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Supplementary appendix

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Supplement to: Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 2021; published online July 8. http://dx.doi.org/10.1016/S0140-6736(21)01429-X.

Appendix 1. Procedures on the screening, Day 0, Day 14 and Day 28 visits and the composition and pharmacological properties of the investigational product

Procedures on screening, Day 0, Day 14 and Day 28 visits

At the screening visit, all volunteers were tested with a SARS-CoV-2 PCR test with pharyngeal and nasopharyngeal swabs and a total antibody test (IgG and IgM). Urine pregnancy tests were given for women of reproductive age. On Day 0, data regarding demographic information, vital signs, medical history, presence of chronic diseases, physical examination findings, adverse events, and concomitant medications were recorded on electronic case report forms, and the first dose of CoronaVac or placebo was administered. Participants were requested to measure their body temperature daily and note it on a diary card. On Day 14, the second dose of CoronaVac or placebo was administered and data regarding physical examination findings, concomitant medications, adverse events, COVID-19 symptoms, and having contact with a person with COVID-19 and diary cards for temperature measurements were collected. Female participants also underwent pregnancy tests. On Day 28, the same procedures as on day 14 except pregnancy testing were repeated. Both cohorts were monitored for PCR-confirmed symptomatic COVID-19 by active surveillance.

Description and composition of investigational products

Vaccine Description and Composition

COVID-19 Vaccine (CoronaVac), Inactivated, is an inactivated whole-virion vaccine with aluminium hydroxide as the adjuvant. COVID-19 vaccine is prepared by a novel coronavirus (CZ02 Strain) inoculated in African green monkey kidney cells (Vero Cells). It is a milky white suspension liquid, which can be layered due to precipitation and quickly dispersed. One dose of COVID-19 vaccine contains 600 SU (1 μg of antigen equals to 200 SU) of SARS-CoV-2 antigen in a 0·5 mL aqueous suspension for injection with 0·45 mg/mL of aluminium. The only active substance in the COVID-19 Vaccine is the inactivated SARS-CoV-2 whole-virion as SARS-CoV-2 antigen developed and manufactured by Sinovac Life Sciences, China. The Medicinal Product is developed entirely based on the features of this active substance; thus, there is no compatibility concern for using this drug substance in the formulation. The components in the COVID-19 vaccine are shown below:

Composition of the COVID-19 Vaccine:

Name of the ingredient	Content per dose
SARS-CoV-2 antigen	600 SU
Aluminium hydroxide (calculated as per aluminium)	0·45 mg/mL
Sodium chloride	9 mg/mL
Phosphate buffer solution*	5·0 mmol/L
Sodium hydroxide	q.s.
Water for injection	q.s. to 0·5 mL

q.s., Quantum satis

Notes: The phosphate buffer is prepared by monosodium hydrogen phosphate and disodium hydrogen phosphate, the content is calculated according to the phosphate ion concentration in the vaccine.

Composition of the Placebo:

Placebo contains aluminium hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride packed in pre-filled syringes of 0·5 mL for each container.

Pharmaceutical development

The inactivation process is performed by adding the β-propiolactone in the virus harvest fluid at a ratio of 1:4000 and inactivated at 2-8°C for 12-24 hours. Following the determined inactivation process, inactivation verification

results show that the SARS-CoV-2 virus can be inactivated completely, demonstrating that the inactivation process is stable.
The development of the COVID-19 vaccine includes the development of vaccine final bulk formulation process and the studies conducted to determine the aluminium adjuvant and solution environment. COVID-19 vaccine is developed to be filled in both vials and pre-filled syringes, the primary packaging materials are supplied by qualified suppliers with certain quality. The vaccine is designed to be stored and transported at 2-8°C, protected from light and avoided from freezing. The temporary shelf-life of the final bulk is determined as 12 months, while the shelf-life of COVID-19 Vaccine (Vero Cell), Inactivated, is temporarily determined as 36 months.

Physical, chemical and biological properties
The COVID-19 Vaccine (Vero Cell), Inactivated contains SARS-CoV-2 antigen as an active ingredient and filled in pre-filled syringe or vials, the dosage is 0·5 mL/600 SU per injection, the excipients of the vaccine is 0·3-0·6 mg/mL of aluminium hydroxide, 9 mg/mL sodium chloride and 5·0 mmol/L phosphate. The pH of the solution is 6·8-7·8. The vaccine is an opalescent suspension in which stratified precipitate may form and can be dispersed by shaking with no clumps shall be found upon shaking. The osmolality of the solution is 250-400 Osmol/kg which is in the range of the human body. The potency of the final bulk shall not be less than 0·5 compared to the reference vaccine, with not less than 60% of the dispensing quantity of the post-dissociation antigen content. No abnormal toxicity shall be presented in the vaccine, the solution shall be sterile and containing not more than 5 EU/dose bacteria endotoxin.

Appendix 2. COVID-19 Surveillance

Participants who experience symptoms suggesting COVID-19 (fever, cough, shortness of breath, difficulty breathing, chill, nasal congestion, muscle pain, headache, sore throat, fatigue, vomiting, diarrhoea, loss of smell, loss of taste) during the follow-up were instructed to call a 24/7 call centre or a study team member who would advise on how to proceed with clinical testing for COVID-19 if necessary, as per the trial working instructions. Additionally, participants got weekly reminders by phone calls through the Interactive Voice Response System (IVRS) to get in touch with the study team if they presented with a symptom, got a diagnosis of COVID-19 or were admitted to the hospital for any reason. Surveillance for COVID-19 symptoms and diagnosis has been done through the IVRS using the script given below. The calls have been organized automatically on a periodic basis depicted on the hours preferred by the participant. The participant is called on the day of the investigational product administration, the next and the other day for the first three days. Thereafter, weekly calls are commenced seven days after the administration of the investigational product.

All of the calls and responses are recorded as Call Detail Records and can be tracked on the IVRS/IWRS. If the participant responds "1-yes" to any of the queries, the response is conveyed to the study site through SMS and e-mail. In this way, site staff can learn which symptom(s) the participant displays and communicates with the participant through phone calls. If the site staff considers these symptoms can be related to COVID-19 or an unsolicited adverse event, the participant is invited to the site for further evaluation.

IVRS system script:

Hello,

Welcome to "the CoronaVac vaccine developed against COVID-19 study" symptom tracing line.

Please press 1 if you have any of the symptoms that we will list in groups, if you don't press 0.

- Fever
- Cough
- Dyspnoea
- Difficulty in breathing

(5 seconds pause)----------

- Shivering
- Stuffy nose
- Sore throat

(5 seconds pause)----------

- Fatigue
- Muscle ache
- Headache

(5 seconds pause)----------

- Diarrhoea
- Vomiting

(5 seconds pause)----------

- Loss of smell
- Loss of taste

(5 seconds pause)----------

- Have you been told that you are a COVID-19 patient since we have last called you?

(5 seconds pause)----------

Beyond these conditions, if you have experienced any other problem press 1, if you haven't press 0.''

(if presses 1): "Please indicate the problem that you have had briefly after the tone."

''The investigator team has been automatically informed on the problem that you have been experiencing.

We wish you healthy days.''

(if presses no number): ''You have not responded. Please press 1 if there are symptoms, press 0 if there are no symptoms.''

(if presses other numbers than 1 and 0): ''You have pressed a wrong number, please press 1 if there are symptoms, press 0 if there are no symptoms.''

At the COVID-19 testing visit, a nasopharyngeal and pharyngeal swab was obtained for PCR testing. Appropriate medical management would be provided to all participants at the respective COVID-19 hospital. After development of a symptom, if the first PCR result was negative, the second PCR test was performed after 24 to 48 hours. If the second test was negative, participants would be followed-up according to the COVID-19 algorithm published by the Ministry of Health. Symptomatic participants would be regularly reviewed over phone calls and home visits and will be managed until the symptoms recover for patients not requiring hospitalisation. A detailed case report form would be completed describing the clinical course and outcome for all hospitalised and non-hospitalised COVID-19 patients. If participants were diagnosed with COVID-19, they would be followed-up according to the COVID-19 algorithm published by the Ministry of Health and an adverse event form would be completed.

Appendix 3. Assessment of severity of adverse events

The severity of clinical adverse events was assessed according to scales based on FDA toxicity grading scales for vaccine clinical trials, as shown in the tables below.

Table S1. Severity grading criteria for local adverse events

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pain	Not affecting or slightly affecting physical activity	Affecting physical activity	Affecting daily life	Loss of basic self-care ability, or hospitalisation
Induration*	Diameter 2·5 to <5 cm or area 6·25 to <25 cm^2 without affecting or slightly affecting daily life	5 to <10 cm in diameter or 25 to <100 cm^2 in area or affecting daily life	Diameter ≥10 cm or area ≥100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or seriously affecting daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Swelling*	Diameter 2·5 to <5 cm or area 6·25 to <25 cm^2 without affecting or slightly affecting daily life	5 to <10 cm in diameter or 25 to <100 cm^2 in area or affecting daily life	Diameter ≥10 cm or area ≥100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or seriously affecting daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Redness*	Diameter 2·5 to <5 cm or area 6·25 to <25 cm^2 without affecting or slightly affecting daily life	5 to <10 cm in diameter or 25 to <100 cm^2 in area or affecting daily life	Diameter ≥10 cm or area ≥100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or seriously affecting daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Rash*	Diameter 2·5 to <5 cm or area 6·25 to <25 cm^2 without affecting or slightly affecting daily life	5 to <10 cm in diameter or 25 to <100 cm^2 in area or affecting daily life	Diameter ≥10 cm or area ≥100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or seriously affecting daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Pruritus	Itching at injection site, relieved within 48 hours	Itching at injection site, did not alleviate within 48 h after treatment	Affecting daily life	..

* The maximum measured diameter or area should be used for induration and swelling, rash and redness; evaluation and grading should be based on functional grade and actual measurement results, and higher grading indicators should be selected.

Table S2. Severity grading criteria for systemic adverse events and vital signs

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	Mild or transient, 3-4 times/day, abnormal stool, or mild diarrhoea lasting less than 1 week	Moderate or persistent, 5-7 times/day, abnormal stool, or diarrhoea >1 week	>7 times/day, abnormal stool, or haemorrhagic diarrhoea, orthostatic hypotension, electrolyte imbalance, requiring intravenous infusion >2 L	Hypotensive shock, hospitalisation
Decreased appetite	Decreased appetite, not affecting food intake	Decreased appetite, reduced food intake, not affecting body weight	Decreased appetite, and significantly reduced body weight	Need intervention (such as gastric tube feeding, parenteral nutrition)
Vomiting	1-2 times/24 hours without affecting activity	3-5 times/24 hours or affecting activity	>6 times within 24 hours or requiring intravenous fluid infusion	Hospitalisation or other nutrition routes due to hypotensive shock
Nausea	Transient (<24 hours) or intermittent and basically normal food intake	Persistent nausea leads to reduced food intake (24-48 hours)	Persistent nausea leads to almost no food intake (>48 hours) or requires intravenous fluids	Life threatening (e.g., hypotensive shock)
Muscle pain (non-inoculated site)	Does not affect daily activities	Slightly affects daily activities	Severe muscle pain, seriously affects daily activities	Emergency or hospitalisation
Joint pain	Mild pain, not affecting daily activities	Moderate pain, requiring analgesics and/or pain interferes with functioning, yet not affecting daily activities	Severe pain, seriously affecting daily activities	Emergency or hospitalisation
Headache	Not affecting daily activities, no treatment required	Transient, slightly affecting daily activities, may need treatment or intervention	Seriously affecting daily activities, need treatment or intervention	Intractability, need emergency or hospitalisation
Cough	Transient, no treatment required	Persistent cough, effective treatment	Paroxysmal cough, uncontrolled treatment	Emergency or hospitalisation
Fatigue	Normal activity is weakened <48 hours, without affecting the activity	Normal activity is weakened by 20%~50% >48 hours, slightly affecting the activity	Normal activity is weakened by >50%, seriously affecting daily activities, unable to work	unable to take care of oneself, emergency or hospitalisation
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., oedema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental activities of daily living	Widespread and constant; limiting self-care activities of daily living or sleep; systemic corticosteroid or immunosuppressive therapy indicated	..
Skin rash (exanthema)†	Present, but asymptomatic	Symptomatic (pruritus/pain), but interferes only slightly with daily activities	Symptomatic, prevents daily activities	Emergency or hospitalisation
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalisation indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated
Vital signs	..	..	..	..
Fever (oral temperature)	37·5～＜38·2℃	38·2～＜38·7℃	≥38·7℃	≥39·7℃, lasting more than 3 days

† Specify if the skin rash is located in any specific body part or if it is widespread.

The severity of the unsolicited clinical adverse events was classified through a numeric scale of one to five, which was created based on the grading depicted in Table S3.

Table S3. Severity grading criteria for unsolicited adverse events

Grade 1 (Mild)	Transient (< 48 hours) or mild discomfort; no medical intervention/therapy required
Grade 2 (Moderate)	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3 (Severe)	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisations possible
Grade 4 (Life-threatening)	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable
Grade 5	Death

Appendix 4. List of participating sites

Centres	Number of volunteers recruited
Turkish Republic Ministry of Health Ankara City Hospital, Ankara, Turkey	976
Ankara University School of Medicine, Ankara, Turkey	881
Hacettepe University School of Medicine, Ankara, Turkey	782
Turkish Republic Ministry of Health İstanbul Provincial Health Directorate University of Health Sciences İstanbul Ümraniye Training and Research Hospital, İstanbul, Turkey	731
Kocaeli University School of Medicine, Kocaeli, Turkey	702
Turkish Republic Ministry of Health İzmir Provincial Health Directorate İzmir Health Sciences University İzmir Tepecik Training and Research Hospital, İzmir, Turkey	635
Turkish Republic Ministry of Health Ankara Provincial Health Directorate Ankara Training and Research Hospital, Ankara, Turkey	468
Bursa Uludağ University Health Application and Research Centre Bursa Uludağ University Hospital, Bursa, Turkey	462
İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey	409
Ege University School of Medicine, İzmir, Turkey	362
Turkish Republic Ministry of Health İzmir Provincial Health Directorate University of Health Sciences Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Turkey	350
İstanbul University İstanbul School of Medicine, İstanbul, Turkey	340
Akdeniz University School of Medicine, Antalya, Turkey	337
Turkish Republic Ministry of Health İstanbul Provincial Health Directorate Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Turkey	334
Acıbadem University Atakent Hospital, İstanbul, Turkey	330
Çukurova University Balcalı Hospital Health Application and Research Centre, Adana, Turkey	322
Marmara University School of Medicine, İstanbul, Turkey	291
Karadeniz Technical University School of Medicine, Trabzon, Turkey	279
Dicle University School of Medicine, Diyarbakır, Turkey	274
Turkish Republic Ministry of Health İstanbul Provincial Health Directorate University of Health Sciences İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey	221
Turkish Republic Ministry of Health Kayseri City Training and Research Hospital, Kayseri, Turkey	219
İnonü University Turgut Özal Health Centre, Malatya, Turkey	208
Gaziantep University Şahinbey Research and Application Centre, Gaziantep, Turkey	199
Turkish Republic Ministry of Health Ankara Provincial Health Directorate Ankara Keçiören Sanatorium, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey	102
Total	10214

Appendix 5. Distribution of COVID-19 cases with regard to the WHO Clinical Progression Scale

Table S4. COVID-19 severity and symptoms of the cases in the efficacy analysis with regard to WHO Clinical Progression Scale (the highest score during the course of the disease is given here)

Patient state	Descriptor	CoronaVac arm n (%)	Placebo arm n (%)	Total n (%)
Ambulatory mild disease	1 Asymptomatic-viral RNA detected	3 (0·05)	6 (0·17)	9 (0·09)
	2 Symptomatic- independent	8 (0·12)	25 (0·7)	33 (0·32)
	3 Symptomatic- assistance needed	1 (0·02)	1 (0·03)	2 (0·02)
Hospitalised: moderate disease	4 Hospitalised (If hospitalisation is for isolation only record the status with an outpatient)- no oxygen therapy	0 (0)	3 (0·08)	3 (0·03)
	5 Hospitalised; oxygen by mask or nasal prongs	0 (0)	2 (0·06)	2 (0·02)
Hospitalised: severe diseases	6 Hospitalised-oxygen by non-invasive or high flow ventilation	0 (0)	1 (0·03)	1 (0·01)
	Total	12 (0·18)	38 (1·07)	50 (0·49)

Appendix 6. Adverse events

Table S5. Adverse events from Day 0 to date of unblinding in the CoronaVac and placebo arms

	CoronaVac arm (n=6646)		Placebo arm (n=3568)		Total (n=10214)		
	Events	Subjects	Events	Subjects	Events	Subjects	P value
	n	n (%)	n	n (%)	n	n (%)	
Total AEs	2633	1259 (18·9)	1212	603 (16·9)	3845	1862 (18·2)	0·0108
Solicited AEs	2243	1148 (17·3)	999	537 (15·1)	3242	1685 (16·5)	0·0039
Unsolicited AEs	390	305 (4·6)	213	169 (4·7)	603	474 (4·6)	0·7358
Systemic AEs	2427	1179 (17·7)	1149	571 (16)	3576	1750 (17·1)	0·0263
Local AEs	206	180 (2·7)	63	52 (1·5)	269	232 (2·3)	<0·0001
AEs within 30 minutes	77	68 (1·0)	50	44 (1·2)	127	112 (1·1)	0·3312
AEs within 0-7 days	2322	1154 (17·4)	1043	556 (15·6)	3365	1710 (16·7)	0·0215
AEs in 8-28 days	268	175 (2·6)	155	93 (2·6)	423	268 (2·6)	0·9359
AEs in >28 days	43	20 (0·3)	14	10 (0·3)	57	30 (0·3)	0·8540
Grade 1 AE	2358	1183 (17·8)	1111	577 (16·2)	3469	1760 (17·2)	0·0377
Grade 2 AE	250	167 (2·5)	92	70 (2·0)	342	237 (2·3)	0·0778
Grade 3 AE	25	22 (0·3)	9	8 (0·2)	34	30 (0·3)	0·3415
Grade 4 AE	..	..	..	..	..	..	..

AE, Adverse event

Table S6. Adverse events from Day 0 to the data cut-off date in the CoronaVac arm

	CoronaVac arm (n=6646)	
	Events	**Subjects**
	n	**n (%)**
Total AEs	2758	1290 (19·4)
Solicited AEs	2326	1178 (17·7)
Unsolicited AEs	432	325 (4·9)
Systemic AEs	2552	1210 (18·2)
Local AEs	206	180 (2·7)
AEs within 30 minutes	..	..
AEs within 0-7 days	2341	1159 (17·4)
AEs in 8-28 days	299	193 (2·9)
AEs in >28 days	118	64 (1)
Grade 1 AE	2472	1209 (18·2)
Grade 2 AE	259	171 (2·6)
Grade 3 AE	27	24 (0·4)
Grade 4 AE	..	..

AE, Adverse event

Table S7. All adverse events from Day 0 to date of unblinding in the CoronaVac and placebo arms

	CoronaVac arm (n=6646)		Placebo arm (n=3568)		Total (n=10214)		
	Events	Subjects	Events	Subjects	Events	Subjects	P value
	n	n (%)	n	n (%)	n	n (%)	
Total AEs	2633	1259 (18·9)	1212	603 (16·9)	3845	1862 (18·2)	0·011
Solicited AEs							
Local AEs							
Pain	169	157 (2·4)	43	40 (1·1)	212	197 (1·9)	<0·0001
Erythema	15	12 (0·2)	5	4 (0·1)	20	16 (0·2)	0·4042
Paraesthesia	11	9 (0·1)	6	5 (0·1)	17	14 (0·1)	1·0000
Swelling	4	4 (0·1)	4	4 (0·1)	8	8 (0·1)	0·4621
Induration	3	3 (0)	2	2 (0·1)	5	5 (0)	1·0000
Pruritus	2	2 (0)	2	2 (0·1)	4	4 (0)	0·6150
Systemic AEs							
Fatigue	660	546 (8·2)	298	248 (7·0)	958	794 (7·8)	0·0228
Headache	447	393 (5·9)	249	212 (5·9)	696	605 (5·9)	0·9538
Myalgia	315	267 (4·0)	128	106 (3)	443	373 (3·7)	0·0071
Chill	176	164 (2·5)	74	63 (1·8)	250	227 (2·2)	0·0217
Fever	130	120 (1·8)	57	52 (1·5)	187	172 (1·7)	0·1922
Diarrhoea	118	106 (1·6)	61	59 (1·7)	179	165 (1·6)	0·8226
Cough	54	50 (0·8)	24	24 (0·7)	78	74 (0·7)	0·6507
Arthralgia	49	47 (0·7)	18	18 (0·5)	67	65 (0·6)	0·2193
Nausea	52	46 (0·7)	8	7 (0·2)	60	53 (0·5)	0·0008
Vomiting	18	17 (0·3)	8	8 (0·2)	26	25 (0·2)	0·7581
Rash	7	7 (0·1)	7	6 (0·2)	14	13 (0·1)	0·3957
Allergic reaction	6	5 (0·1)	1	1 (0)	7	6 (0·1)	0·6718
Decreased appetite	1	1 (0)	3	2 (0·1)	4	3 (0)	0·2808
Pruritus	3	3 (0)	0	0 (0)	3	3 (0)	0·5562
Swelling	2	2 (0)	1	1 (0)	3	3 (0)	1·0000
Other	1	1 (0)	0	0 (0)	1	1 (0)	1·0000

AE, Adverse event; SAE, Serious adverse event

Table S8. Distribution of serious adverse events

Serious Adverse Events	CoronaVac arm	Placebo arm
	N=6646	N=3568
Acute cerebellar infarction		1
Acute myocardial infarction		1
Systemic allergic reaction	1	
Bone fracture due to fall		1
Breast cancer	1	
Encephalitis*	1	
Ovarian cyst	1	
Rhinoplasty operation		1
Upper gastrointestinal bleeding	1	
Thyroid cancer		1
Seizure	1	
Total	6	5

*final definitive diagnosis after a brain biopsy was obtained as infiltrative glial neoplasm

Serious adverse events which might have a causal relationship with the investigational product

Allergic reaction

A 40 years old female participant, with no known allergies and a medical history of anxiety (on escitalopram treatment) developed vertigo, redness and numbness in her mouth for a couple of minutes right after having received the first dose of the investigational product on November 23, 2020, at 14:16. These symptoms resolved spontaneously without any medical intervention. At the same day in the afternoon, the subject reported that she developed a similar allergic reaction but did not inform the site or the primary investigator and had taken steroid and antihistaminic drugs by herself. The next day, on November 24, 2020 around 15:20, the subject developed tachycardia, numbness, redness and swelling in the mouth, had presyncope and was about to lose her consciousness for a short period of time. The adverse event was treated with pheniramine and dexamethasone intravenously, and ketotifen, prednisolone, famotidine and cetirizine orally. She was hospitalised overnight for follow-up and discharged on November 25, 2020. The blinding was unveiled, and the participant was found to receive the vaccine as the investigational product. Serious adverse event was classified as severe and a probable causal relationship with the investigational product was deemed. Later on, she has reported that a similar allergic reaction was triggered after eating almond at home. She continued using ketotifen, prednisolone, famotidine and cetirizine orally until December 7, 2020.

Seizure

A 57 years old female participant developed fever and a seizure on December 17, 2020 which required hospitalisation. The subject was on candesartan and hydrochlorothiazide for hypertension and on escitalopram for anxiety. She received the first dose of the investigational product on December 16th, 2020, at 11:25 am. Serious adverse event was classified as severe. As the patient was concurrently diagnosed to have a urinary tract infection which was deemed to cause the fever resolving after appropriate antibiotic therapy, the site reported no causal relationship with the investigational product. The patient was discharged on December 18, 2020 in a good condition. After unblinding, it was noticed that the participant was in the vaccine arm.

Encephalitis

A 45 years old female participant with a medical history of Hashimoto thyroiditis on L-thyroxine treatment and asthma, received the second dose of the investigational product on January 5th, 2021 at 11:30 am. She suffered from a seizure on February 17th, 2020. She was hospitalised in another hospital on February 22nd, 2021 due to suspected encephalitis. MR spectroscopy on the same day revealed hyperintense lesions (T1) at cortical and subcortical regions of the left frontal lobe, at bilateral corona radiata and left thalamus. It is thought that these findings might be related to COVID-19 vaccine associated encephalomyelitis. Serious adverse event was classified as severe and a possible causal relationship with the investigational product was deemed. After unblinding, it was revealed that the participant was in the vaccine arm. After hospitalisation, desloratadine +montelukast, levetiracetam orally and d-formoterol fumarate+budesonide by inhalation were initiated. Viral screening PCR was negative. Protein, chloride and glucose levels in the cerebrospinal fluid (CSF) were within normal range and there were no cells in the CSF smear. She was referred to another hospital for further evaluation where a thorough evaluation for possible underlying aetiologies was undertaken. The patient underwent a stereotactic brain biopsy from the right centrum semiovale for a definitive diagnosis. Pathological examination of the brain biopsy revealed a hypercellular brain

parenchyma with atypical cellular infiltration, highly suspicious of infiltrative glial neoplasm. The morphological and immunohistochemical findings did not support a process of demyelination, vasculitis or inflammation. As a result of the discussions between the medical, neuroradiology and pathology teams, it was concluded that there were no signs of inflammation or demyelination and the patient was diagnosed to have glial neoplasm. The patient was then referred to the Medical Oncology Department for planning the necessary treatment procedures.

Appendix 7. CoronaVac Vaccine Study Group

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