian clinical trial have been completed with two doses of vaccination and entered the monitoring period. The monitoring time is 75 days.

Efficacy after 14 days with two doses of vaccination

(Data as of January 11, 2021)

	Cases (n) / Monitored number (N)		Efficacy (95%CI)
	Vaccine N=798	Placebo N=804	
Total	7/798	18/804	65.30% (18.95%,85.10%)

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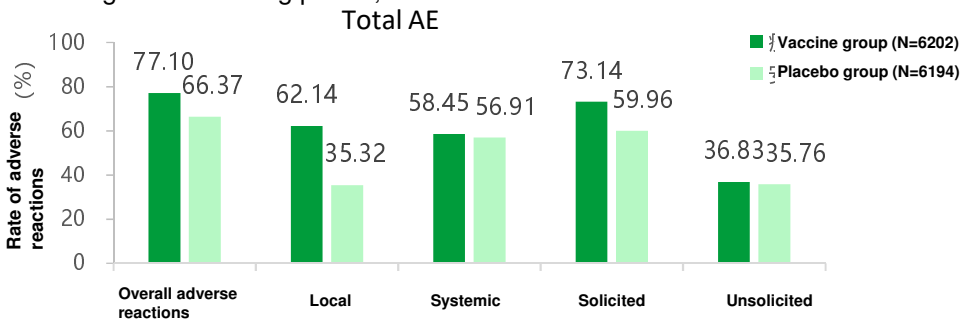
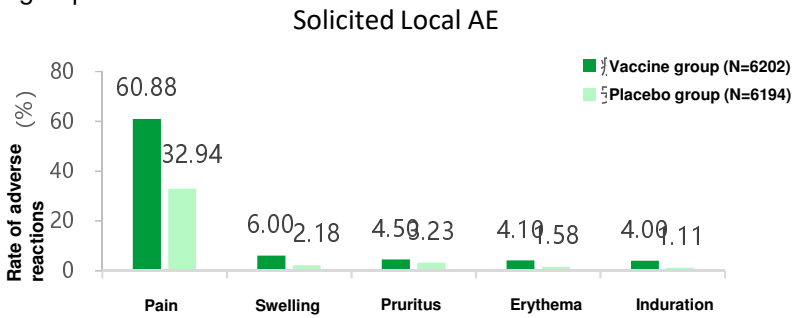
3.4 Phase III Clinical Trial-Safety Data

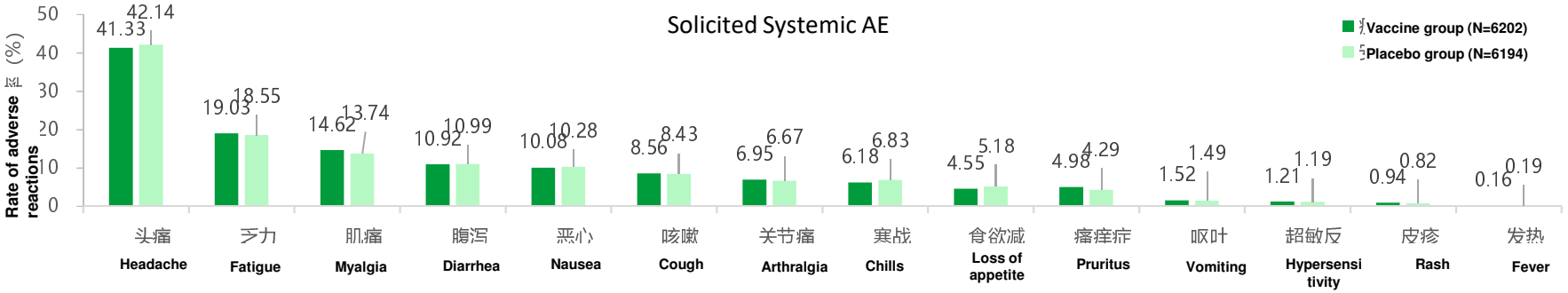
Solicited Adverse Events

Phase III CT Data _ Safety（Brazil）

- The overall incidence of adverse reactions was 77.10% in the vaccine group and 66.37% in the placebo group, with local and collective adverse reactions as the main;
- The incidence of local adverse reactions was 62.14% in the vaccine group and 35.32% in the placebo group. The incidence of systemic adverse reactions was 58.45% in the vaccine group and 56.91% in the placebo group;
- The most common symptoms were pain at the inoculation site, headache, fatigue and myalgia;
- During the monitoring period, there was no severe disease or VED in the vaccine group.







Phase III CT Data _ Safety（Turkey）

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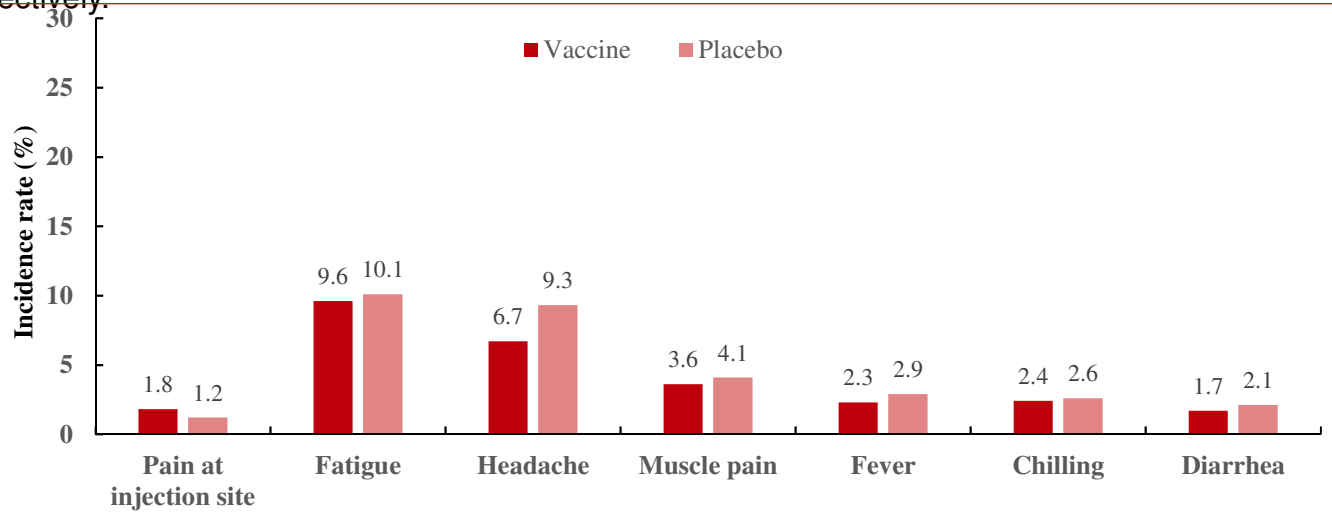
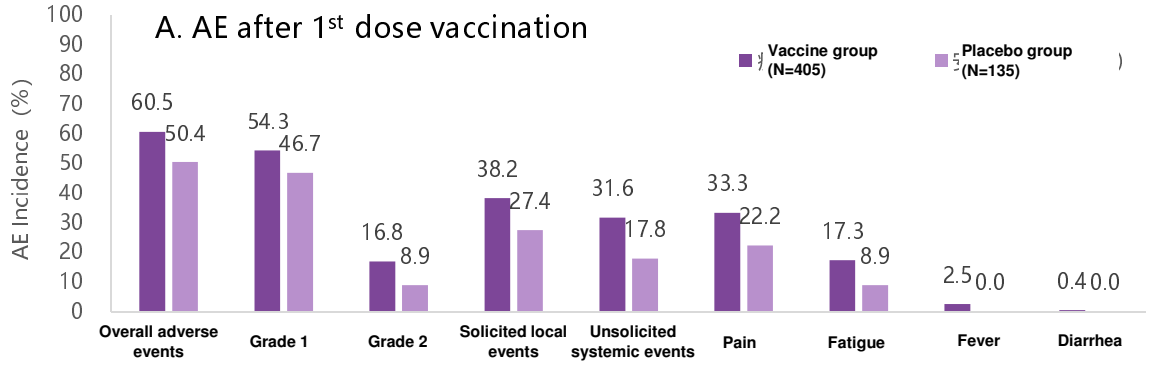
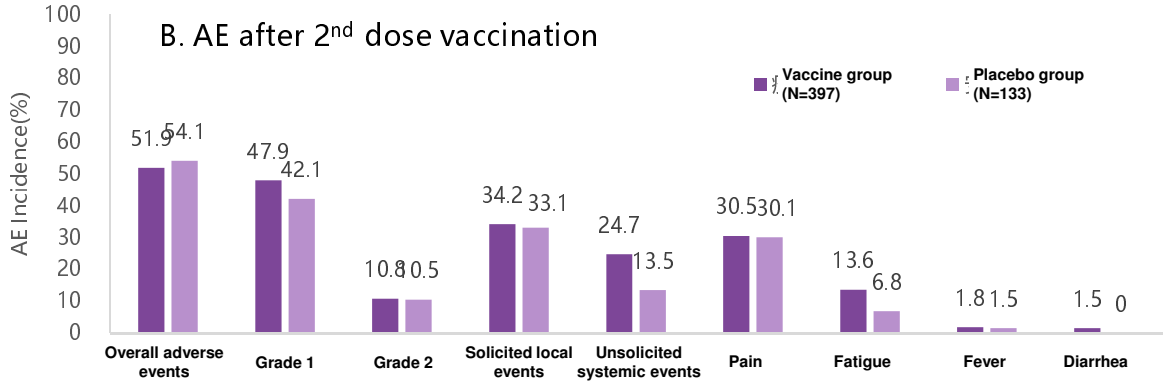
Adverse Event Incidence Rate

- Based on the safety analysis of 10,216 subjects, and the overall safety of the vaccine was favorable. The most frequent adverse events were listed below.
- The incidence rate of fatigue and headache were 9.6% and 6.7% in the vaccine group, respectively.



Phase III CT Data _ Safety (Indonesia)





Interim analysis of Safety Data

The overall safety of the vaccine in 540 subjects was favorable. From the beginning of vaccination to 28 days after the two doses of vaccination, the incidence of AEs in the vaccine group and the placebo group was 71.6% and 71.0%, respectively. The incidence of adverse events after the first dose and the second dose was 60.5% and 51.9% respectively. The main AEs were grade 1, and the incidence of AEs after the 1st dose and 2nd dose were 54.3% and 47.9% respectively. The main symptoms were pain at the vaccination site, and the incidence of pain after the first dose and the second dose were 33.3% and 30.5% respectively. During the monitoring period, there were no severe cases of new coronary artery disease and no VED.

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3 3.5 Phase III Clinical Trial- Bridging clinical trials

Immunogenicity Data of Bridging clinical (Schedule 0,14)

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Immunogenicity and non inferiority in commercial scale versus pilot scale for healthy adults aged 26-45

	Commercial scale	Pilot scale	Non inferiority Test
Positive rate (%)	93.23	90.73	Non inferiority
95%CI	(89.38, 96.01)	(86.41, 94.03)	
GMT (1:X)	17.91	18.52	
95%CI	(15.93, 20.13)	(16.46, 20.83)	

Immunogenicity and non inferiority in the elderly aged 60 and above compared with healthy adults aged 18-59

	Elderly	Adult	Non inferiority Test
Positive rate (%)	82.47	91.58	Inferiority
95%CI	(77.19,86.96)	(88.79, 93.87)	
GMT (1:X)	11.82	18.21	
95%CI	(10.50, 13.30)	(16.74, 19.80)	

The immunogenicity of the pilot scale and commercial scale vaccines comply with the non inferiority standard, but the immunogenicity of the elderly was slightly lower than that of the adults, which did not comply. It suggested the schedule 0,28 shall be considered for elderly which can achieve higher antibody levels.

Bridging clinical _ Cross neutralization

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Sr. No.	Strain Code	Origin	S protein614 (D/G)	Nucleotide 28144 (L/S)	Neutralization antibody GMT(1：X)	Neutralizing antibody Seroconversion rate
1	CZ02（Vaccine strain）	Zhejiang (Taizhou)	D	S	33.7	98.8%
2	WZL	Beijing (Xinfadi)	G	L	17.9	98.8%
3	WGF	Zhejiang (Wenzhou)	D	S	46.7	100.0%
4	ZJY	Britain	D	L	15.4	97.5%
5	SSH	Swizerland	G	L	21.4	97.5%
6	JWL	America	D	S	21.0	100.0%
7	ZYF	Italy	G	L	20.6	97.5%
8	HAC	Italy	G	L	9.3	80.0%
9	HJL	Italy	G	L	17.2	98.8%
10	ZXZ	Spanish	G	L	15.6	91.3%
11	QHF	Spanish	G	L	14.9	96.3%
12	NOOR	Afghanistan	D	S	11.4	86.3%

- The cross neutralization test was performed on 11 strains of isolates from different countries with immunized human serum of COVID-19 Vaccine (Vero Cell), Inactivated (CZ02 strain). The positive rate was between 80%-100% and GMT (1:) of serum antibody titer between 9.3~46.7. After immunization with COVID-19 vaccine, there was a good cross reaction between serum and all strains.

- Recently, the Institute of zoology, Chinese Academy of Medical Sciences and CDC of Guangdong Province have conducted cross neutralization evaluation on the sera of vaccinated patients with British and South African strains respectively. The evaluation results show that the human sera immunized with vaccines can effectively neutralize the mutated virus strains imported from Britain and South Africa, and the neutralization effect is lower than that of domestic virus strains.

Summary of Phase III Clinical Study

克尔来福™ CoronaVac™ 新型冠状病毒灭活疫苗

- 600SU with the schedule 0,14 was vaccinated by emergency use procedures in the three countries, it showed good safety without vaccine enhancement disease (VED).
- The overall efficacy of the schedule 0,14 in phase III clinical trial of the emergency use was 50.65%, 83.50%, 65.30% in Brazil, Turkey and Indonesia, respectively.
- According to the comprehensive analysis data of clinical trials in Brazil, the efficacy on mild cases need medical care was 83.70%, and the efficacy on hospitalized and severe cases was 100%; according to the data of clinical trials in Turkey, the efficacy on hospitalized cases was 100%.

克尔来福™
CoronaVac™
新型冠状病毒灭活疫苗

4 Emergency Use

Emergency Use

克尔来福™ CoronaVac™ 新型冠状病毒灭活疫苗

- CoronaVac® has been approved for emergency use or conditional marketing authorization by 37 authorities.

- Up to April 22, more than 270 million doses have been distributed and more than 160 million doses have bee used globally


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