

Appendix

1. Supplementary materials
2. Clinical trial protocol phase III

Table S1: Concomitant diseases in the volunteers included in the phase 3 study

Concomitant diseases	Total, n	Vaccine group, n	Placebo group, n
Chronic bronchitis	27	23	4
Arterial hypertension	149	118	31
Iron deficiency anaemia	41	31	10
Chronic pyelonephritis	23	19	4
Hepatitis A virus (HAV)	11	9	2
Hepatitis B virus (HBV)	64	47	17
Hepatitis C virus (HCV)	23	20	3
Chronic cholecystitis	1	1	0
Chronic sinusitis	12	8	4
Urolithiasis disease	1	0	1
Chronic prostatitis	1	0	1
Rheumatoid arthritis	1	1	0
Type II diabetes	9	8	1
Psoriasis	2	2	0
Chronic pancreatitis	7	7	0
Obesity	28	22	6
Human immunodeficiency virus (HIV)	10	6	4
Allergies	127	105	22
Chronic gastritis	8	6	2
Chronic heart failure	46	16	30
Cardiac ischemia	2	2	0
Gastritis	4	3	1
Tachycardia	3	2	1
Stomach ulcer	3	1	2
Osteochondrosis, disc protrusion	6	6	0
Hemorrhagic vasculitis	1	0	1
Glaucoma	1	1	0
Vitiligo	3	2	1
Meningitis	1	1	0
Pneumonia	3	3	0
Chronic pyelonephritis, rare exacerbation	6	4	2
Chronic tonsillitis, rare exacerbation	7	7	0

Osteoarthritis	3	3	0
Adnexitis	2	2	0
Atherosclerosis	1	1	0

Table S2: Any foreseen AEs within 7 days after the first or the second vaccination

Any foreseen AEs	AEs after the first vaccination		AEs after the second vaccination	
	Vaccine (n=2400) (%)	Placebo (n=600) (%)	Vaccine (n=2329) (%)	Placebo (n=585) (%)
Any foreseen local and systemic AEs	740 (30.83)	43 (7.17)	283 (12.15)	49 (8.38)
<i>Local reactions</i>	707 (29.46)	36 (6.0)	300 (12.89)	20 (3.42)
Pain at the injection site	465 (19.37)	33 (5.5)	143 (6.14)	15 (2.56)
Swelling	74 (3.08)	2 (0.33)	47 (2.02)	0 (0.0)
Hyperaemia	121 (5.04)	1 (0.17)	69 (2.96)	3 (0.51)
Infiltrate	42 (1.75)	0 (0.0)	28 (1.20)	0 (0.0)
Itching	5 (0.21)	0 (0.0)	9 (0.39)	1 (0.17)
<i>Systemic reactions</i>	216 (9.0)	13 (2.17)	173 (7.43)	83 (14.19)
Fever	26 (1.08)	1 (0.17)	15 (0.64)	8 (1.37)
Headache	44 (1.83)	3 (0.50)	42 (2.0)	14 (2.39)
Cough	19 (0.79)	1 (0.17)	9 (0.39)	6 (1.02)
Weakness	35 (1.46)	1 (0.17)	16 (0.69)	18 (3.08)
Diarrhoea	8 (0.33)	0(0.0)	6 (0.26)	1 (0.17)
Sore throat	29 (1.20)	2 (0.33)	15 (0.64)	7 (1.19)
Insomnia	7 (0.29)	1 (0.17)	5 (0.21)	1 (0.17)
Increased blood pressure	3 (0.13)	1 (0.17)	4 (0.17)	0 (0.0)
Vomiting	1 (0.04)	2 (0.33)	1 (0.04)	0 (0.0)
Nausea	9 (0.37)	0 (0.0)	1 (0.04)	0 (0.0)
Dizziness	2 (0.084)	0 (0.0)	6 (0.26)	2 (0.34)
Rheum	13 (0.54)	2 (0.33)	21 (0.90)	6 (1.02)
Chills	2 (0.084)	0(0.0)	6 (0.26)	4 (0.68)
Abdominal pain	3 (0.125)	0(0.0)	2 (0.08)	0 (0.0)
Joint pain	3 (0.125)	0(0.0)	5 (0.21)	4 (0.68)
Sleepiness	4 (0.17)	0(0.0)	1 (0.04)	1 (0.17)
Malaise	4 (0.17)	1 (0.17)	3 (0.51)	3 (0.51)
Fatigue	3 (0.125)	0(0.0)	2 (0.08)	2 (0.34)
Anosmia	1 (0.04)	0(0.0)	2 (0.08)	2 (0.34)
Any serious AEs	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Data are presented as n (%)

Table S3: Demographic characteristics of study participants according to Centers, ITT population

	Vaccine group (n=2400)			Placebo group (n=600)		
	Centre 1 n=800	Centre 2 n=800	Centre 3 n=800	Centre 1 n=200	Centre 2 n=200	Centre 3 n=200
Sex						
Female, (%)	393 (49.12)	443 (55.38)	359 (44.88)	84 (42.0)	117 (58.5)	86 (43.0)
Male, (%)	407 (50.88)	357 (44.62)	441 (55.12)	116 (58.0)	83 (41.5)	114 (57.0)
Ethnicity						
White, (%)	56 (7.0)	63 (7.88)	13 (1.63)	21 (10.5)	17 (8.5)	8 (4.0)
Asian, (%)	744 (93.0)	737 (92.12)	787 (98.37)	179 (89.5)	183 (91.5)	192 (96.0)
Age, years						
Median (IQR)	33 (25.0, 45.0)	34 (26.0, 45.0)	37 (29.0, 46.0)	32 (25.0, 44.0)	35 (26.0, 48.0)	36 (29.0, 45.0)
18-55, (%)	719 (89.87)	744 (93.0)	762 (95.2)	179 (89.5)	179 (89.5)	196 (98.0)
>55, (%)	81 (10.13)	56 (7.0)	38 (4.8)	21 (10.5)	21 (10.5)	4 (2.0)
Body-mass index*						
Median (IQR)	24.01 (21.45, 27.17)	23.88 (21.22, 26.35)	26.01 (22.83, 29.34)	24.01 (21.46, 27.41)	23.12 (20.86, 25.66)	26.41 (22.98, 30.05)
<25, (%)	482 (60.25)	184 (23.0)	298	62 (31.0)	142 (71.0)	64 (32.0)
25-30, (%)	206 (25.75)	83 (10.38)	175	18 (9.0)	41 (20.5)	51 (25.5)
≥30.0:obese	112 (14.0)				17 (8.5)	

Data are presented as numbers (%). *The body-mass index is the weight in kilograms divided by the square of the height in meters.

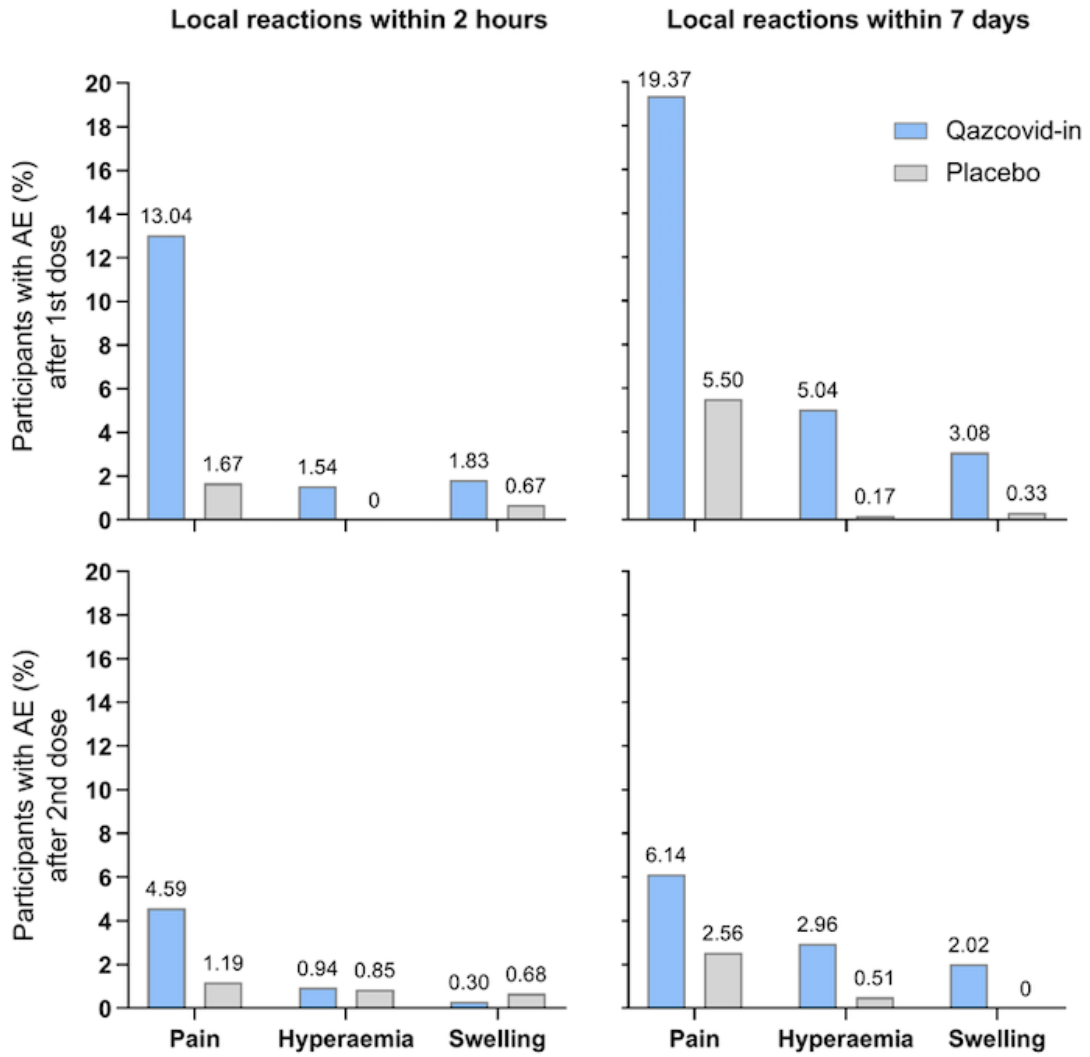


Figure S1. Local reactions recorded within 2 hours and 7 days after the first dose (upper panel) and the second dose (lower panel) of the QazCovid-in® vaccine or placebo

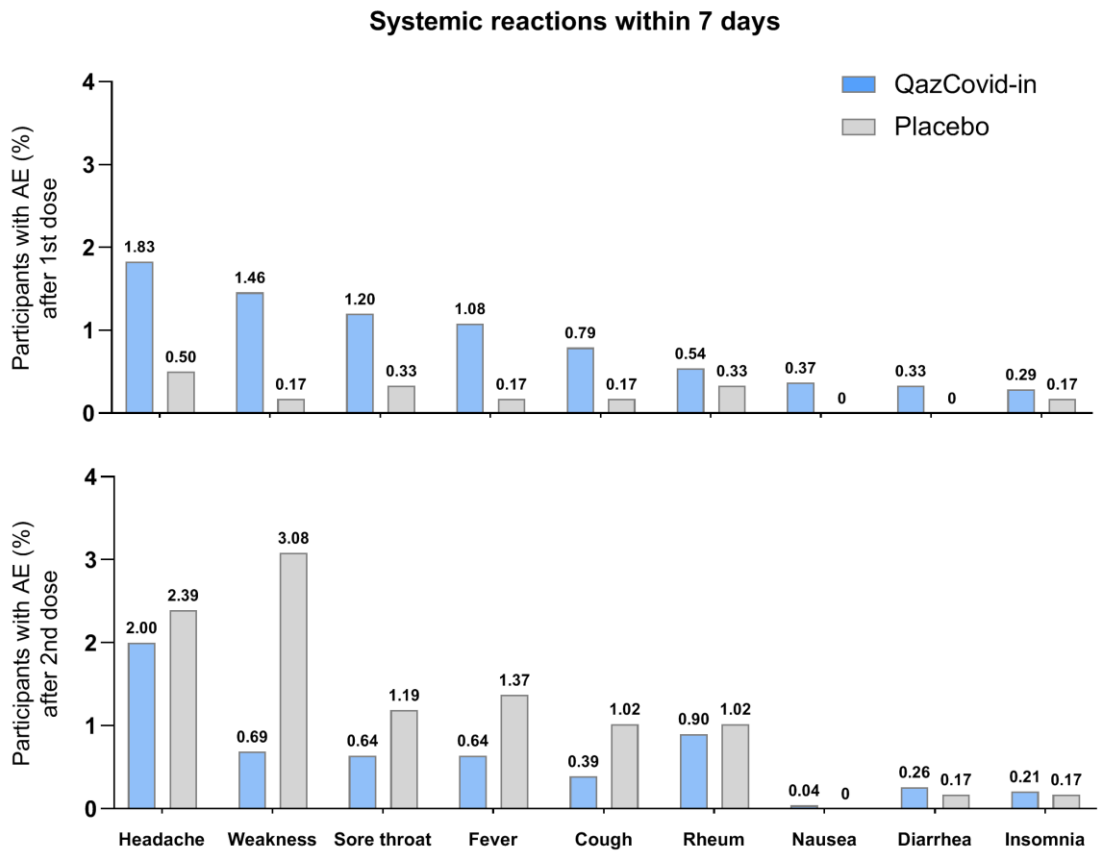


Figure S2. Systemic reactions recorded within 7 days after the first dose (upper panel) and the second dose (lower panel) of the QazCovid-in® vaccine or placebo

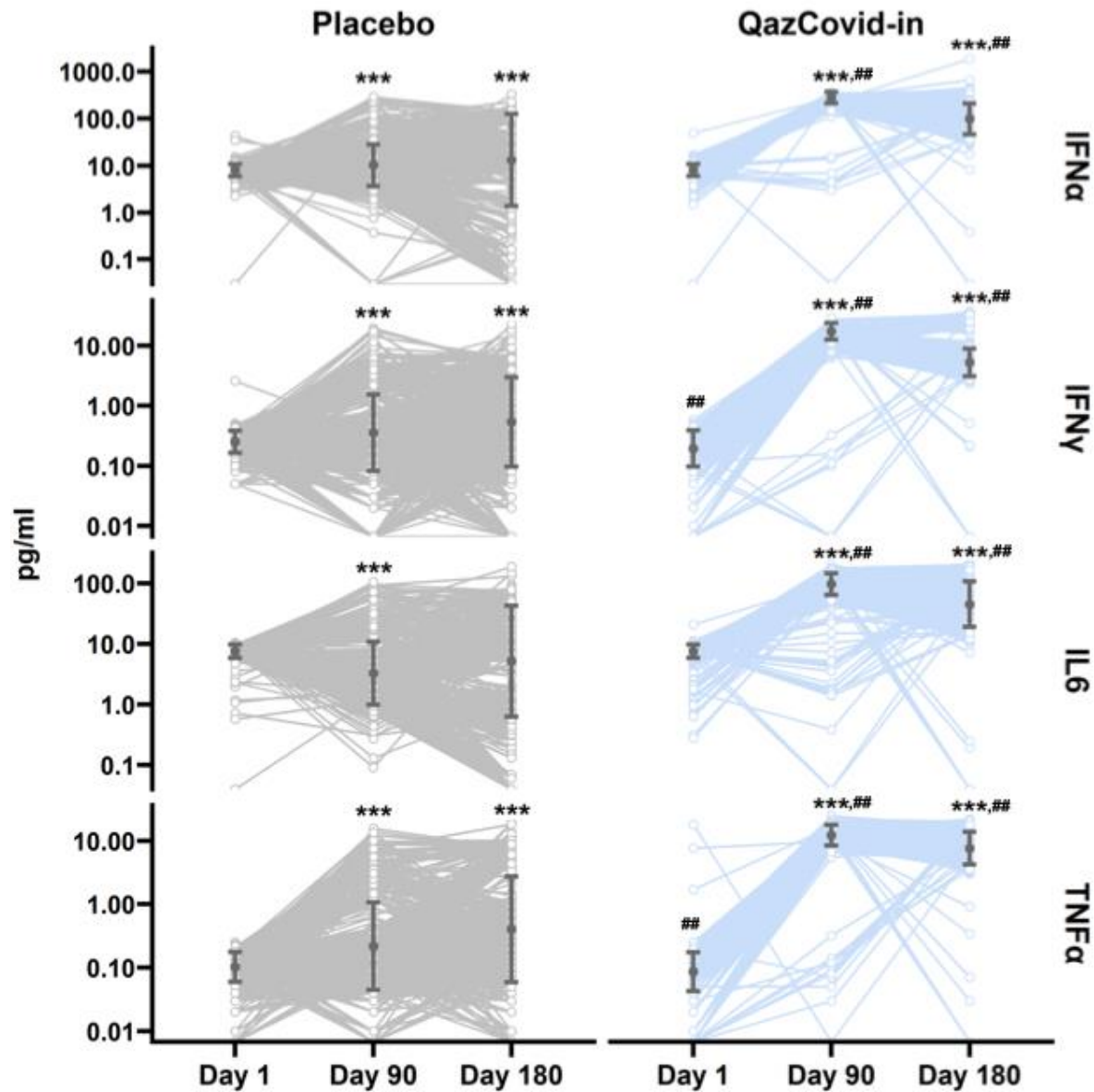


Figure S3. Cytokine profiles in placebo and vaccine groups

Individual values of IFN- α , IFN- γ , IL-6, and TNF- α cytokines for each subject are shown as small open circles with error bars representing Mean \pm SD for each time point. All concentrations are presented as pg/mL after the background subtraction. A statistically significant difference between the placebo and QazCovid-in groups at different time points is marked with ## ($p < 0.0001$); statistically significant difference between the time points within groups compared to Day 1 is marked with *** ($p < 0.00001$). *Post-hoc* multiple pairwise comparisons were made by the Wilcoxon test with Hochberg correction.

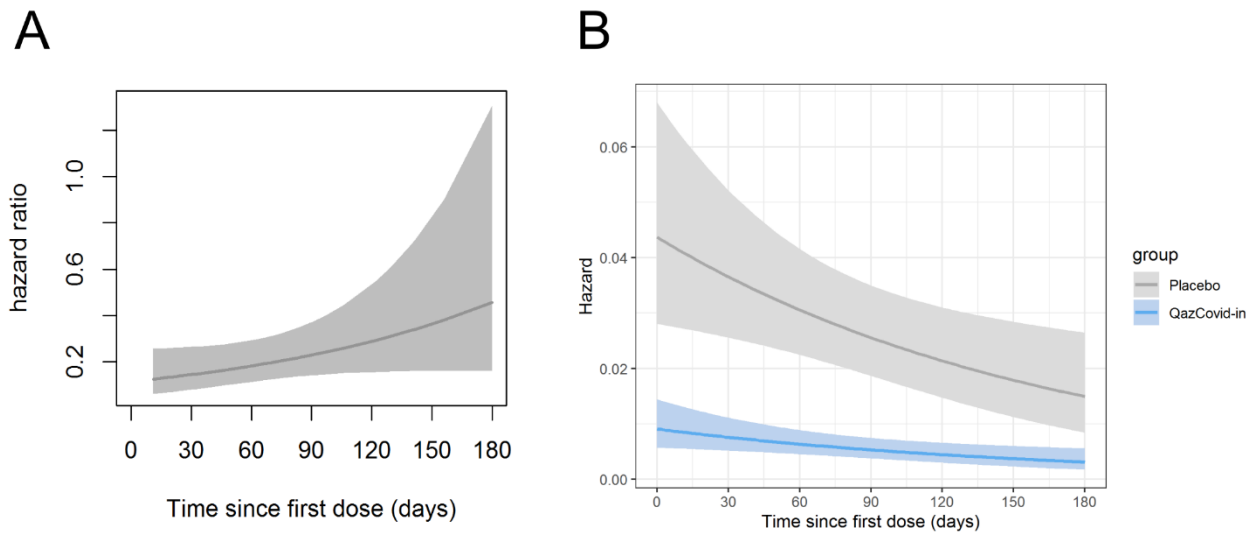


Figure S4. Time dependence of hazard functions for the symptomatic, PCR-confirmed COVID-19 in participants who received at least one dose of vaccine or placebo.

(A) Hazard ratio as a function of time for the symptomatic, PCR-confirmed COVID-19. The reference group is Placebo. Hazard ratio was calculated using a Cox proportional hazards model, assuming the interaction between time and group arm. (B) Hazard as a function of time plotted separately for Placebo and QazCovid-in group. Data was visualised using RStudio Version 1.4.1106, package casebase (version 0.10.1). Shaded area presents the 95% confidence interval.

MULTI-CENTERED, RANDOMIZED, BLIND, PLACEBO-CONTROLLED PHASE III CLINICAL TRIAL ON EVALUATION OF PROPHYLACTIC EFFICIENCY, SAFETY, AND IMMUNOGENICITY OF QAZCOVID-IN®-INACTIVATED VACCINE AGAINST COVID-19 IN HEALTHY ADULT VOLUNTEERS

Identification code: QAZCOV-III-01/2020

Phase of the trial: phase III

Version: 3.0

Date of issue: 17th of December 2020

DECLARATION OF CONFORMITY

This trial will be implemented in accordance with present Protocol of the clinical trial, as well as with requirements of the Good Clinical Practice (GCP) Guide (On the approval of good pharmaceutical practices, Standard of the Good Clinical Practice (GCP) according to appendix 2 of the Order №392 dated 27.05.2015 (as amended and supplemented by № MH RK-71 dated 08.05.2019)) as established by current regulatory orders: Order of the MH RK dated 2nd of April 2018 №142 (amended and supplemented as for 01.06.2020) «On approval of the Rules for conducting preclinical (nonclinical) studies, clinical trials, clinical and laboratory tests of medical devices for *in vitro* diagnostics, as well as requirements for preclinical and clinical bases "and the provision of the public service "Issuance of a permit for conducting a clinical trial and (or) testing of pharmacological and medicinal products, medical devices», Code of the Republic of Kazakhstan «On the health of the people and the health care system» dated 7th of July 2020 № 360-VI 3PK.

Documents of the informed consent for participation in present study include provisions on consent to participate in study, explicated in the Declaration of Helsinki by the World Medical Association.

All substantive staff of the present study (individuals responsible for preparation and implementation of the study) must be trained on «Good Clinical Practice (GCP)» including issues: 8th edition of Declaration of Helsinki of the World Medical Association, protection of study subjects' rights, a process approach in implementing clinical trials, standard operating procedures ensuring objectivity and quality of the clinical trial implementation etc. before interaction with subjects of the study or gaining access to their confidential information, relevant for the study.

AGREEMENT OF THE RESEARCHER

Name of the clinical trial: Multi-centered, randomized, blind, placebo-controlled phase III clinical trial on evaluation of prophylactic efficiency, safety, and immunogenicity of QazCovid-in®-inactivated vaccine against COVID-19 in healthy adult volunteers

Number of the protocol: QAZCOV-III-01/2020

Date of the protocol approval: 18th of December 2020

I agree:

1. To assume responsibility for proper implementation of the clinical trial in present clinical center.
2. That I am familiar with and will comply with Provision of Good Clinical Practice (GCP) and all applicable regulating requirements.
3. To implement the present clinical trial in accordance with present protocol
4. To guarantee that all staff members, assisting me in the clinical trial, are adequately aware of the test vaccine, official duties and functions described in the protocol.
5. Not to make amendments to the protocol without agreement of the Sponsor, as well as without preliminary review and written endorsement from Central committee of bioethics of MH RK, except in cases related to the need in immediate elimination of risks for subjects of the study.
6. That I carefully studied rules of proper use of the vaccine described in the present protocol, and any other information provided by the Sponsor.
7. That I am informed about confidentiality of information, including medical, clinical, toxicological, and other data, as well as information related to activities of the Sponsor.
8. That all data, documents, any records, and information provided by the Sponsor, or obtained, prepared by me, my staff, or consultants during the study are owned by the Sponsor.

5.3.	Phase of the study	
5.4.	Description of type of the clinical study	
5.5.	Design of the phase III clinical trial	
5.6.	Procedures and visits of the phase III clinical trial	
5.7.	Description of measures for minimization (elimination) of subjectivity	
5.7.1.	Procedure of randomization	
5.7.2.	Procedure of masking the test preparation	
5.8.	Description of treatment, dosage, and application schemes of the preparations under examination. Also includes description of the pharmaceutical form, package, labeling of the preparations under examination	
5.8.1.	Description of method of the phase III clinical trial of QazCovid-in®-inactivated vaccine against COVID-19	
5.8.2.	Description of the test preparation	
5.8.2.1.	Prepared form of the medicinal preparation	
5.8.2.2.	Supply of the vaccine under examination and placebo to the research center	
5.8.2.3.	Package and labeling	
5.8.2.4.	Storage and stability	
5.8.2.5.	Expiration date	
5.8.3.	Description of the preparation for comparison	
5.8.4.	Dosage and injection method of the preparations	
5.9.	Expected duration of participation of subjects in the study, description of order and duration of all study periods, including the follow-up period, if such is provided	
5.10.	Description of the rules for termination or exclusion criteria for individual subjects, parts of the study, or the entire study	
5.11.	Procedure of accounting preparations under examination, including preparations for placebo and comparison, if any	
5.12.	Storage of randomization codes and procedures for their opening	
5.13.	List of information registered in IRC	
6.	Selection and exclusion of subjects	
6.1.	Inclusion/exclusion criteria for subjects	
6.1.1.	Inclusion criteria for subjects	
6.1.2.	Exclusion criteria for subjects	
6.2.	Criteria for termination of participation of subjects in the study – termination of application of the preparation (treatment under examination), as well as procedures determining:	
6.2.1.	Time and terms of exclusion of subjects from the study (treatment with the test preparation)	
6.2.2.	Collection of data on types and time for patients, excluded from the study	
6.2.3.	Procedure for substituting subjects	
6.2.4.	Follow-up observations on subjects, excluded from treatment with the test preparation	
6.3.	Completion of the clinical study	
6.3.1.	Completion of the study according to the protocol of the study	
6.3.2.	Temporary suspension and/or early termination of the study	
7.	Treatment of the subjects	
7.1.	Conducted treatment, including names of all medications, their dosage,	

	frequency of application, routes, and methods of administration, as well as duration of the treatment, including periods of follow-up observations for each of the subjects' group (by groups of treatment with test preparation, by groups of treatments under investigation, or by study groups)	
7.1.1.	Screening and vaccination procedure	
7.1.1.1	Identification of the study subjects	
7.1.2.	Order and duration of stages of phase III clinical study of QazCovid-in®-inactivated vaccine against COVID-19	
7.1.2.1.	Screening examination and vaccination	
7.1.3.	Visits, unscheduled by the scheme of the study	
7.1.4.	Description of the test preparation and placebo preparation	
7.1.4.1.	Description of the test preparation	
7.1.4.1.1.	Prepared form of the test preparation	
7.1.4.2.	Description of the preparation for comparison	
7.1.4.3.	Dosage and method of administration of preparations	
7.2.	Medicinal preparations (therapy types) allowed (including emergency care) or not allowed for use before and/or during the study	
7.2.1.	Concurrent medications and concurrent treatments	
7.2.2.	Medicinal preparations of untargeted application	
7.2.3.	Using medicinal preparations of untargeted application	
7.3.	Methods of controlling adherence to procedures by subjects	
8.	Evaluation of efficacy	
8.1.	List of the efficacy parameters	
8.1.1.	Evaluation of humoral immunity	
8.1.2.	Evaluation of cellular immunity	
8.1.3.	Evaluation of prophylactic efficacy	
8.1.4.	Clinical confirmation of coronavirus SARS-CoV-2 infection	
8.1.5.	Laboratory confirmation of coronavirus SARS-CoV-2 infection	
8.2.	Methods and time of evaluation, registration, and analysis of efficacy parameters	
8.2.1.	Description of methodology for evaluation of humoral and cellular immunity	
8.2.1.1.	Method of the express test for identification of IgM/IgG antibodies of coronavirus SARS-CoV-2 infection	
8.2.1.2.	Identification of specific antibodies by enzyme-linked immunosorbent assay (ELISA)	
8.2.1.3.	Identification of neutralizing antibodies against SARS-CoV-2 virus	
8.2.1.4.	Method of evaluation of parameters for cellular immunity	
8.2.1.5.	PCR method for identification of RNA of the coronavirus SARS-CoV-2	
8.2.1.6.	Rules for sampling clinical materials for coronavirus SARS-CoV-2 infection analysis	
9.	Evaluation of safety	
9.1.	List of the safety parameters	
9.2.	Methods and time of evaluation, registration, and analysis of safety parameters	
9.2.1.	Adverse events occurring after administration of the test test preparation	
9.2.2.	Adverse events	
9.2.3.	Severe adverse events	

9.2.4.	Procedures for identification of pathological alterations in laboratory indicators	
9.3.	Procedures for final reporting, registration, and communicating about adverse events and intercurrent diseases	
9.3.1.	Reporting adverse events and severe adverse events	
9.3.2.	Medical supervision in case of adverse events and severe adverse events	
9.3.3.	Reporting cases of suspected unforeseen severe adverse events (SUSAE)	
9.3.4.	Method and duration of observations on subjects after occurrence of adverse events	
10.	Evaluation of safety and efficacy of the test preparation in laboratory tests	
10.1.	Evaluation of clinical indicators	
10.1.1.	Identification and classification of adverse events	
10.1.2.	Specific clinical signs and symptoms of particular importance	
10.1.3.	Anamnesis	
10.1.4.	Physical examination	
10.2.	Evaluation of laboratory indicators and biological samples	
10.2.1.	Identification of antibodies against chronic viral infections	
10.3.	Blood samples	
10.3.1.	Blood sampling	
10.4.	Pregnancy test	
10.5.	Blood chemistry test	
10.6.	Clinical analysis of blood with leukogram determination	
10.7.	General urinalysis	
11.	Statistical aspects of the clinical study	
11.1.	Description of statistical methods to be used, including time of each interim analysis	
11.2.	Projected number of subjects. In case of multi-centered studies projected number of subjects in each center is determined. Rationale for sample size, including explanations and calculations for justification of statistical power and clinical feasibility of the study.	
11.2.1.	Populations for statistical analysis	
11.2.2.	Projected number of subjects	
11.2.3.	Analysis of safety	
11.2.4.	Analysis of immunogenicity	
11.2.5.	Rationale for sample sizes	
11.3.	Applied level of significance	
11.4.	Criteria for termination of the study	
11.5.	Procedures of accounting absent, not analyzable, and falsified data	
11.6.	Procedures of reporting any deviations from the initial statistical plan (all deviations from the initial statistical plan are described and justified in the protocol and/or in the final report of the study)	
11.7.	Guidelines for the selection of subjects for analysis	
12.	Direct access to primary data (documentation)	
13.	Quality control and quality assurance	
13.1.	Monitoring	
13.2.	Audit and inspection	
13.3.	Amendments to the protocol	

13.4.	Deviations from the protocol	
14.	Ethical aspects	
14.1.	Ethical standards and criteria for good clinical practice	
14.2.	Informed consent for participation in the study	
14.3.	Inclusion of women, minorities, and children	
14.4.	Identification and confidentiality of the information about subjects	
14.5.	Informing subjects about study results	
14.6.	Continuing use of samples, collected during the study	
15.	Data operation and data recording	
15.1.	Obligations in working with data	
15.2.	Data collection methods	
15.3.	Deadlines for provision of reports	
15.4.	Storage of the study documentations	
16.	Funding	
17.	Insurance	
18.	Publications	
18.1.	Interim and final report of the study, and rights for publishing study materials	
19.	Appendices	
	Appendix 1	

1. LIST OF ABBREVIATIONS

AE	Adverse events
Al ⁺³	Aluminium hydroxide
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BSL-3	Biological safety level 3 laboratory
⁰ C	Temperature degree in Celcius
C.B.Sc.	Candidate of biological sciences
C.M.Sc.	Candidate of medical sciences
C.V.Sc.	Candidate of veterinary sciences
CBC	Complete blood count
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPE	Cytopathic effect
CRF	Case report form
CS MSE RK	Committee of science of the Ministry of education and science of the Republic of Kazakhstan
CSEC MH RK	Committee of sanitary and epidemiological control of the Ministry of healthcare of the Republic of Kazakhstan
D,d	Day (of the study)
D.B.Sc.	Doctor of biological sciences
D.M.Sc.	Doctor of medical sciences
DH	Department of healthcare
DHZhR	Department of healthcare of Zhambyl region
DMEM	Dulbecco's Modified Eagle Medium
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FSBI	Federal state budgetary institution
GCP	Good clinical practice
HBsAG	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Conference on the Harmonization of Requirements for the Registration of Medicinal Products used in Humans
IgE	Immunoglobulins of class E
IgG	Immunoglobulins of class G
IgM	Immunoglobulins of class M

IPE	International institute for post-graduate education
LLP	Limited liability partnership
mg	Milligram
MH RK	Ministry of healthcare of the Republic of Kazakhstan
ml	Milliliter
<i>N</i>	Quantity (usually refers to the number of subjects)
NAb	Neutralizing antibody
NaCl	Sodium chloride
NCEMMD	Republican state enterprise on the right of economic management "National center for expertise of medicines and medical devices" of the Ministry of healthcare of the Republic of Kazakhstan
NR	Neutralization reaction
NSCP RK MH RK	Republican state enterprise on the right of economic management "National scientific center of phtisiopulmonology" of the Ministry of healthcare of the Republic of Kakhstan
NSEI	Non-state educational institution
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PHA	Phytohaemagglutinin
PI	Principal investigator
prof.	Professor
PVC	Polyvinyl chloride
RAS	Russian academy of sciences
RF	Russian Federation
RIBSP	Republican state enterprise on the right of economic management "Research institute for biological safety problems" of the Committee of science of the Ministry of education and science of the Republic of Kazakhstan
RK	Republic of Kazakhstan
RNA	Ribonucleic acid
RSE on the REM	Republican state enterprise on the right of economic management
RT-PCR	Reverse transcription PCR with real time detection
SARS- CoV	Severe acute respiratory syndrome coronavirus 2
SAV	Severe adverse events
SD	Standard deviation
SOP	Standard operating procedure
SUE on the REM	State utility enterprise on the right of economic management
SRI	Scientific research institute
st.	Street
STP	Scientific and technical program
TCD50	Tissue culture infectious dose
Vero	Culture of epithelial cells of the kidney of the African green monkey (<i>Chlorocebus aethiops</i>)

WFI	Water for injections
WHO	World Health Organization

INFORMATION ABOUT THE SPONSOR AND IMPLEMENTERS

Sponsor of the study

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3. Rationale for the clinical study

3.1. Names and descriptions of test preparations

3.1.1. Name of the test preparation – QazCovid-in®-inactivated vaccine against COVID-19

Subject of the present clinical study is cultural, inactivated, purified vaccine for COVID-19 prophylaxis, suspension for intramuscular injection. Vaccine is based on inactivated, purified coronavirus strain «SARS-CoV-2/KZ_Almaty/04.2020». Active substance of the preparation is obtained using Vero cell cultures. Test vaccine preparation was manufactured in the Republican state enterprise on the right of economic management «Research institute for biological safety problems» of the Committee of science of the Ministry of education and science of the Republic of Kazakhstan (State license for pharmaceutical activities №ФД64900005FH, kind of activity – production of pharmaceuticals).

Active substance:

Active substances: Purified, inactivated, whole virion strain «SARS-CoV-2/KZ_Almaty/04.2020» of coronavirus SARS-CoV-2

Pharmaceutical form:

Vaccine is provided in liquid form and contains purified vaccine strain in phosphate-buffered saline, suspension for intramuscular administration, 0,5 ml (1 dose) in a vial.

Disease (according to ICD-10):

Section U07.1. COVID-19, virus is identified

Indication for application:

Specific prophylaxis of COVID-19 (against coronavirus infection)

ATC code

J07BX

Pharmacotherapeutic group:

Anti-infectious preparation for systemic application. Vaccines. Antiviral vaccines. Other antiviral vaccines.

Active substance: purified inactivated strain «SARS-CoV-2/KZ_Almaty/04.2020» of coronavirus SARS-CoV-2 is produced by culturing virus on Vero cell cultures with subsequent inactivation and purification. Test preparation (Verum): QazCovid-in® contains not less than $5,0 \pm 0,5$ µg of purified, inactivated, whole virion strain «SARS-CoV-2/KZ_Almaty/04.2020» of coronavirus SARS-CoV-2 in 0,5 ml buffer solution.

Composition of the QazCovid-in® - inactivated vaccine against COVID-19 is presented in the Table 1.

Table 1 - Composition of the QazCovid-in® - inactivated vaccine against COVID-19

Ingredient	Function	Concentration per dose (0,5 ml)
Active substances		
SARS-CoV-2/KZ_Almaty/04.2020	Active ingredient	$5,0 \pm 0,5$ µg
Auxiliary substances		
Aluminium hydroxide (Al ³⁺)	Adjuvant	$0,25 \pm 0,05$ mg

KH ₂ PO ₄	Buffer component	0,00019 g/L
Na ₂ HPO ₄	Buffer component	0,0028 g/L
NaCl	Buffer component	0,008 g/L
WFI (water for injection)	Buffer component	Up to 0,5 ml

3.1.1.1. Release form and package

Vaccine is provided in liquid form and contains purified vaccine strain in phosphate-buffered saline, suspension for intramuscular administration, 0,5 ml (1 dose) in a vial, by 10 vials in PVC tape. Instruction manual in Kazakh and Russian languages is provided in the package.

Vials are transported and stored at temperature regime +2⁰C to +8⁰C.

50 vials are placed in the cardboard box or in the carton pack or in the group box. Instruction manual in Kazakh and Russian languages is provided in the box. Labels from labeling or writing paper are stuck on the vials, packs, and boxes. Boxes with packs are placed in cardboard box or in the carton packs or in plywood box with lignin.

3.1.2. The term placebo – sodium chloride, solution for injections (0,9%)

Placebo (sodium chloride, 0,9% solution for injections) is provided in the form of sterile solution in ampoules or vials of 0,5ml. Dose for intramuscular administration is 0,5 ml, 1 ampoule of placebo will be used only for 1 subject in the study.

Trademark: Sodium chloride

International nonproprietary name: none

Pharmaceutical form: Solution for injection 0,9% 5ml

Composition: 5 ml of solution contains:

Active substance – sodium chloride 45.0mg

Auxiliary substance – water for injections.

Description

Transparent, colorless, salty liquid

Pharmacotherapeutic group

Other non-therapeutic substances. Solvents.

ATC code V07AB

Method of administration and dosage

Subcutaneous, intramuscular, intravenous.

Release form and package

5 ml in neutral glass ampoules

Manufacturer

JSC «Himfarm», Kazakhstan

Owner of the registration certificate

JSC «Himfarm», Kazakhstan

Shymkent city, Rashidov st.

Tel/Fax: +7(7252) 561342

Email address: standart@santo.kz

3.2. Summary of potentially clinically important results of pre-clinical and clinical studies relevant for the present study

Pre-clinical studies of the immunobiological preparation QazCovid-in® - inactivated vaccine against COVID-19 were conducted in two laboratory facilities of research institutions Republican state enterprise on the right of economic management "Research institute for biological safety problems" of the Committee of science of the Ministry of education and science of the Republic of Kazakhstan (Gvardeyskiy township of Korday district, Zhambyl region) and Republican state enterprise on the right of economic management "National center for expertise of medicines and medical devices" of

the Ministry of healthcare of the Republic of Kazakhstan (Almaty city) using different animal models (white mice, rats, rabbits, Guinea pigs, ferrets, Syrian hamsters, and Rhesus macaques (*Macaca mulatta*)). Summary table of pre-clinical studies is presented in the Appendix 1.

Conducted pre-clinical studies allowed to draw following conclusions:

1. The results of the study of the safety, abnormal, acute and subchronic toxicity of the new immunobiological drug QazCovid-in®-vaccine inactivated against COVID-19 allow us to classify the drug as a class 5 practically non-toxic medicinal substances. The course administration of the vaccine didn't affect the body of laboratory animals, according to macroscopic studies and histological studies didn't reveal changes in the internal organs of white mice and rats.
2. There were no changes in the general condition of the experimental animals, and signs of even moderate shock weren't detected in the animals of the experimental groups when studying the allergizing properties of the test material on the model of immediate hypersensitivity in guinea pigs.
3. Analysis of the results obtained on the study of the conjunctival test in guinea pigs allows us to conclude that the study preparation doesn't have allergenic properties.
4. The vaccine doesn't cause delayed-type hypersensitivity reactions in white laboratory mice.
5. The investigated vaccine did not have a damaging effect on the reproductive function in rats of both sexes and did not cause disturbances in the development of offspring: male and female rats.
6. Immunobiological preparation - QazCovid-in® - inactivated vaccine against COVID-19 has a high immunogenic potential, because causes the production of neutralizing antibodies as well as antibodies detected by ELISA in the blood serum of white mice, Syrian hamsters and ferrets.
7. QazCovid-in®- inactivated vaccine against COVID-19 safety meets the requirements of the State Pharmacopoeia of the Republic of Kazakhstan, the European Pharmacopoeia and the World Health Organization for vaccines.

The results of preclinical trials of QazCovid-in®- inactivated vaccine against COVID-19 make it possible to recommend the vaccine for clinical trials on research subjects.

A randomized, blind, placebo-controlled clinical trial of phase I and a randomized, open-label clinical trial of phase II of QazCovid-in®- inactivated vaccine against COVID-19 in healthy adult volunteers aged 18 years and older is carried out at the National Scientific Center for Phthiopulmonology of the Ministry of Health of the Republic of Kazakhstan (Protocol No. QAZCOV-III-01/2020 version 3.0 dated September 07, 2020 year and version 4.0 of 10/22/2020). In accordance with the Protocol, an interim report on day 42 of the 1st phase of clinical trials on November 13, 2020 (version No. 2.0) was submitted, as well as an interim report on day 42 of the II phase of clinical trials on December 14, 2020 (version "No. 2.0).

According to the results of the study of reactogenicity, safety and immunogenicity on the 42nd day of clinical trials of phase I of QazCovid-in®- inactivated vaccine against COVID-19 with double intramuscular immunization of volunteers aged 18 to 50 years, they indicate good tolerance, low reactogenicity and safety of the vaccine, as well as sufficient immunogenic activity of the vaccine against SARS-CoV-2 virus.

According to the results on the 42nd day of the phase 1 clinical trial according to the QAZCOV-III-01/2020 protocol, QazCovid-in®- inactivated vaccine against COVID-19 was characterized by good tolerance and was safe with a double intramuscular injection. During the studies, there were no serious adverse events noted in the group of vaccinated. The occurrence of local adverse events observed in the vaccinated group, all adverse events were classified as foreseeable, characteristic of inactivated vaccines with injection. All local reactions detected within 7 days after the vaccine / placebo injection were temperate, lasting from 1 to 3 days and did not require the use of drugs. There was one negative phenomenon of mild manifestation (an increase in body temperature to 37.1C on the 1st day after vaccination). There were no changes in instrumental and laboratory parameters (according to the results of general and biochemical blood tests, urinalysis, ECG) after vaccination.

The research results indicate that the QazCovid-in vaccine, after a double injection, forms a humoral and cellular immune response against the SARS-CoV-2 virus. A good IgG antibody response to coronavirus infection is developing.

Vaccination with QazCovid-in®- inactivated vaccine against COVID-19 provides a significant increase in the level of cellular immunity. The most important thing is that the vaccine provides the formation of neutralizing antibodies in titers of the same order as the most promising vaccines against COVID-19, which are currently undergoing phase III clinical trials.

Study of reactogenicity, safety and immunogenicity of of QazCovid-in®- inactivated vaccine against COVID-19 with double intramuscular immunization of volunteers aged 18 to 50 years, they indicate good tolerance, low reactogenicity and safety of the vaccine, as well as sufficient immunogenic activity of the vaccine against SARS-CoV-2 virus on the 42nd day of phase I clinical trials.

The study of the immunogenicity and safety of QazCovid-in®- inactivated vaccine against COVID-19 with a single and double injection in healthy subjects aged 18 years and older on the 42nd day of the II phase of clinical trials indicates good tolerance, low reactogenicity and safety of the vaccine, as well as sufficient immunogenic activity of the vaccine against SARS-CoV-2 virus, which is more pronounced after double vaccination.

According to the results on the 42nd day of the phase II clinical trials according to the QAZCOV-III-01/2020 protocol, QazCovid-in®- inactivated vaccine against COVID-19 was characterized by good tolerance and was safe with a double intramuscular injection. During the studies, there were no serious adverse events noted in the group of vaccinated. The occurrence of local adverse events observed in the vaccinated group, all adverse events were classified as foreseeable, characteristic of inactivated vaccines with injection. All local reactions detected within 7 days after the vaccine / placebo injection were temperate, lasting from 1 to 3 days and did not require the use of drugs.

Important that the vaccine is safe not only for subjects between the ages of 18 and 50, but also for citizens over 50, which is evidence of the safety of the vaccine against the new coronavirus for older citizens. The safety of the vaccine for older people is important because it is the population over 50 years of age that is at risk of infections the SARS virus. Clinical studies have shown that the vaccine is safe not only for people between the ages of 18 and 50, but also for volunteers over 50.

The results of clinical trials on the 42nd day of phase II indicate that double vaccination is the most optimal vaccination scheme for specific prevention of COVID-19. The data from the clinical studies carried out indicate the high immunostimulating activity of the inactivated QazCovid-in®- inactivated vaccine against COVID-19 vaccine against the new coronavirus infection COVID-19, which can provide reliable protection against the disease of vaccinated people. According to the results of the study, with a double vaccination, the inactivated QazCovid-in®- inactivated vaccine against COVID-19 vaccine forms group immunity in 100% of healthy vaccinated persons, regardless of age.

Results of the study of antibodies in all age groups indicate that 100% of those vaccinated the QazCovid-in after the first vaccination is marked seroconversion observed 4x and greater increase in antibody titer. The second immunization with the the QazCovid-in vaccine of persons of all age groups led to an increase in the level of antibodies. Studies have found that the level of seroconversions after double vaccination of persons 50 years of age and older reached 100%

As a result of research can bring the following conclusion: according to the results of the study of reactogenicity, safety and immunogenicity on the 42nd day of clinical trials of phase I of QazCovid-in®- inactivated vaccine against COVID-19 with double intramuscular immunization of volunteers aged 18 to 50 years, they indicate good tolerance, low reactogenicity and safety of the vaccine, as well as sufficient immunogenic activity of the vaccine against SARS-CoV-2 virus, which is more pronounced after double vaccination.

The results of preclinical trials, data on the 42nd day of clinical trials of phases I and II suggest the need for phase III clinical trials on a larger sample of volunteers to get an answer to the question about the effectiveness of QazCovid-in®- inactivated vaccine against COVID-19.

3.3. Brief description of known and potential risks and benefits for subjects of the study

3.3.1. Potential health risks for subjects of the study

The risks of participating in this clinical study refer to the risks associated with the experimental nature of the study.

Risks associated with the use of the investigational vaccine

The risks associated with the use of the investigational vaccine are due to the possible occurrence of adverse reactions, including general and local post-vaccination reactions and complications. As a result of the use of the vaccine, minor adverse reactions may occur, such as soreness, swelling and redness at the injection site, less often systemic reactions such as fever, pain in muscles or joints, and headache. These symptoms are usually mild, do not require medical intervention, and last from 1 to 3 days. However, the possibility of developing serious or allergic reactions exists. Individuals involved in a clinical trial will be closely monitored by qualified medical personnel. In the planned clinical trial, safety control measures in the first hours and days after vaccination will include observation of the research subject's condition within 2 hours after vaccination, planned visits to the research center, self-monitoring of the well-being of the research subjects and timely informing in case of signs of SARS and for suspected COVID-19, as well as registration of local and systemic adverse events by telephone. Further safety assessment will be carried out by interviewing and examining study subjects at visits on the 21st, 42nd, 90th and 180th days after vaccination. Thus, the General period for assessing the safety of vaccination is at least 6 months after the introduction of the vaccine. The duration of observation of study subjects after vaccination, the list of procedures for assessing the reactogenicity and safety of the vaccine, the frequency and timing of their implementation are consistent with the recommendations for assessing the safety of vaccines.

In case of a severe reaction research subjects may come to an unscheduled visit to the research center, where they will receive the necessary medical care and provided medical supervision.

If necessary, the research subject will be transferred to the appropriate medical institution to receive inpatient treatment, while the treatment will be free for the research subject, at the expense of the sponsor, a course of treatment can be prescribed in two bases:

-if the city of Almaty, then the subjects of research will be centralized to the Limited Liability Partnership Clinic of the International Institute of Postgraduate Education, Almaty city, Toraigyrov street 49/1

- if the city of Taraz, then hospitalization and examination will be scheduled at PUC on the REM "DHAZR City Multidisciplinary Hospital", Taraz city, Al-Farabi street, house 2 "B"

Risks associated with research procedures

The risks associated with testing procedures are due to the procedure for taking blood samples from a vein for immunological studies and laboratory safety studies. In total, about 100 ml of blood will be drawn from the subject during the clinical study. During the blood sampling procedure, dizziness, weakness, pre-fainting, pain at the venipuncture site, hemorrhage formation, blood clot formation or inflammation of the forearm vein may occur. The procedure will be performed by qualified staff of the research center in compliance with the rules of asepsis. In the incident of adverse events, the subjects of the study will be immediately provided with the necessary assistance.

When performing electrocardiography, the test subject may feel some discomfort at the electrode attachment site. In some cases, bruises may remain after the sensors installed on the chest (when using suction cups).

In addition, in rare cases, there may be an allergic skin reaction (for example, in the form of a rash and / or a burning sensation) to the conductive gel and to the adhesive if Velcro sensors are used.

Other risks taken by the subjects of a clinical trial are determined by its experimental nature, since its exact result is not known. If cases of new coronavirus infection are detected throughout the study, conditions will be created for these individuals to receive qualified medical care throughout the entire period of their treatment.

3.3.2. Known potential benefit

QazCovid-in®- inactivated vaccine against COVID-19 is intended for use in clinical practice for the prevention of COVID-19 coronavirus infection. Potential health benefits in this clinical study can only be obtained by study subjects randomized to the study group of the QazCovid-in vaccine - they will receive free prophylaxis of coronavirus infection and undergo a medical examination. Subjects of the study assigned to the observation group, based on the results of a medical examination, will receive additional information about their health status. The clinical examination will be free of charge. There is no other known potential benefit to study subjects who voluntarily choose to participate in this clinical study.

Participation in this clinical study will contribute to obtaining information about the preventive efficacy, safety and immunogenicity of QazCovid-in®- inactivated vaccine against COVID-19, the development of which is a huge contribution to protecting the health of the world's population.

Thus, the risk / benefit ratio in this clinical trial on double immunization with the preparation appears to be acceptable.

3.4. Description and rationale for injection method, dosage, dosage regime, and the course of treatment

3.4.1. Rationale for the dosage and injection method

Analysis of the results of preclinical studies carried out in the RSE on the REM "Scientific Research Institute of Biological Safety Problems" of the Science CM ES RK and RSE on the REM National Center for Expertise of Medicines and Medical Devices of the Committee for Quality Control and Safety of Goods and Services of the MH RK, indicates the formation of a protective immune response in the scheme of double immunization with an interval of at least 21 days in laboratory animals (mice, guinea pigs, rhesus monkeys). In a comparative assessment of the immunogenic and protective properties of the vaccine in different doses, it was found that the effectiveness of vaccination depends on the level of the immunizing dose, an increase in which significantly increases the immunogenic and protective properties of the vaccine. The results of preclinical trials made it possible to recommend the conduct of phase I clinical trials of QazCovid-in®- inactivated vaccine against COVID-19.

Analysis of the results for the 42nd day of the II phase of clinical trials conducted at the clinical base of the FTIZIO, to study of reactogenicity, safety and immunogenicity on the 42nd day of clinical trials of phase I of QazCovid-in®- inactivated vaccine against COVID-19 with double intramuscular immunization of volunteers aged 18 to 50 years, they indicate good tolerance, low reactogenicity and safety of the vaccine, as well as sufficient immunogenic activity of the vaccine against SARS-CoV-2 virus. The results on the safety and immunogenicity of QazCovid-in®- inactivated vaccine against COVID-19 made it possible to recommend a phase II clinical trial.

Since people over 50 years old are at a high risk of developing complications and lethal outcome with COVID-19, this category of people, according to WHO recommendations, should be vaccinated against COVID-19 in the first place. This served as the basis for the development of the design of the phase II study and the inclusion in the planned study of persons over the age of 50 years. During phase II clinical trials, the issue of determining the immunogenic efficacy of the vaccine with a single and double injection was also resolved. Analytical processing of the results on the 42nd day of the II phase of clinical trials conducted at the clinical base of the FTIZIO allows us to conclude that the study of reactogenicity, safety and immunogenicity on the 42nd day of clinical

trials of phase I of QazCovid-in®- inactivated vaccine against COVID-19 with double intramuscular immunization of volunteers aged 18 to 50 years, they indicate good tolerance, low reactogenicity and safety of the vaccine, as well as sufficient immunogenic activity of the vaccine against SARS-CoV-2 virus, which is more pronounced after double vaccination.

The results of the I and II phases clinical trials of QazCovid-in®- inactivated vaccine against COVID-19, indicating the safety and immunogenicity of the vaccine, allow planning a III phase of clinical trials involving several thousand subjects. It should be noted that the planned phase III clinical trial provides for a double injection of the QazCovid-in®- inactivated vaccine against COVID-19 vaccine and placebo intramuscularly in a single dose - 0.5 ml with an interval of 21 days for subjects aged 18 years and older. Based on the results of the III phase clinical trial, the prophylactic efficacy, safety and immunogenicity of QazCovid-in®- inactivated vaccine against COVID-19 will be assessed according to a double scheme of injection, since it is double vaccination that contributes to the formation of more stable immunity. The duration of the entire period of a phase III clinical trial is no more than 6 months.

For the administration of the vaccine, the intramuscular way of administration was chosen, because inactivated vaccines are administered by injection, and this route of administration is preferred, since it implies better absorption of the vaccine. The volume of the administered dose is 0.5 ml and this vaccine is injected into the deltoid muscle of the non-dominant arm.

3.5. Statement of compliance of the clinical trial to the protocol, the present Standard, and regulatory requirements

This clinical trial will be carried out in accordance with the data of the Study Protocol, as well as with the requirements of the Guidelines for Good Clinical Practice (GCP) (application 2 of the Order of the Ministry of Health of the SD RK No. 329 dated 05/27/2015 (with amendments and additions No. MH RK-71 dated 08.05 .2019) "On the statement of good pharmaceutical practices", "Standard of good clinical practice (GCP)");

Order of the Ministry of Health of the Republic of Kazakhstan dated April 2, 2018 No. 142 (with amendments and additions as of 06/01/2020) "On approval of the Rules for conducting preclinical (nonclinical) studies, clinical trials, clinical laboratory tests of medical devices for in vitro diagnostics, and "Requirements for preclinical and clinical bases" and "Issuance of a permit for conducting a clinical trial and (or) testing of pharmacological and medicinal products, medical devices"; Code of the Republic of Kazakhstan "On people's health and health care system" dated July 7, 2020 No. 360-VI LRK.

Documents informed consent to participate in this clinical trial include provisions on consent to participate in a clinical trial, as set out in the Helsinki Declaration of the World Medical Association.

All the main personnel of this clinical trial (persons responsible for its preparation and conduct) must undergo Good Clinical Practice (GCP), which includes questions: 8th edition of the Declaration of Helsinki by the World Medical Association, protection of the rights of research subjects; process approach in conducting clinical trials, etc. " prior to interacting with research subjects or gaining access to their confidential data related to the clinical trial.

3.6. Description of the population under examination

Phase III clinical study of inactivated vaccine QazCovid-in®- inactivated vaccine against COVID-19 will be included 3000 healthy subjects aged 18 years and older, which will be distributed in the ratio of 1: 4 into 2 groups:

The main group - 2,400 research subjects - will be vaccinated QazCovid-in®- inactivated vaccine against COVID-19 vaccine. All research subjects will be tested for safety, immunogenicity and immunity strength.

Control group - 600 study subjects, these subjects will be vaccinated placebo, in which, upon confirmation of the diagnosis of SARS-CoV-2 coronavirus infection, the incidence will be compared with the main group.

3.7. References to literature sources and data relevant for the study and providing rationale for the present study

3.7.1. General information and scientific rationale

This study is a multicenter, randomized, blinded, placebo-controlled phase 3 study. The aim of the study is to evaluate the efficacy, safety and immunogenicity of QazCovid-in®- inactivated vaccine against COVID-19 in comparison with placebo in volunteers over the age of 18 years. The research design and methodology were developed in accordance with the recommendations of the FDA [1], EMA [2], EEU [3] guidelines, and regulatory documents of the Republic of Kazakhstan.

Due to the lack of registered vaccines for the prevention of new coronavirus infection, the use of placebo as a study drug is warranted. For ethical reasons, in order to achieve vaccine efficacy in the largest number of volunteers, the vaccine and placebo grouping will be done in a 4: 1 ratio (2,400 volunteers in the vaccine group and 600 volunteers in the placebo group).

The main objective of the study is to prove the superiority of QazCovid-in®- inactivated vaccine against COVID-19 in comparison with placebo in terms of immunological efficacy. This study design is due to the extreme relevance of the issue of the availability of vaccines in a short time for the prevention of new coronavirus infection.

Used in this efficacy / immunogenicity assessment - the seroconversion level, the geometric mean titer and the fold increase in the titer of serum specific antibodies to SARS-CoV-2 - are generally accepted in the study of the immunogenicity of vaccines.

Evaluation time points for humoral immunity - Day 0, Day 21, Day 42, Day 90, Day 180 and for cellular immunity - Day 0, Day 90, Day 180 correspond to the objectives of the study and were selected based on previous clinical studies of QazCovid-in®- inactivated vaccine against COVID-19.

The study of cellular immunity indicators led to the tasks of a previously performed clinical trial of the I/II phase, the detailed results of these studies are given in the interim report I/II phase, the researcher's brochure and are briefly summarized in section 3.2. of this Protocol. The amount of accumulated data is sufficient, for this reason the study of these parameters is not the purpose of this study.

According to the results of the 42nd day of the CT phase, the formation of cellular immunity is shown with the preservation of indicators on the 42nd day of the study and, accordingly, to confirm the increase or decrease in cellular immunity indicators within the framework of phase III, cellular immunity will be determined on the terms of day 1, day 90 and day 180 of the study.

The evaluation of preventive effectiveness (the study of the incidence of COVID-19) in this study is exploratory in nature due to the limited sample size.

In the RSE on the REM "Scientific Research Institute of Biological Safety Problems" of the Science CM ES RK, based on the results of the implementation of the Scientific and Technical Program "Development of a vaccine against coronavirus COVID-19" for 2020-2022, a technology for the manufacture of an inactivated vaccine for the prevention of COVID-19 was developed and preclinical studies of the safety, immunogenicity and protective activity of the vaccine were carried out.

The creation of an immunobiological drug that can prevent the further development of the pandemic becomes a condition of socio-economic well-being and the main task for ensuring the biological safety of the Republic of Kazakhstan.

There are currently four known genera of coronaviruses ($\alpha, \beta, \gamma, \delta$) which have been identified in humans [1,2,3]. At the end of 2019, a new coronavirus infection was registered in Wuhan (China), which received the official name COVID-19 [4]. The infection has rapidly spread to all countries of the world and causes irreparable damage to the health of the world's population.

On March 11, 2020, the WHO declared pandemic COVID-19. The rapid spread of the infection has practically stopped the life of the entire planet Earth, and the severe symptoms of the disease have led to the death of those infected due to the development of pneumonia [5].

In the Republic of Kazakhstan, measures were promptly taken to strengthen sanitary and quarantine measures to prevent the spread of infection, laboratory diagnostics of a new infection was established; a clinical treatment protocol and algorithms for anti-epidemic measures were approved, and sanitary and epidemiological control was strengthened [6, 7, 8].

In the Republic of Kazakhstan, the first cases of COVID-19 were registered on March 13, 2020. According to official statistics, as of August 8, there were 97829 cases of infection registered in Kazakhstan, 71609 patients recovered, and 1189 patients died.

The lack of effective treatments and, most importantly, the impossibility of preventing infection by preventive vaccination has determined vaccine development and some have now entered phase III clinical trials. The urgency of vaccine development is vital to contain the pandemic and prevent new outbreaks of the disease [9, 10].

Considering the enormous national importance of the need to create an effective means of specific prevention of COVID-19, for the first time in the Republic of Kazakhstan, a technology has been developed for the manufacture of a candidate vaccine against the SARS-CoV-2 coronavirus. The developed inactivated vaccine is intended for specific prevention of COVID-19 and will allow it to carry out further effective anti-epidemic work on the prevention and elimination of COVID-19 in the territory of the Republic of Kazakhstan.

In the Republic of Kazakhstan and the countries of Central Asia, similar work on the development of inactivated vaccines, conducting preclinical trials and clinical trials is not carried out, and these studies are a significant scientific event in the field of creating and introducing new immunobiological drugs into medical practice. The most important achievement of these clinical trials is a significant contribution to ensuring the epidemiological and immunobiological safety of the Republic of Kazakhstan.

The scientific significance of the research is that for the first time in the Republic of Kazakhstan, using the latest achievements of biotechnology, a technology for manufacturing a candidate inactivated vaccine against COVID-19 has been developed, preclinical trials have been conducted and clinical trials are planned.

The development, testing and introduction into production in the future of an inactivated vaccine against COVID-19 will allow:

- to improve the epidemiological situation of COVID-19 coronavirus infection.
- to promptly carry out measures to prevent and eliminate COVID-19 coronavirus infection in the Republic of Kazakhstan.
- - meet the needs of the country's population for an effective vaccine against the COVID-19 coronavirus infection.
- improve the socio-economic situation in the country for infectious diseases.
- timely conduct preventive and anti-epidemic measures aimed at preventing the spread of the coronavirus infection COVID-19 in Kazakhstan.

The organization of production, testing, registration and release of the domestic vaccine will give an impetus to the further development of the biological industry of the Republic of Kazakhstan.

Similar work on the creation and testing of means for specific prevention of a new coronavirus infection using an inactivated virus is being carried out in the People's Republic of China and the Russian Federation, while other countries are moving towards the creation of subunit, vector vaccines, DNA or RNA vaccines [11,12].

The creation of effective means of specific prevention of infectious diseases is the main task in the system of anti-epidemic measures. When developing the technology for manufacturing inactivated vaccines, the entire virus complex is used as an immunogenic component, resulting in the most complete antiviral immunity. Only live vaccines, which are considered the best in terms of protection against infection, compete with inactivated vaccines in terms of the quality of immunity created.

The main advantages of inactivated vaccines against COVID-19 are that in the conditions of a non-standard mechanism for developing immunity to SARS-CoV-2, it is advisable to use an inactivated virus that retains a full set of antigenic determinants. The inactivated viral biological product induces the synthesis of neutralizing antibodies and the formation of cellular immunity. The creation of technological platforms for obtaining vaccines from the whole virion allows for a rapid process of their industrial production. The development of a vaccine based on attenuated viruses is a long process with unpredictable results.

Considering the above, the most optimal solution for the prompt creation of a vaccine against coronavirus infection is to develop a technology for the production of an inactivated vaccine.

The fundamental difference of domestic development from the known analogues from China and Russia is that our technology used epidemiologically relevant virus strain of the Republic of Kazakhstan, a modern technological strategy of virus cultivation in cell culture and a more advanced purification system. These circumstances indicate that the proposed technology of vaccine production has fundamental differences from the available foreign counterparts.

Successful trials, organization of industrial production and introduction into medical practice of the inactivated vaccine against COVID-19 in the future will improve the epidemiological well-being in the territory of the Republic of Kazakhstan for the COVID-19 coronavirus infection. These events provide an opportunity to gain extensive experience in the creation and testing of effective immunobiological drugs to ensure the immunobiological safety of the Republic of Kazakhstan and the further development of domestic biotechnology, virology, vaccinology and immunology. The performed studies fully comply with: The Law of the Republic of Kazakhstan of February 18, 2011 No. 407-IV «On Science» and the Sanitary and epidemiological rules and norms «Sanitary and epidemiological requirements for the device and working conditions of microbiological, virological and parasitological laboratories» of January 21, 2004 N 8.01.001.04. Order of the Minister of Health of the Republic of Kazakhstan of January 21, 2003 N 63.

The planned clinical trials are the final part of the research work aimed at developing the technology for manufacturing and testing an inactivated vaccine against coronavirus infection and are of great socio-economic importance for the Republic of Kazakhstan.

The results of preclinical trials in the Research Institute for Biological Safety Problems SC MES RK and the National Center for Drug Expertise Committee for Quality Control and Safety of Goods and Services MH RK allow us to recommend clinical trials of the QazCovid-in®-vaccine inactivated against COVID-19. The vaccine was produced on the basis of the Research Institute of Biological Safety Problems of the Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan (State License for Pharmaceutical Activity No.FD64900005FH [type of activity-production of medicines]).

3.7.2. Modern approaches in prophylaxis of COVID-19

Currently, various types of vaccines against COVID-19 are being developed: RNA vaccines, DNA vaccines, subunit, vector, live and inactivated [13]. For many decades, inactivated vaccines have

proven their safety and effectiveness in solving biological safety in the fight against such dangerous human diseases as influenza and poliomyelitis [14, 15].

In Russian Federation, Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products has developed a production technology of inactivated vaccine against COVID-19, preclinical trial already finished and start of clinical investigation is planned. Data upon preclinical trial indicates the safety and immunogenicity of vaccine.

4 inactivated vaccines against COVID-19 were developed in China. Sinovac Biotech Ltd, Wuhan Institute of Biological Products/Sinopharm and Beijing Institute of Biological Products/Sinopharm are performing the phase III of clinical investigation of inactivated vaccine against COVID-19, while Institute of Medical Biology, Chinese Academy of Medical Sciences – phase II of clinical investigation of inactivated vaccine against COVID-19. Data of preclinical trial and clinical investigation displays a safety and immunogenicity of developed inactivated vaccines [17, 18, 19].

Research Institute for Biological Safety Problems is supplied by all necessary conditions to develop a production technology of inactivated vaccine against COVID-19: BSL-3 type laboratory, up-to-date equipment and qualified specialists with high experience in development of tools of specific prevention of human, animal and bird infectious diseases.

The final result of National and Technical Program of RI BSP KS MES «Development of vaccine against coronavirus COVID-19» for 2020-2022 years is development and producing of inactivated vaccine against COVID-19, program is registered at the website of World Health Organization as candidate vaccine against COVID-19. Creation, performing of preclinical trial and clinical investigations of inactivated medical immunobiological preparation against COVID-19 is the main purpose of RI BSP KS MES to solve issues of people prevention from COVID-19 and state task for scientifically and technically support biological safety at RK.

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4. Aim and objectives of clinical trial, phase III of QazCovid-in®- inactivated vaccine against COVID-19

4.1 Aim of trial

The aim of the trial is evaluation of efficacy, safety and immunogenicity of QazCovid-in®-inactivated vaccine against COVID-19 comparing to placebo at volunteers aged 18 years and older.

4.2 Tasks of the study

Main task

The main purpose of the trial is getting an evidence of superiority of QazCovid-in®-inactivated vaccine against COVID-19 in comparison with placebo by level of seroconversion (the proportion of individuals with a fourfold or higher increase in antibody titers to SARS-CoV-2) for day 21, day 42, day 90 and day 180 after vaccination.

Additional tasks

1. Assess immunogenicity of QazCovid-in®- inactivated vaccine against COVID-19 in comparison with placebo by following parameters:
 - Geometric mean titre in serum antibodies to SARS-CoV-2 for day 21, day 42, day 90 and day 180 after vaccination.
 - Level of seroconversion (the proportion of individuals with a fourfold or higher increase in antibody titers to SARS-CoV-2) for day 21, day 42, day 90 and day 180 after vaccination.
 - Multiplicity of increase in geometric mean titre in serum antibodies to SARS-CoV-2 for day 21, day 42, day 90 and day 180 after vaccination.
 - Determination of level of intracellular cytokines production by antigen activated T-lymphocytes using the method of flow cytometry (day 1 – before vaccination, for day 90 and day 180).
2. Assess the vaccine efficiency (search analysis) by following parameters:
 - Frequency of COVID-19 confirmed cases within 6 months after vaccination (excluding of COVID-19 cases occurring in first 14 days after vaccination).
 - Confirmed case of COVID-19: presence of clinical manifestations and positive test for SARS-CoV-2 RNA virus laboratory analysis.
 - Frequency of COVID-19 confirmed cases which require hospitalization (excluding of COVID-19 cases occurring in first 14 days after vaccination).
 - Frequency of COVID-19 confirmed cases with severe proceeding (excluding of COVID-19 cases occurring in first 14 days after vaccination).
 - Frequency of deaths from COVID-19 (excluding of COVID-19 cases occurring in first 14 days after vaccination).
3. Assess safety of vaccine use in comparison with placebo.

5. Design of trial

5.1 Main parameter of clinical trial evaluation

The primary parameter of trial is level of seroconversion (the proportion of individuals with a fourfold or higher increase in antibody titers to SARS-CoV-2) for day 21, day 42, day 90 and day 180 after vaccination.

5.1.1. Estimation of immunogenicity and duration of induced post vaccine immunity.

5.1.1.1. Humoral immune response

Data analysis of post vaccine humoral immune response to twofold intramuscular injection of QazCovid-in®- inactivated vaccine against COVID-19.

Indicators of main tasks will be evaluated before vaccination, for day 21, day 42, day 90 and day 180 after vaccination by the following criteria:

- Production of *SARS-CoV-2 IgG antibody* at the blood serum samples (day 1 – before vaccination, day 21, day 42, interim data for day 90 and final data for day 180) according to ELISA.
- Determination of *SARS-CoV-2 neutralizing antibodies (VNA)* at the blood serum samples (day 1 – before vaccination, day 21, day 42, day 90 and day 180) according to data of neutralization reactions (NR).

5.1.1.2. Cell immune response

According to the results of day 42 of I/II phase of clinical trial, it was showed that forming of cell immunity with perpetuation of parameters on day 42 of trial and in order to confirm increase or decrease of cell immune indexes within phase III, cell immunity will be defined for day 1, day 90 and day 180 of trial.

• Evaluation of antigen specific cell immune response (T-cell response) using the method of flow cytometry (day 1 – before vaccination, day 90 and day 180).

5.2. Additional parameters of clinical study evaluation

Number of virologically confirmed cases (by PCR analysis) of COVID-19 disease of any severity after 14 days – 180 days after vaccination at the vaccine group in comparison with placebo group.

5.2.1 Evaluation of preventive efficacy

Evaluation of preventive efficacy will be performed by two characteristics:

EFFICACY INDEX

$$K = b/a$$

where,

K - efficacy index,

a – morbidity among vaccinated by vaccine,

b - morbidity among vaccinated by placebo.

EFFICACY COEFFICIENT

$$E = 100 * (b-a) \% / b$$

where,

E – efficacy coefficient,

a – morbidity among vaccinated by vaccine,

b - morbidity among vaccinated by placebo.

The evaluation of SARS-CoV-2 coronavirus infection morbidity rate among vaccinated by vaccine and placebo will be performed before day 180 after vaccination.

5.2.2. Safety evaluation of QazCovid-in®- inactivated vaccine against COVID-19

According to the aim and tasks of phase III clinical trial, the additional task is to study the safety at whole period of research.

Below, the clinical and laboratory parameters which should be evaluated by preparation safety are listed:

- specific clinical signs and symptoms of particular importance;
- anamnesis;
- physical observation.

As safety profile of vaccine, the person share at which development of undesirable conditions were indicated will be determined by the following categories:

- undesirable conditions of immediate action occurring within two days after each vaccination and revealed by the medical staff and using the information reported by vaccinated person to clinical medical staff.
- Post vaccine reactions (expected clinical manifestations of local and systematic nature) usually observed because of intramuscular vaccination and occurring within the period after two hours until 7 days after injection of any dose of vaccine or placebo and revealed by the medical staff and using the information reported by vaccinated person to clinical medical staff.
- Undesirable manifestations (including unexpected clinical appearance) occurring within 7 days after injection of any dose of vaccine or placebo and revealed by the medical staff and using the information reported by vaccinated person to clinical medical staff.
- All serious undesirable manifestations occurring within the period up to 3 weeks after each (or occurring once) vaccination, until the end of study up to 6 months after first vaccination revealed by the medical staff and using the information reported by vaccinated person to clinical medical staff or registered by vaccinated person at self-control journal. Also pathological changes of laboratory tests data of blood and urine samples collected for day 1, day 21, day 42, day 90 and day 180 after vaccination.
- Over the whole period of study, undesirable manifestations connected to disease or clinically significant state formation entailed the service of medical emergency team or doctor visit in case if the mentioned activities were not connected to treatment of widespread disease, should be registered at undesirable manifestations form regardless of their severity and presence of casual connection with vaccination.

It is important to separate undesirable manifestations characterized by intensity and dangerous symptoms.

Researcher should determine connection between symptoms occurring because of vaccination with their evaluation by the following categories: «probable», «possible», «remote/improbable», «unrelated».

Table 3 – Evaluation of causal relation of side reactions as a result of vaccine injection

Determination of interrelation	Characteristics of casual relation
PROBABLE	Development of clinical manifestations occurs at specified time interval after vaccine injection and cannot be proved by presence of any concurrent disease and taking any medicine. The manifestations vanish after some time or level of development is decreasing when vaccination is finished.
POSSIBLE	Data availability that confirm the causal relation with vaccine injections; it can be related with any disease or

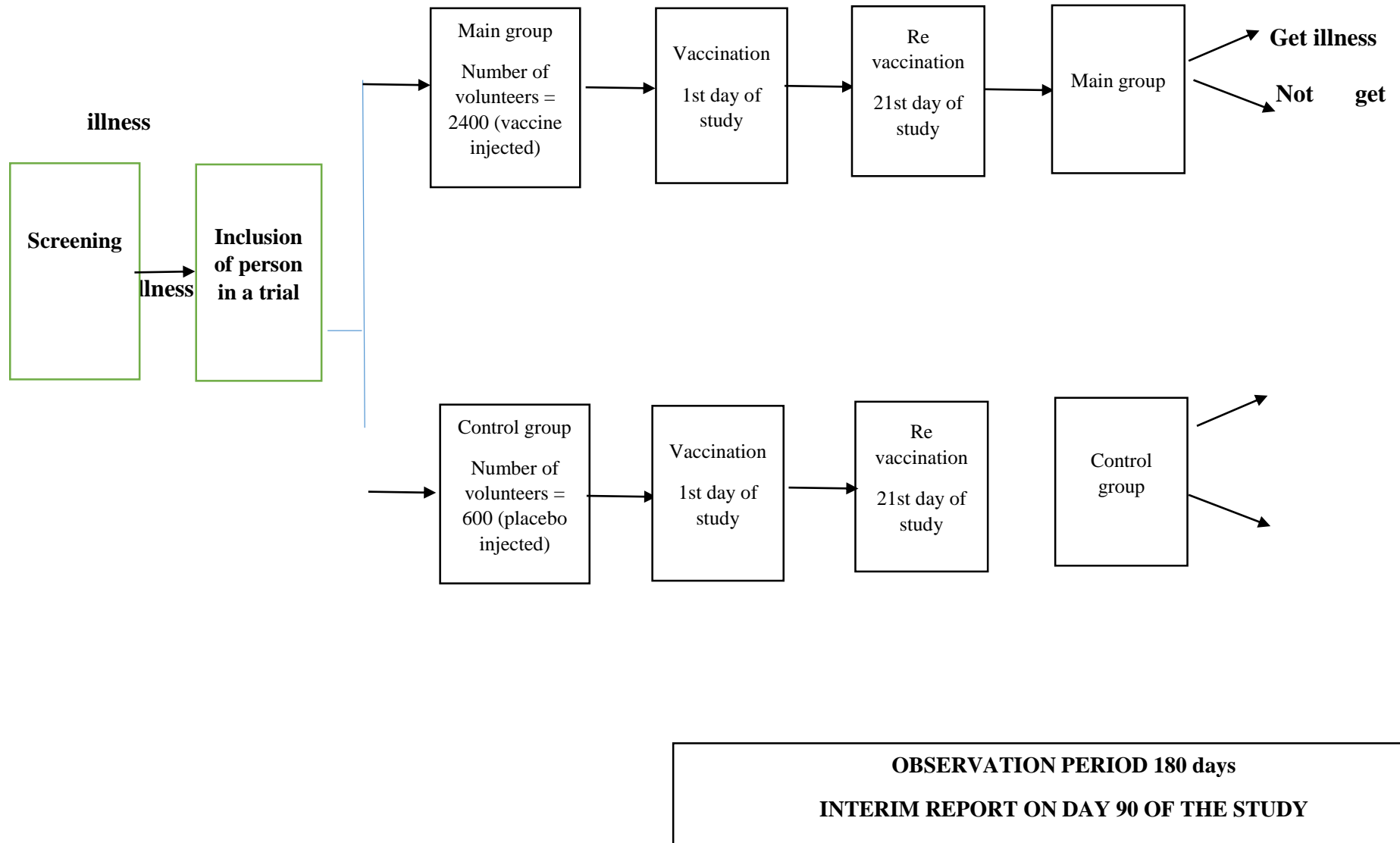
	taking medicine. Occurs in certain acceptable time intervals after vaccine injection. Correspondence of reaction to response standard presumably connected with injected vaccine should be taken into account.
REMOTE/IMPROBABLE	No side effect occurs in acceptable time interval after vaccine injection; casual connection is possible but improbable. It can be relevant to any disease or taking medicine. No correspondence of response standard presumably connected with injected vaccine.
UNRELATED	Side effect don't occur in acceptable time intervals after vaccine injection. It can be relevant to any disease or taking medicine.

5.3 Phase of the study: Phase III

5.4 Description of type of the clinical study

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5.5 Design of the phase III clinical trial



5.6.Procedures and visits of the phase III clinical trial

Procedure of study	Date of examination (the serial number of the study day)									
	Screening D1	D2- D7	D8- D20	D21±2	D22- D27	D28- 41	D42±2	D43- D89	D90 ¹ ±2	D180 ² ±2
Visits	B1			B2			B3		B4	B5
Informing process and sign of informed consent form	X									
Blood sampling for SARS-CoV-2 serology (by ICA)	X									
Basic demographic data collection Anamnesis data collection	X									
Physical observation and evaluation of vital parameters	X			X			X		X	X
Blood sampling for clinical and biochemical test	X			X			X		X	X
General urine test	X			X			X		X	X
ECG	X									
Pregnancy urine test	X			X						
Blood sampling for HIV, hepatitis B and C	X									
Evaluation of criteria to inclusion/non inclusion	X									
Injection of preparation	X			X						
Registration of undesirable manifestations with immediate action within 2 hours after vaccine injection	X			X						
Registration of local and systematic undesirable manifestations by the phone with participant (daily)			X	X	X					
Informing of participant about the self-registration diary journalizing and self-registration of unexpected undesirable manifestations		X	X			X				

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5.7 Description of measures for minimization (elimination) of subjectivity

5.7.1. Procedure of randomization

The clinical study is multicenter, randomized, double-blind, placebo-controlled (assigned in to 3 groups in a ratio 1:4 to vaccine or placebo injection) phase III trial of QazCovid-in®- inactivated vaccine against COVID-19.

Health subjects of trial (men and women) aged at 18 and older will participate in trial. Procedure of coding of studied vaccine or placebo for phase III trial will be performed using envelope system or software. According to this document, regardless of its further detailing, each study subject will be randomly assigned a coded preparation according to a technique that involves the injection of the studied vaccine or placebo in a ratio of 1: 4. Double-blind, randomized trial will be performed. Subjects will not know which preparation will be used (placebo or vaccine). The procedure for ensuring random distribution of people into the main and control groups will be carried out in the following way:

1. The randomization will be done by the Sponsor's responsible employee; this employee will prepare a randomization sheet which will be placed in an opaque sealed envelope.
2. The randomization sheet is a table that contains a sequential list of drug distribution codes (continuous numbering by the number of study subjects), randomly divided into two groups - Group № 1 - Vaccine (2400 people) and Group № 2 – Placebo (600 people) in the ratio 1:4.

5.7.2. Procedure of masking of examined preparation

In QazCovid-in®- inactivated vaccine against COVID-19, vaccine and placebo will be indistinguishable by appearance, form and presented in liquid form. But, because the vaccine and placebo must be clearly identifiable, the preparation of the vaccine and placebo will be entrusted to the sponsor's employee who works in an open, unmasked mode and is aware of the names of the coded drugs. This employee will not take part in the procedure of preparation injection, nor will the research subjects be informed to them about which of the preparations, vaccine or placebo, was applied. The procedures for preparing the vaccine or placebo for injection to subjects and filling the dispensers for challenge of fluid will be performed by staff in a separate room. The filled devices will be carefully handed over to the blind administering agent. The preparation of the vaccine and placebo for injection and syringe filling will be carried out under the close supervision of an independent staff member. To ensure strict adherence to the randomization schedule, the randomization procedure will also be closely monitored. The preparation, vaccine or placebo injected to each subject will be registered in the CRF under the appropriate code.

For all clinical trial personnel, for whom a blind mode is provided, work in this mode will remain for up to 90 days of the study. In the event that a study subject develops serious undesirable manifestations that qualifies as possibly related to the study drug, full information about the drug injected may be reported to the investigator if it is deemed necessary for further treatment of serious undesirable manifestations at that subject. In such cases, the cancellation of the blind study regimen is carried out after prior consultation with the study sponsor.

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5.8 Description of treatment, dosage, and application schemes of the preparations under examination. Also includes description of the pharmaceutical form, package, labeling of the preparations under examination

5.8.1. Description of method of the phase III clinical trial of QazCovid-in®-inactivated vaccine against COVID-19

The clinical study is multicenter, randomized, double-blind, placebo-controlled (assigned in to 3 groups in a ratio 1:4 to vaccine or placebo injection) phase III trial to evaluate preventive efficacy, safety and immunogenicity of QazCovid-in®- inactivated vaccine against COVID-19.

Health subjects of trial (men and women) aged at 18 and older will participate in trial.

3000 subjects will be take part in trial in a ratio 1:4, so 2400 person – for vaccine injection and 600 – for placebo injection.

Procedure of coding of studied vaccine or placebo for phase III trial will be performed using envelope system or software. According to this document, regardless of its further detailing, each study subject will be randomly assigned a coded preparation according to a technique that involves the injection of the studied vaccine or placebo in a ratio of 1: 4.

On the day of the screening study, prior to the injection of the vaccine, subjects will be screened to determine their suitability for participation in the study based on medical history, physical examination, serological tests for SARS-CoV-2 (express test) coronavirus infection, ECG results, and urine samples for pregnancy will be analyzed in women.

Blood and urine samples for standard biochemical, hematological blood tests, immunological studies for chronic viral infections (human immunodeficiency virus, hepatitis B and C viruses, as well as humoral and cellular immunity to SARS-CoV-2) will be taken from persons who fully meet the inclusion / exclusion criteria and are admitted to vaccination. The results obtained are intended to determine the baseline health status of study subjects prior to injection of the vaccine, but not for screening purposes. The vaccine or placebo will be given twice on days 1 and 21. After injection of the vaccine or placebo, all subjects will be monitored by the investigators for at least 2 hours. For the next 7 days after each vaccination (from 2 to 7 and from 22 to 27 days of the study), daily phone calls are scheduled to the study subjects to monitor the development of adverse reactions (adverse events). Subjects will receive daily phone calls to register adverse events. From 8 to 20 and from 28 to 41 days of the study, the subject will keep records in the self-observation diary for self-registration of all cases of development of adverse reactions, as well as taking medicine.

From the 43rd to the 89th and from the 91st to the 179th days of the study, the subjects of the study will be monitored by researchers, doctors will make monthly calls to register adverse events and weekly calls to evaluate the effectiveness of the QazCovid-in ® – inactivated vaccine against COVID-19. In the detection of adverse events (local and systemic reactions) and signs of ARVI and coronavirus infection, the subject informs the researcher about this by the phone number specified in the informed consent. After the completion of the entire observation period, 180 days, there is no observation for the study subjects according to the test protocol.

The study subjects ' visits to the clinical center are scheduled on the 1st, 21st, 42nd, and 90th days for an interim medical examination, as well as on the 180th day of the study for the final control medical examination in the clinical study. The procedures provided on the specified days, include a doctor's examination, as well as procedures for collecting blood samples from the subjects of the study for immunological studies, women will also have a urine test for pregnancy. In order to assess the safety of the test vaccine, medical monitoring of the health status of the study subjects will be carried out within two hours after each administration of the test vaccine.

PCT	Protocol of the clinical trial		
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On the day of vaccination and the next 6 days after the administration of the test vaccine, control over the development of AES (adverse events) will be carried out daily by phone with the subject of the study. In the following days, the subjects of the study will carry out self-observation to independently account for the development of their unadjusted AES after active observation until the final visit for a comprehensive medical examination (day 180 of the study). To determine the humoral immune response to the administration of the test vaccine, a blood sample from some of the study subjects will be collected on the 1st, 21st, 42-1 and 90-1, as well as the final control visit on the 180th day of the study. To determine the cellular immune response to the administration of the test vaccine, blood samples from some of the study subjects will be collected on the 1st, 90th, and final control visit on the 180th day of the study.

5.8.2. Description of the test preparation

Title: QazCovid-in ® - inactivated vaccine against COVID-19 liquid, suspension for intramuscular administration.

Active ingredients: One dose (0.5 ml) contains active substances: 5.0 ± 0.5 mcg / dose of purified inactivated SARS-Co V-2 virus: strain "SARS-Co V-2/KZ_Almaty|04.2020", excipients: aluminum hydroxide (Al+3), sodium chloride, sodium hydrophosphate, potassium dihydrophosphate, water for injection.

Specification: in vials of 0.5 ml (1 dose), purified inactivated virus "SARS-CoV-2/KZ_Almaty|04.2020" in a dose (0.5 ml) - 5.0 ± 0.5 5 mcg / dose. The vaccine is a colorless transparent liquid with a loose white precipitate. After shaking for 1-2 minutes, a homogeneous suspension of whitish color is formed.

Manufacturer: Republican state enterprise on the right of economic management "Research Institute of Biological Safety Problems" of the Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan (State License for pharmaceutical activity No. FD64900005FH [type of activity - production of medicines]).

5.8.2.1. Ready-made form of the preparation

The vaccine is presented in liquid form, contains an inactivated purified strain "SARS-Co V-2/KZ_Almaty|04.2020" of the SARS-Co V-2 virus in an aluminum hydroxide adjuvant and a phosphate salt buffer: 0.5 ml (1 dose) in vials for intramuscular use. 10 bottles in a package made of PVC film. The package contains instructions for use in the state and russian languages.

50 packages are placed in a cardboard box or in a pack of cardboard boxes or in a group box. The box contains instructions for use in the state and russian languages. Labels made of label paper or writing paper are pasted on bottles, packages and boxes. Boxes with packages are placed in a box made of cardboard box or in a group box, or in a plywood box, laying lignin.

5.8.2.2. Supply of the test vaccine and placebo to the research center

The researcher or clinical trial coordinator will be personally responsible for receiving the vaccine and the placebo and its use, or will appoint a staff member responsible for all vaccine operations. The customer and / or Sponsor, together with the researcher or the person responsible for the vaccine and placebo operations, will determine the schedule (date\dates and deadline/deadlines) for the delivery of the vaccine and placebo to the study centers. The sponsor's delivery of the investigational preparations, vaccines and placebos, to the research centers will be carried out with the staff of the Research Institute of Biological Safety Problems.

The person responsible for receiving the vaccine and the placebo is required to verify compliance with the cold chain during the transport of the vaccine by constantly monitoring the temperature regime and / or filling out a special cold chain monitoring form. In each case of receipt of the test vaccine and placebo in the clinical centers of the study, the employee responsible for the operations with the vaccine and placebo must put his signature and the date of receipt of the vaccine in the relevant documents. One copy of each signed document will be

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archived at the researcher's workplace, and the others will be returned to the Research Institute of Biological Safety Problems.

5.8.2.3. Packaging and labelling

The vaccine is presented in liquid form, contains an inactivated purified strain "SARS-Co V-2/KZ_Almaty|04.2020" of the SARS-Co V-2 virus in an aluminum hydroxide adjuvant and a phosphate salt buffer: 0.5 ml (1 dose) in vials for intramuscular use. 10 bottles in a package made of PVC film. The package contains instructions for use in the state and russian languages.

50 packages are placed in a cardboard box or in a pack of cardboard boxes or in a group box. The box contains instructions for use in the state and russian languages. Labels made of label paper or writing paper are pasted on bottles, packages and boxes. Boxes with packages are placed in a box made of cardboard box or in a group box, or in a plywood box, laying lignin.

5.8.2.4. Storage and stability

The test vaccine and placebo should be stored at a temperature of +2°C to +8°C. It is necessary to monitor the temperature regime daily and record the temperature indicators in the appropriate form. In the case of a power outage from the main power source, a backup power supply or storage location should be provided. The test vaccine or placebo should not be used in the presence of damaged primary packaging, unclear labeling, or changes in the physical properties of the preparation (color and transparency).

In the case of a cold chain disorder, the preparation should not be used and the researcher or the person responsible for the operation of the vaccine should contact the Sponsor for further instructions. In such cases, the researcher must obtain written consent from the Sponsor before the investigational vaccine or placebo is used.

5.8.2.5. Expiration date

At the beginning of the study, the data allow you to set the shelf life of 1 year, at the moment, the term of the stability study is 6 months. The shelf life stability study is ongoing and the results will be reported to the expert organization.

5.8.3. Description of the preparation for comparison

Placebo (sodium chloride 0.9% solution for injection) will be provided as a sterile solution in ampoules or vials of 5.0 ml. The dose for intramuscular administration is 0.5 ml.

Trade Name: Sodium Chloride

International Nonproprietary Name: None

Dosage form: Solution for injection 0.9% 5 ml

Composition:

5 ml of the solution contains
active substance-sodium chloride 45.0 mg,
excipient: water for injection.

Description

Transparent, colorless liquid with a salty taste

Pharmacotherapy Group

Other non-medicinal products. Solvents.

ATX code V07AB

Method of administration and dosage

Subcutaneously, intramuscularly, intravenously.

Release form and packaging

5 ml per ampoule of neutral glass.

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5 ampoules are packed in a contour cell package made of polyvinyl chloride film and aluminum foil. Each package contains an ampoule scarifier. When packing ampoules with notches, rings and dots, scarifiers are not inserted. Contour packages are placed in cardboard boxes.

The group package contains approved instructions for medical use in the state and Russian languages according to the number of packages.

Storage conditions

Store in a dry place, at a temperature not exceeding 30°C.

Shelf life: 5 years

Manufacturer

JSC "Himpharm", Kazakhstan

Owner of the registration certificate

JSC "Himpharm", Kazakhstan,

Shymkent, Rashidova str., without a number, phone: 560882

Telephone number 7252 (561342)

Fax number 7252 (561342)

Email address standart@santo.kz

5.8.4. Dosage and injection method of the preparations

In the III phase of clinical trial, the vaccine will be administered twice intramuscularly to the deltoid muscle area of the non-dominant arm in a volume of 0.5 ml on the 1st and 21st days of the study. Vaccinated individuals should be closely monitored for at least 2 hours to ensure that the necessary medical care is provided in the event of a rare anaphylactic reaction after the use of the vaccine.

5.9. Expected duration of participation of subjects in the study, description of order and duration of all study periods, including the follow-up period, if such is provided.

The total duration of participation of each subject in the clinical study will not exceed 180±2 days. The study includes 5 visits. From the 8th to the 20th days (№1 Self-Observation Diary) and from the 28th to 41st days of the study (№2 Self-Observation Diary), self-control and the filling out of the diary by the subject is carried out, with the possibility of consulting a researcher doctor by the phone indicated in the Self-Observation Diary №1 and №2. From the 43rd to the 89th and from the 91st to 179th days of the study, the subjects of the study will be under the control of the researchers, doctors will make monthly calls to register adverse events and weekly calls to evaluate the effectiveness of the vaccine QazCovid-in® - inactivated vaccine against COVID-19. If adverse events (local and systemic reactions) and signs of ARVI and coronavirus infection are detected, subject informs the investigator about this by phone specified in the informed consent. After the completion of the entire observation period, 180 days, the observation of the study subjects according to the test protocol is not provided.

5.10. Description of the rules for termination or exclusion criteria for individual subjects, parts of the study, or the entire study

The research subject may voluntarily terminate his participation in the study at any stage of its conduct. The Principal Investigator may exclude a research subject from a clinical trial at any time if:

- the investigator decides that the research subject should be excluded in the interests of the subject;
- the subject of the study has a serious adverse event associated with the administration of the drug;

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- the subject of the research refuses to cooperate or is undisciplined;
- the subject of the study was included in violation of the rules of the protocol;
- the research subject suffers from any other significant adverse events;
- the research subject receives / needs additional treatment that may affect the immunological response to the administration of the investigational drug;
- the research subject requires inpatient treatment during the clinical research;
- if the subject's health condition deteriorates;
- positive pregnancy test (for women);
- in the event that the resulting side effects of the drug are so serious that the continuation of the study is unacceptable.

The sponsor has the right to terminate the research at any time. Regulatory authorities have the right to terminate the study if the ethics of the clinical trial are violated, or due to serious adverse events. The Researcher transmits data about the subjects excluded from the study to the Sponsor and the Study Monitor within 24 hours in the form of a report containing information on the status of the study subject in the end of the clinical study.

5.11. Procedure of accounting preparations under examination, including preparations for placebo and comparison, if any.

The researcher keeps a record of received and used drugs and their distribution to each of the study subjects in a special Investigational Drug Register and Placebo (presented in Appendix 4). At the end of the study, a copy of the Drug Registration Form must be provided to the Sponsor. Accurate information about when and how much the drug was administered to each study subject should be available for review at any time.

After preparation and administration of the drug, all used vials, syringes and needles in which the vaccine was contained must be autoclaved and destroyed. At the end of the clinical study and, if necessary, during the study, the investigator is obliged to return to the Sponsor all unused containers with drugs, as well as the drug and placebo (presented in Appendix 5).

After the database is closed, the clinical trial monitor will conduct a complete inventory of drugs. During the course of the study, the contact of the clinical trial monitor, a copy of the completed Investigational Distribution Register by authorized personnel with the appropriate qualifications of the investigational drug, will be prepared only when it is necessary to clarify any issues related to the investigational drug.

5.12. Storage of randomization codes and procedures for their opening

The investigator must ensure that the envelopes with the randomization codes are stored securely to exclude unauthorized access to them. The Sponsor must regularly monitor the storage mode and condition of the envelopes. for all research staff, for which a blind study mode is provided, work in this mode will remain up to 90 days of the study.

On the 90th day of the clinical study of the III phase of a multicenter, randomized, blind, placebo-controlled study, the data will be blinded, i.e. the randomization code will be opened and statistical processing of the data will begin for analysis and preparation of an interim report on the distribution of study subjects by placebo group and the study vaccine.

If in research subjects develop a serious adverse event (SAE), if necessary, information about which blood sample corresponds to the research subject can be communicated to the investigators, after agreement with the Sponsor but only to the study and if there is a probable connection between the SAE and the administration of the study drug. The inclusion of this research subject in the final analysis is agreed with the Research Sponsor.

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In case of accidental or deliberate disclosure of the randomization code, the researcher is obliged to immediately inform the Customer about this, to state in writing the essence and reason for such a decision / incident.

5.13. List of information registered in IRC

All information, the receipt of which is provided by the protocol of the clinical trial, is subject to registration in the IRC. All source documents and reports of laboratory clinical and laboratory studies, which must certify the accuracy and completeness of the information entered.

Each IRC must be certified by the signature of the investigator with the date, confirming that the studies should be carefully checked by the executors for the quality of all specified data, and certifying that everything fully reflects all stages of participation, his responsibility for the data presented is reliable and the research subject in the clinical trial.

Clinical safety data and all laboratory data (virological and immunological) will be transferred to the IRC from the study report forms. Dates of visits for control meals and laboratory procedures will be indicated on all forms. When joining a clinical study, each research subject will be assigned an individual research subject number, this number will be used in all reports and the research database, and will indicate from which particular individual the data was obtained. Entering IRC data into the database, checking their accuracy, identifying the research subject by an individual number and processing the entered data will be carried out using special software for working with databases. The data obtained in the course of clinical research, registered in the IRC, will be based on laboratory data include:

- biographical information;
- medical history;
- clinical data (signs and symptoms, prescribed or not prescribed drug therapy);
- safety data based on the results of physical, instrumental (ECG) and laboratory tests (hematological and biochemical data, urinalysis data);
- data from immunological laboratory tests.

6. Selection and exclusion of subjects:

Phase III of the clinical trial of QazCovid-in® inactivated against COVID-19 vaccine will include 3,000 healthy subjects aged 18 years and older, male and female, who will be distributed in a 1: 4 ratio for the study preparation: main group (2400 people) and control group (600 people) with two time vaccinations on the 1st and 21st days of the study.

6.1. Inclusion / exclusion criteria for subjects

6.1.1. Inclusion criteria for subjects

1. Subject's signed and dated informed consent to participate in the study.
2. Healthy male and female subjects aged 18 and over.
3. Ability and voluntary willingness to carry out all visits provided for in the study for follow-up medical supervision.
4. Volunteer willingness to use methods of reliable contraception throughout the entire period of his participation in the study.
5. Negative results for antibodies IgM, IgG to SARS-CoV-2.
6. No history of COVID-19 coronavirus infection.
7. Lack of close contacts over the past 14 days with persons suspected of being infected with SARS-CoV-2, or persons who have a laboratory-confirmed diagnosis of COVID-19 coronavirus infection.

6.1.2. Exclusion criteria for subjects

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1. Complicated allergic history, drug intolerance, including hypersensitivity to any of the drug, as well as a history of serious adverse events with components of the study vaccine administration (such as allergic reactions, respiratory failure, angioedema, abdominal pain).
2. Acute illness with fever (body temperature $\geq 37,1$ ° C) at the time of screening.
3. History of chronic alcohol and / or drug use.
4. Positive results for antibodies IgM, IgG to SARS-CoV-2.
5. Women with a positive urine pregnancy test.
6. Simultaneous treatment with immunosuppressive drugs, incl. corticosteroids (2 weeks) in the period 4 weeks before the administration of the study preparation.
7. Acute or chronic clinically vascular system, gastrointestinal tract, liver, blood system, skin, endocrine, neurological and psychiatric diseases or impaired renal function (asthma, diabetes, thyroid disease, arrhythmia, myocardial infarction, severe hypertension, not controlled by medicines, etc.), identified according to the data of the medical history, physical examination, which, in the opinion of the researcher, may affect the result of the study.
8. History of platelet disorder or other blood clotting disorders, which may cause contraindications to intramuscular administration.
9. History of leukemia or neoplasm.
10. Persons with autoimmune diseases.
11. A history of Guillain-Barré syndrome or other neuroimmunological disease.
12. Subjects who received antiviral drugs, immunoglobulins or blood transfusions or any other investigational drug within 4 weeks prior to study drug administration;
13. Subjects who received anti-inflammatory drugs 2 days before study drug administration;
14. Participation in any other clinical research within the last 6 months.
15. Subjects with a concern that they will not comply with the study requirements, or persons with severe physical or mental disabilities that may affect the completion of the study.
16. Voluntary refusal to study.
17. Vulnerable research subjects.

6.2. Criteria for termination of participation of subjects in the study – termination of application of the preparation (treatment under examination), as well as the procedures that determine the termination:

6.2.1. Time and terms of exclusion of subjects from the study (treatment with the preparation under examination)

6.2.1.1. Reasons for exclusion and termination of subjects from the study (early termination of the study)

A research subject included in a clinical trial may terminate participation in it for several reasons:

- The investigator decides to suspend the research subject from participation in the research if he / she is found to be unfit for clinical research or if he / she loses the previously recognized suitability, develops undesirable phenomena that require termination of participation in the research, or because the subject does not have conscious desire and sequential execution of the study for the research procedures.
- The research subject independently voluntarily terminates participation in the research.
- Medical monitoring of the subject's health has been lost.
- The study was terminated early by the decision of the Sponsor.

6.2.1.2. Exclusion and termination of a subject's participation in a study within a certain time frame of the study

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6.2.1.2.1. Termination by the subject of participation in the study during the screening examination

In the event that it is established that the subject does not meet the criteria for inclusion/exclusion, the subject should be assigned a number of the subject of the study, but information about him is not subject to registration in the CRF. At the same time, only the reasons and date of exclusion from the study should be indicated in the Register of Research Subjects.

6.2.1.2.2. Termination by a subject of participation in the study due to erroneous inclusion in the study

If the subject of the study does not meet the criteria for inclusion/exclusion, but was included in the study due to an oversight, the investigator must terminate his participation in the study and inform the Sponsor of this case. If this subject has already participated in the randomization procedure and has already received the study preparation, vaccine / placebo, it is necessary, if possible, to conduct a full course of observation at the clinical center during the entire period stipulated by the study protocol. However, in this case, a statistical analysis of the data obtained and its inclusion in the final answer will not be carried out.

6.2.1.2.3. Discontinuation by a study subject due to the development of conditions meeting the exclusion criteria after administration of the study vaccine to the study subject

In the event that the subject develops a concomitant disease that is a criterion for exclusion from the study, or, for any reason, if its treatment requires use of drugs inappropriate for this study, it may be as a reason for exclusion of subject from the study. In all cases of this kind, you should immediately seek advice from the Sponsor.

6.2.1.2.4. Termination by the subject of participation in the research due to violation of the research protocol

The behavior of the research subject is assessed as incomplete research in the presence of any of the following conditions:

- Violation of the rules for staying in the clinical department.
- Missing, incorrect or insufficiently completion of self-observation Diary records
- Skipping a scheduled medical examination of the study scheme of the visit for the control
- Inconsistency of the subject's behavior during any of the study procedures during the study visit for the control medical examination provided for by the study scheme (except in cases of exclusion of subjects from the study).
- Failure of the subject to provide information to the researcher about the occurrence of any undesirable or serious undesirable phenomenon in him / her.

6.2.1.2.5. Termination of the subject's participation in the study in connection with the withdrawal of informed consent

In the event that the research subject declares that he / she does not want to further participate in the research and that the informed consent signed by him / her to participate in the research is terminated after the administration of the first or second dose of the study vaccine, placebo, research subject to be asked to complete the procedures that provided on the day of refusal. If possible, the subject should indicate the reasons for the ending participation in the research.

6.2.1.2.6. Termination by the subject the participation in the study due to the development of a serious adverse event

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All research subjects who terminated participation in the study have the right to visit for a follow-up medical examination in case of the occurrence of an undesirable event or in connection with the appearance of any symptoms that pose a threat for health (changes in vital signs and results of laboratory research).

In the event that the subject of the study develops a serious adverse event that caused his / her early termination of participation, full medical monitoring of this person will continue until the symptoms of SAE disappear, the diagnosis of SAE is confirmed, the transition of the acute stage of SAE to chronic, stabilization of the state or during such a period of time that will be recognized as clinically justified. However, in cases where early termination of participation in the study is due to SAE, the clinical prognosis for which is relatively favorable (for example, the diagnosis is known and in a week the subject's condition should be completely normalized), it is considered possible to carry out periodic medical supervision, provided that all planned medical activities are registered in the research subject's CRF.

6.2.1.3. Procedure for termination of participation in a study by a subject

In the event of an early termination of participation in a clinical trial by a subject for any reason, the researcher must make every effort to comply with the following:

The subject should be interviewed to obtain accurate information about the development of any AE (serious or not classified as serious) within six months of study vaccine product administration following termination of participation in a clinical trial. Whenever possible, the researcher should obtain visual or physical confirmation of the development of the AE, about the development of which information was obtained.

An attempt should be made to fully complete all procedures provided for in the study design if the early termination of participation in the study occurred before the 180th day of the study. The sponsor of the study must be informed within 24 hours of all cases of early study completion by the subject. Termination by a subject of participation in a study by the decision of the investigator of clinical participation is possible if the subject of the above exclusion criteria or if the continuation of his / her participation in the study poses a threat to his / her health.

After the administration of the study vaccine or placebo, the subject may be excluded from participation in the study by the decision of the investigator only if he/she develops adverse events for vaccination, which the investigator qualifies as posing a threat to the health of the subject; after the termination of participation in the study, the subject may be assigned a course of treatment for two bases at the expense of the sponsor:

- if the cities of Almaty, then the subjects will be centrally sent to the Clinic of the International Institute of Postgraduate Education, 49/1 Toraighyrov Street, Almaty.
- if the city is Taraz, then hospitalization and examination will be scheduled at the SCE on the REM «City multidisciplinary hospital of the Health Department of the Akimat of Zhambyl Region» Taraz, Al-Farabi str. d. 2 «B».

6.2.2 Collection of data on types and time for patients, excluded from the study

If a study subject terminates participation in a clinical trial early for any reason, an attempt will be made to fully complete all procedures required by the study design and scheduled for (a) day 21 (except for the administration of the investigational vaccine/placebo), if early termination of study participation occurred before day 21 of the study but after the first dose of study vaccine/placebo, or on day b) day 180 if early termination of study participation occurred before day 180 of the study but after the second dose of study vaccine/placebo. However, in this case, there will be no statistical analysis of the data obtained and its inclusion in the final report.

6.2.3. Procedure for substituting subjects

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New study subjects are included in the clinical trial to replace study subjects who have not fully completed the Protocol study. New subjects from among the screened subjects (reserve subjects) will have to complete the study. Reserve subjects arrive at the beginning of the tests together with the subjects of the main composition. If no replacement is required, the backup subject is released home. At the same time, communication is maintained with it, and it complies with the protocol requirements. If the need for replacement occurs no later than 2 hours after the start of the study-the reserve subject is included in the study instead of the retired subject, the study is conducted on the same day. If the need for replacement occurs more than 2 hours after the start of the study, the reserve subject arrives at the research center by invitation and, after signing the informed consent, is included in the study undergoes the screening procedure and the vaccination procedure. In this case, the reserve subject takes the studied drugs in the same sequence as the retired subject should have taken according to the scheme to the research center by invitation after signing the randomization.

The obtained data of the retired principal subject will not be included in the statistical analysis and in the final report.

6.2.4 Follow-up observations on subjects, excluded from treatment with the preparation under examination

All subjects of the study who have stopped participating in the clinical trial will have the right to visit during the entire period of the clinical trial (up to 180 days) in the event of adverse events or in connection with the appearance of any symptoms that pose a threat to health (changes in vital signs or laboratory results).

6.3. Completion of the clinical study

6.3.1. Completion of the study according to the protocol of the study

The end of the study in accordance with the study protocol is provided on the day of the last visit of the last subject of the study for a control medical examination, as indicated in the study scheme. It should be noted that each group of subjects of the study, this day falls on different dates.

6.3.2. Temporary suspension and/or early termination of the study

The decision to temporarily suspend a clinical trial may be made by the Sponsor, the Ministry of Health of the Republic of Kazakhstan, and the Central Commission for Bioethics of the Ministry of Health of the Republic of Kazakhstan, who are in charge of this study, as well as by the researcher at any time if there are concerns related to the safety of the study drug. Factors of concern include, for example, the development of SAE that led to a fatal outcome, an unexpectedly large number of individuals who were found to have released the virus after the first or second dose of the test drug, and an unusually high incidence of SAE. The sponsor has the right to temporarily suspend the study if it is found that the standards of the Good «Clinical Practice Guide» (GCP) aren't met.

In the event of new data indicating an increase in the risk level for the study subjects, the clinical trial will be suspended until the Sponsor, the Ministry of Health of the Republic of Kazakhstan, and the Central Commission for Bioethics of the Ministry of Health of the Republic of Kazakhstan, analyze this data and make an agreed decision that the study can be continued.

7. Treatment of the subjects

7.1. Conducted treatment, including names of all medications, their dosage, frequency of application, routes, and methods of administration, as well as duration of the treatment, including periods of follow-up observations for each of the subjects' group (by groups of

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treatment with preparation under examination, by groups of treatments under investigation, or by study groups)

7.1.1. Screening procedure and vaccination

Prior to inclusion in the clinical trial, each subject of the study must first sign an informed *Consent Form* for participation in the study, then a screening examination of each subject will be conducted, including a set of procedures, including laboratory tests, collection of medical history data, ECG and physical examination. Each subject participating in the survey will be assigned an identification number. To select the required number of seronegative subjects for the SARS-CoV-2 virus, the study is supposed to be examined by the ICA method.

The screening results will determine the suitability of the research subject for participation in the clinical research. The primary stage of screening will be the rapid ICA test for the presence of IgM / IgG antibodies against the SARS-CoV-2 virus. The following stages of screening can only be passed by those research subjects in whom only the control (C) line is positive. If a healthy subject is determined to be eligible for the study at all other stages, the study vaccine or placebo will be vaccinated on the same day.

7.1.1.1. Identification of research subjects

The research center will maintain a list of research subjects included in the clinical trial, which will include the subject's number, full name of the subject, date of birth, date of inclusion of the subject in the study, date of completion by the subject of the study, the number of visits completed and the reason for the completion of the study.

7.1.2 Order and duration of stages of phase III clinical study of QazCovid-in®-inactivated vaccine against COVID-19

Prior to inclusion in the study to assess the preventive effectiveness, safety and immunogenicity of the QazCovid-in ® vaccine, a screening examination of each subject of the study will be conducted, including a set of various procedures, including laboratory tests, collection of medical history data and physical examination.

7.1.2.1. Screening examination and vaccination

1. The physician-researcher will inform the subjects about the screening procedures. On that day, the subject must sign an informed consent form to participate in the study.
2. Interviewing the subject to collect initial demographic information (name, date of birth, gender, race and nationality, etc.).
3. Collection of blood samples from the subject to assess the presence of IgM, IgG antibodies to SARS-CoV-2 by the express method of ICA.
4. The study will include only those subjects who, according to the ICA for the SARS-CoV-2 coronavirus, have negative indicators.
5. Subject is interviewed by a physician-researcher to collect detailed medical history data. The researcher will verify the information obtained to confirm whether the subject should participate in further procedures.
6. Physical examination of the subject by a physician-researcher. The researcher will review the results obtained and familiarize the subject with them to confirm the feasibility of his / her participation in further procedures.
7. From female subjects, urine samples will be collected for pregnancy testing.
8. All subjects will undergo an electrocardiogram (ECG).
9. Upon recognition of the eligibility of the research subject for participation in the clinical trial, the research subject by randomization will be included in the main or in the observation group.

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10. Prior to the administration of the test vaccine or placebo, a blood sample will be taken from all subjects of the study to assess the humoral and cellular immune response to SARS-CoV-2 IgG(ELISA), HIV, hepatitis B and C, as well as to assess the biochemical parameters and the general blood test (GBT) with the determination of the blood leukocyte formula. The results of serological, biochemical and clinical analysis of blood samples taken from the subject on the first day of the study are only necessary to determine the initial state of health of the subjects.

11. The subject of the study will be administered a single dose of the test vaccine or placebo by the nurse of the vaccination office.

12. The subject will be closely monitored for two hours after administration of the study drug to detect the possible development of any immediate adverse events. If the subject develops an immediate adverse event, he/she will be given the necessary treatment.

13. The subject of the study will be informed that if he/she develops any further AE that requires medical intervention, he / she should inform the researcher as soon as possible and seek the necessary medical assistance. When visiting a doctor, the subject must necessarily inform him about his participation in this study and provide him with the contact information of the researcher.

14. In the evening, the physician-researcher will ask about the subject's state of health by telephone. If the subject has an adverse event requiring medical attention, he/she will be offered hospital admission and receive the necessary treatment.

7.1.2.2. From the 2nd to the 7th day of the study

1. The physician-researcher will interview the research subject by telephone about the possible occurrence of any adverse signs and symptoms. All research subjects will be strongly encouraged to self-report any health problems or adverse symptoms to the research staff.

7.1.2.3. From the 8th to the 20th day of the study

1. Subjects of the research will independently keep records in Self-observation Diaries No. 1 to account for the development of any local or systemic adverse events in them.

2. The subject of the study will be informed that if he/she develops any further AE that requires medical intervention, he / she should inform the researcher as soon as possible and seek the necessary medical assistance. When visiting a doctor, the subject must necessarily inform him about his participation in this study and provide him with the contact information of the researcher.

7.1.2.4. The 21st day of the study is the day of the visit to the clinical center for the second dose of the vaccine.

1. Subjects must report to the research center on the morning of the study. The research staff member must confirm the identity of each of them.

2. The researcher will work with the subject to check the records in the Self-Observation diary #1, collect medical history data for the interim period (day 8-20), and ask him/her about any new health problems that may have occurred since the previous medical history was completed.

3. Collection of blood samples will be carried out to assess the biochemical parameters and indicators of the general blood count (CBC) with the determination of the indicators of the leukocyte formula. In addition, a whole blood sample will be taken from the test subject on the same day for the purpose of assessing the humoral and cellular immune response.

4. Urine samples will be collected for urine analysis.

5. From female subjects, urine samples will be collected for pregnancy testing. Any abnormal change in study results will be recorded as an AE and will be the object of the researcher's

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analysis to determine whether a second dose of the test vaccine should be administered to that subject.

6. The physician-researcher will perform a physical examination of the subject of the study and register the data obtained in the CRF. The researcher will analyze the results obtained, inform the subject with them, and if any AE occurs, each case of AE will be registered in the corresponding section (s) of the CRF.

7. In the event that the subject's suitability for continued participation in the study is confirmed, the study subject will undergo procedures to administer the study vaccine or placebo and assess the safety and immunogenicity of the vaccine.

8. In the event that the subject is determined to be unsuitable for further continuation of the study on the introduction of a second dose of the test vaccine or placebo, the researcher must cancel the re-vaccination of this subject, but the exclusion of this subject from the study must follow the procedures specified in paragraph 9 below.

9. Prior to administration of the study vaccine, a serum sample will be taken from the subject for serological testing to determine antibodies to SARS-CoV-2.

10. A second dose of the study vaccine will be administered to the subject.

11. The subject will be closely monitored for two hours after administration of the study drug to detect the possible development of any immediate adverse events. If the subject develops an immediate adverse event, he/she will be given the necessary treatment, and this case of AE will be registered in the CRF.

12. The subject of the study will be informed that if he/she develops any further AE that requires medical intervention, he / she should inform the researcher as soon as possible and seek the necessary medical assistance. When visiting a doctor, the subject must necessarily inform him about his participation in this study and provide him with the contact information of the researcher.

7.1.2.5. From the 22nd to the 27th day of the study

1. The physician-researcher will interview the research subject by telephone about the possible occurrence of any adverse signs and symptoms. All research subjects will be strongly encouraged to self-report any health problems or adverse symptoms to the research staff.

7.1.2.6. From the 28th to the 41st day of the study

1. Subjects of the research will independently keep records in Self-observation Diaries No. 2 to account for the development of any local or systemic adverse events in them.

2. The subject of the study will be informed that if he/she develops any further AE that requires medical intervention, he / she should inform the researcher as soon as possible and seek the necessary medical assistance. When visiting a doctor, the subject must necessarily inform him about his participation in this study and provide him with the contact information of the researcher.

7.1.2.7. 42nd day of the study

1. Subjects must report to the research center on the morning of the study. The research staff member must confirm the identity of each of them.

2. The physician-researcher will perform a physical examination of the subject of the study and register the data obtained in the outpatient card. The researcher will analyze the results obtained, inform the subject with them, and if any AE occurs, each case of AE will be registered in the corresponding section (s) of the outpatient card.

3. A blood sample will be taken from the study subjects to assess the humoral immune response to SARS-CoV-2.

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4. The subject of the study will be informed that if he/she develops any further AE that requires medical intervention, he / she should inform the researcher as soon as possible and seek the necessary medical assistance. When visiting a doctor, the subject must necessarily inform him about his participation in this study and provide him with the contact information of the researcher.

7.1.2.8 From day 43 to day 89 of the study

1. Subjects will receive weekly phone calls to record the development of any local or systemic adverse events and to evaluate the effectiveness of the study drug.

2. The subject of the study will be informed that if he/she develops any further AE that requires medical intervention, he / she should inform the researcher as soon as possible and seek the necessary medical assistance. When visiting a doctor, the subject must necessarily inform him about his participation in this study and provide him with the contact information of the researcher.

7.1.2.9. 90th day of the study

1. Subjects must report to the research center on the morning of the study. The research staff member must confirm the identity of each of them.

2. The physician-researcher will perform a physical examination of the subject of the study and register the data obtained in the outpatient card. The researcher will analyze the results obtained, inform the subject with them, and if any AE occurs, each case of AE will be registered in the corresponding section (s) of the outpatient card.

3. A blood sample will be taken from the study subjects to assess the humoral immune response to SARS-CoV-2.

4. The subject of the study will be informed that if he/she develops any further AE that requires medical intervention, he / she should inform the researcher as soon as possible and seek the necessary medical assistance. When visiting a doctor, the subject must necessarily inform him about his participation in this study and provide him with the contact information of the researcher.

7.1.2.10. from the 91st to the 179th day of the study

1. Subjects of the research will independently keep records in Self-observation Diaries No. 2 to account for the development of any local or systemic adverse events in them.

2. The subject of the study will be informed that if he/she develops any further AE that requires medical intervention, he / she should inform the researcher as soon as possible and seek the necessary medical assistance. When visiting a doctor, the subject must necessarily inform him about his participation in this study and provide him with the contact information of the researcher.

7.1.2.11. The 180th day of the study is the day of the final visit to the research center

1. Subjects must report to the research center on the morning of the study. The research staff member must confirm the identity of each of them.

2. The physician-researcher will perform a physical examination of the subject of the study and register the data obtained in the outpatient card. The researcher will analyze the results obtained, inform the subject with them, and if any AE occurs, each case of AE will be registered in the corresponding section (s) of the outpatient card.

3. A blood sample will be taken from the study subjects to assess the humoral immune response to SARS-CoV-2.

4. The research staff member will complete the registration of the data received on the day of the subject's final visit for a follow-up medical examination, and the subject will be informed of the completion of his/her participation in the study.

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7.1.3. Visits, unscheduled by the scheme of the study

Subjects are entitled to unscheduled visits to the study center during office hours if they develop any AE or if he/she has a medical need for medical intervention.

All results of examinations conducted during unplanned study visits are to be recorded in the subject's CRF. In the case of an unplanned visit, the follow-up procedures must not be performed before the time limits specified in the above study scheme.

7.1.4 Description of the preparation under examination and placebo preparation

7.1.4.1 Description of the preparation under examination

Name: QazCovid-in®-vaccine inactivated against COVID-19 liquid, suspension for intramuscular injection.

Active substance: One dose (0.5 ml) contains the active ingredients: 5.0±0.5 µg/dose purified inactivated whole-virion strain "SARS-CoV-2/KZ_Almaty/04.2020" of COVID-19 virus, excipients: aluminum hydroxide (Al+3), sodium chloride, sodium hydrophosphate, potassium dihydrophosphate, water for injection.

Specification: in 0.5 ml vials, purified inactivated strain "SARS-CoV-2/KZ Almaty/04.2020" in a dose (0.5 ml) - 5.0±0.5 micrograms/dose. The vaccine is a colorless transparent liquid with a loose white precipitate. After shaking for 1-2 minutes, a homogeneous suspension of whitish color is formed.

Manufacturer: production base of RSE on the REM "Scientific Research Institute of Biological Safety Problems" of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (State license for pharmaceutical activities № ФД64900005FH, type of activity - production of medicines).

7.1.4.1.1. Prepared form of the preparation under examination

The study preparation QazCovid-in®-vaccine inactivated against COVID-19 is intended for intramuscular single or double administration. One dose (0.5 ml) contains the active ingredients: 5.0±0.5 µg/dose purified inactivated whole-virion strain "SARS-CoV-2/KZ_Almaty/04.2020" of COVID-19 virus, excipients: aluminum hydroxide (Al+3), sodium chloride, sodium hydrophosphate, potassium dihydrophosphate, water for injection. The vaccine is presented in liquid form, contains an inactivated purified strain «SARS-CoV-2/KZ_Almaty/04.2020» of the SARS-CoV-2 virus in an aluminum hydroxide adjuvant and a phosphate-salt buffer: 0.5 ml (1 dose) in vials of suspension for intramuscular use. 10 bottles in a package made of PVC plastic sheeting. The package contains instructions for use in the official national language and Russian languages. 50 packages are placed in a cardboard box or in a box made of cardboard or in a group box. The box contains instructions for use in the official national language and Russian languages. Vials, packages and boxes are glued with labels made of label paper or writing paper. Boxes with packages are placed in a cardboard box or in a cardboard box or group box or in a plywood box, lined with lignin.

7.1.4.2. Description of the preparation for comparison

Placebo (sodium chloride 0.9% solution for injection) will be provided as a sterile solution in ampoules or vials of 5.0 ml. The dose for intramuscular administration is 0.5 ml.

Trade Name: Sodium Chloride

International Nonproprietary Name: None

Dosage form: Solution for injection 0.9% 5 ml

Composition:

5 ml of the solution contains the active substance-sodium chloride 45.0 mg,

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excipient: water for injection.

Description

Clear, colorless liquid with a salty taste

Pharmacotherapy Group

Other non-medicinal products. Solvents.

ATX code V07AB

Method of administration and dosage

Subcutaneously, intramuscularly, intravenously.

Release form and packaging

5 ml per ampoule of neutral glass. 5 ampoules are packed in a contour cell package made of polyvinyl chloride plastic sheeting, and aluminum foil. Each package contains an ampoule scarifier. When packing ampoules with notches, rings and dots, scarifiers are not inserted. Contour packages are placed in cardboard boxes.

Group packaging is enclosed with approved instructions for use in the official national language and Russian languages according to the number of packages.

Storage:

Store in a dry place, at a temperature not exceeding 30°C.

Shelf-life: 5 years

Manufacturer

JSC «Himpharm», Kazakhstan

Owner of the registration certificate

JSC "«Himpharm», Kazakhstan,

Shymkent, Rashidova str., no number, tel: 560882

Phone number 7252 (561342)

Fax number 7252 (561342)

Email address standart@santo.kz

7.1.4.3. Dosage and method of administration of preparations

In a phase III clinical trial, the vaccine will be administered twice intramuscularly to the deltoid region of the non-dominant arm in a 0.5 ml volume on days 1 and 21 of the study to a main group of 3000 study subjects. Vaccinated subjects should be closely monitored for at least 2 hours for possible necessary medical care in case of a rare anaphylactic reaction after vaccine administration. The distribution of study subjects into 2 groups for the administration of the test vaccine will be carried out in a ratio of 1:4, the main group-2400 study subjects (the vaccine will be administered), the control group-600 study subjects (the placebo will be administered).

7.2. Medicinal preparations (therapy types) allowed (including emergency care) or not allowed for use before and/or during the study

7.2.1. Concurrent medications and concurrent treatments

During the course of this clinical trial, all concomitant medications used will be monitored and recorded. In case the subject is diagnosed with the presence and development of a pathological condition, which isn't a criterion for exclusion from the study, the treatment of such conditions should be carried out according to the usual plan provided for such conditions. Information on concomitant medications taken (trade name, dosage or dosage change, indications for use, start and end date of administration) must be registered in the case report form (CRF). All subsequent changes in treatment during the study period must also be recorded in the CRF. Women included in the study who are taking oral contraceptives to prevent pregnancy must continue taking these drugs for the duration of the study. The use of these drugs must also be registered with the CRF.

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7.2.2. Medicinal preparations of untargeted application

Any medical immunobiological preparations (including blood products), as well as other immunomodulatory preparations are contraindicated. These drugs may be prescribed for vital signs, but this will result in the exclusion of the subject from the clinical trial. Subjects will be advised not to take drugs with analgesic and antipyretic activity for prophylactic purposes, since these drugs can mask the reactivity of the test vaccine.

7.2.3. Using medicinal preparations of untargeted application

In the case that a situation arises during a clinical trial in which the treatment of adverse clinical events or AEs requires the administration and use of off-target or off-protocol medications, the administration of such medications is permitted. However, the Sponsor must be informed within 24 hours of the use of such medications. Information on the medication (trade name, dosage or change in dosage, indications for use, start and end date of administration) must be recorded in the CRF. All further changes in treatment during the study period must also be recorded in the CRF. The investigator will continue to medically monitor the subject's condition until the symptoms that caused the protocol violation have disappeared (in the case of early termination of study participation) or until the last date of study participation provided for in the study design (study termination). In the case that a research subject needs to take non-targeted or non-protocol medications to treat an adverse event that requires termination of study participation, the researcher must follow the procedures outlined under «Procedures for termination of study participation by a research subject».

7.3 Methods for monitoring adherence with procedures by subjects

The study will be conducted in accordance with the procedures outlined in the protocol. The duty of the investigator is to control strict adherence to the study subjects of the schedule of visits for the follow-up medical examination and all research procedures without violating the intervals established between them.

For the personnel participating in the study, special data collection forms will be developed, which will also provide a place for recording all actually performed manipulations (even if these manipulations do not require data registration) in the required sequence. All personnel participating in the study must have completed mandatory training prior to commencing the study.

The clinical center will be monitored to confirm that the rights of the research subject are respected and that the research procedures are in accordance with the protocol, including the injection of the investigational vaccine, the acquisition of clinical data and collection of biological samples, and the establishment that the procedures are performed at a high professional level.

8. Evaluation of efficacy

8.1 List of the efficacy parameters

The main objective of the study is to prove the superiority of the QazCovid-in®-inactivated vaccine against COVID-19 in comparison with placebo in terms of seroconversion (the proportion of individuals with a four-fold and more increase in antibody titers to SARS-CoV-2) on the 21st, 42nd, 90th and 180th days after vaccination.

1. To evaluate the immunogenicity of the QazCovid-in®-inactivated vaccine against COVID-19 in comparison with placebo according to the following indicators:
 - Geometric mean titer of serum antibodies to SARS-CoV-2 on the 21st, 42nd, 90th, 180th days after vaccination.
 - seroconversion rate (the proportion of individuals with a four-fold and more increase in antibody titers to SARS-CoV-2) on the 21st, 42nd, 90th and 180th days after vaccination.

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- The multiplicity of the increase in the geometric mean titer of serum antibodies to SARS-CoV-2 on the 21st, 42nd, 90th and 180th days after vaccination.
 - Determination of the level of intracellular cytokine production by antigen-activated T-lymphocytes using flow cytometry (day 1 before vaccination, day 90 and day 180).
2. Evaluate the effectiveness of the vaccine (exploratory data analysis) according to the following indicators:
- The frequency of confirmed cases of COVID-19 within 6 months after vaccination (except for cases of COVID-19 within the first 14 days after vaccination). Confirmed case of COVID-19: clinical presentation and positive laboratory test for SARS-CoV-2 virus RNA
 - Frequency of confirmed cases of COVID-19 requiring hospitalization (excluding COVID-19 cases within the first 14 days after vaccination).
 - Incidence of severe COVID-19 (excluding COVID-19 cases within the first 14 days after vaccination).
 - Rate of death from COVID-19 (excluding COVID-19 cases within the first 14 days after vaccination).

8.1.1 Evaluation of humoral immunity

- Production of IgM, IgG antibodies to SARS-CoV-2 virus proteins in blood serum samples (1st day - before vaccination, 21st day before the second vaccination, 42nd, 90th and 180th days) according to ELISA.
- Determination of virus-neutralizing antibodies (VNA) to SARS-CoV-2 virus in blood serum samples (1st day - before vaccination, 21st day - before the second vaccination, 42nd, 90th and 180th days) according to the neutralization reaction data (NR)

8.1.2 Evaluation of cellular immunity

- Assessment of antigen-specific cellular immune response (T-cell response) using flow cytometry (1st day - before vaccination, 90 and 180 days)

8.1.3 Assessment of preventive effectiveness

The assessment of preventive effectiveness will be carried out according to two indicators:

EFFICIENCY INDEX

$$K=b/a$$

Where,

K - efficiency index

a - morbidity among those vaccinated with the study vaccine

b - morbidity among vaccinated placebo.

EFFICIENCY COEFFICIENT

$$E=100*(b-a)\%/b$$

Where,

E - Efficiency coefficient

a - morbidity among those vaccinated with the study vaccine

b - morbidity among vaccinated placebo.

Assessment of the incidence of SARS-CoV-2 coronavirus infection among those vaccinated with the study vaccine will be carried out up to 180 days after vaccination.

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8.1.4. Clinical confirmation of coronavirus SARS-CoV-2 infection

Throughout the study (Days 1-180), viral respiratory infections and SARS-CoV-2 coronavirus infection will be monitored.

Diagnostic criteria in adults:

Complaints and anamnesis

Incubation period - 2-14 daysю

- increased body temperature (or no increase)
- generalized weakness, malaise
- sweating
- myalgia and body aches
- headache
- sore throat
- cough (rare dry with a small amount of stubborn sputum, can be painful, paroxysmal)
- tightness in chest, burning, pain, compression in the chest (it is impossible to breathe in deeply)
- Smell and taste disorders
- diarrhea
- restless behavior (agitation)
- conjunctivitis (rarely)
- rash (requires clarification of the cause)

With severe course

- dyspnea (at the time of examination or in the dynamics of the disease)
- labored breathing, feeling lack of air
- heart palpitations
- nausea, emesis
- stomach ache
- pain in the region of the heart
- persistent headache
- dizziness
- uroschesis

Features of the course of COVID-19 in elderly and senile people

- atypical picture of the disease without fever, cough, dyspnea
- delirium
- delusion
- tachycardia
- decrease in blood pressure
- fall
- functional decline
- conjunctivitis

8.1.5. Laboratory confirmation of coronavirus SARS-CoV-2 infection

If the main symptoms of viral respiratory infections and SARS-CoV-2 coronavirus infection are identified, the following will be carried out: collection of swabs (2 replicates) from the nasopharynx to diagnose COVID-19 coronavirus infection by PCR, venous blood sampling for detection of antibodies of IgG/IgM classes to SARS-CoV-2 coronavirus by ELISA.

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The timing of the collection of clinical material is important, since the highest concentration of the virus in the respiratory organs of a person is recorded within the first 3 days after the onset of signs of the disease. If the subject of the study is suspected of having a coronavirus infection with SARS-CoV-2 and the symptoms of viral respiratory infections are detected after a medical examination, the following algorithms are used:

- Taking a swab from the nose and oropharynx on the 1st day of treatment, with a negative result in PCR and further suspicion of coronavirus infection, repeat on the 3rd day after treatment;
- Blood sampling for the detection of class IgG/IgM antibodies to the SARS-CoV-2 coronavirus by ELISA;
- blood sampling for blood chemistry tests and complete blood count;
- collection of urine for clinical urine tests.

Biomaterial from patients, except to blood chemistry tests, complete blood count and urine, is delivered centrally to one laboratory - Omicron 3D LLP in Almaty, in compliance with the requirements of triple packaging in accordance with the sanitary rules and Sanitary and epidemiological requirements for laboratories using hazardous chemical and biological substances by an approved order N684 MH RK dated by 8.09.2017.

Based on the results of the analyzes of the subject of the study, the doctors will prescribe the appropriate treatment.

8.2 Methods and time of evaluation, registration, and analysis of efficacy parameters

8.2.1. Description of methodology for evaluation of humoral and cellular immunity

8.2.1.1. Method of the express test for identification of IgM/IgG antibodies of coronavirus SARS-CoV-2 infection

The combined test kit for the determination of IgM/IgG antibodies to the COVID-2019 coronavirus implements a rapid immunological analysis for the presence of IgM/IgG antibodies to the SARS-CoV-2 (COVID-19) virus in human serum, plasma and whole blood.

The test kit contains test cassettes with isolated reaction regions coated with anti-human antibodies IgM and IgG, latex particles labeled with the SARS-CoV-2 (COVID-19) virus spike protein and nucleocapsid protein.

During the analysis, the samples interact with the recombinant antigens of the SARS-CoV-2 (COVID-19) virus, which are labeled on latex particles. The reaction mixture migrates along the test cassette and reacts with IgM and/or IgG antibodies, staining one or both control lines. Coloring one of two or both control lines indicate a positive result for the SARS-CoV-2 (COVID-19) coronavirus. In addition, if the test is performed correctly, another (control) line on the test cassette will be colored (internal control of the test kit).

Test method. Before testing, all components of the test kit (test cassette, pipettes and buffer solution) should be warmed up to room temperature.

Remove the test cassette from the sealed foil bag and use it for testing immediately. The best results are obtained by using the cassette immediately after unpacking it.

Place 10 µl of serum or blood plasma or 20 µl (1 drop) of the patient's whole blood into the sample well (S), then add about 80 µl (about 2-3 drops) of buffer solution there and start the stopwatch (timer).

Watch for the appearance of colored (one, two or three) lines. Wait 10-15 minutes and determine the presence/absence of colored lines. After 15 minutes of testing, the results are invalid.

Interpretation of results. IgG-positive result corresponds to the stained IgG and control lines (C). This means that the test detected IgG antibodies to COVID-19 in the analyzed sample (i.e. the patient is infected with COVID-19 viruses).

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An IgM-positive result corresponds to the colored lines of the IgM and control (C). This means that the test detected IgM antibodies to COVID-19 in the analyzed sample (i.e. the patient is infected with the COVID-19 virus).

IgG- and IgM-positive results correspond to the colored lines YGG, YGM, and control (C). In this case, the color intensity of the lines does not have to be the same. The result means that the test detected IgG and IgM antibodies to COVID-19 in the analyzed sample (i.e. the patient is infected with the COVID-2019 virus).

A negative result corresponds to the color of control line C only.

An invalid result is obtained when the C control line does not appear on the test cassette.

8.2.1.2. Identification of specific antibodies by enzyme-linked immunosorbent assay (ELISA)

The method of determination is based on a two-stage "indirect" version of the enzyme-linked immunosorbent assay. At the first stage of the analysis, the specific antibodies contained in the test samples bind to the recombinant SARS-CoV-2 antigen immobilized on the surface of the plate wells. In the second stage, the conjugate of monoclonal antibodies to human IgG with horseradish peroxidase interacts with antigen-IgG complexes. During incubation with a tetramethylbenzidine solution, the solution stains in the wells containing the formed antigen-IgG-conjugate complexes. The intensity of the staining is proportional to the concentration of IgG to SARS-CoV-2 in the analyzed sample. After stopping the reaction, the results of the analysis are recorded by measuring the optical density in the wells of the plate. The assessment of the humoral immune response will be performed using blood samples collected on the 1st day of the study before the first vaccination, on the 21st, 42nd, 90th and 180th days of the study.

8.2.1.3 Identification of neutralizing antibodies against SARS-CoV-2 virus

Virus neutralizing antibodies are detected by examining blood serum samples using a neutralization reaction. The reaction is performed with a two-fold dilution of the test blood serum against the SARS-CoV-2 virus at a dose of 100 TCID₅₀

To detect virus-neutralizing antibodies to the SARS-CoV-2 virus, blood samples are collected from test subjects and serum is isolated from it. To set up the reaction, an equal volumetric amount of a virus with a titer of 100 TCID₅₀ is added to each tube with two-fold dilutions of the studied blood serum samples and this mixture is kept at a temperature of 37°C for 60 minutes. Then the mixture of each dilution of the test blood serum with the virus is added in equal volumetric amounts to 4 wells of a 96-well plate with a monolayer culture of Vero cells. The cell culture, inoculated with the reaction mixture, is cultured at a temperature of 37°C for 5 days.

The account of the neutralization reaction is carried out by inhibition of the CPE of the virus in the inoculated cell culture with positive reproduction of the virus in the control wells, in which the working dilution of the virus was titrated. The CPE of the virus should appear in all control wells inoculated with its working dilution in dilutions of 10-1, 10-2 and no more than 50% of the wells of 10-3 dilution.

The neutralizing titer of blood serum is the highest dilution that delays or prevents the reproduction of the virus in at least 50% of the wells with a monolayer of cell culture inoculated with a mixture of blood serum and virus.

8.2.1.4 Method of evaluation of parameters for cellular immunity

Cellular immunity will be assessed by reliable (more than 2 standard deviations from the preliminary mean) increments of the post-vaccination level (%) of CD4+ and CD8+ T-cells with the phenotype of memory cells.

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To study the cellular immune response, whole blood samples (WBI method) or peripheral blood lymphocytes isolated no later than 2 hours after blood sampling will be used. Assessment of the cellular immune response will be performed using blood samples collected on the 1st day of the study before vaccination, the 7th day of the study, 21st day (before the second vaccination), 27th and 42nd days.

Using the ELISA method, the level of vaccine-stimulated production of cytokines (IFN-gamma, TNF-alpha and IL-2) by antigen-activated CD4+, CD8+ T-lymphocytes will be assessed.

For research, 2 ml of peripheral blood sampled in the morning, on an empty stomach, will be added into a vial prepared in advance, closed with a rubber stopper, containing 4 ml of sterile maintenance medium DMEM (Biolot), with heparin (2.5 U/ml), gentamicin (100 µg/ml) and L-glutamine (0.6 mg/ml). To determine the spontaneous production of cytokines, 2 ml of the obtained blood solution is used, mitogen-induced production - 10 µl of a solution of phytohemagglutinin (PHA, Sigma) with a concentration of 1 mg/ml will be added to 1 ml of diluted blood, antigen-induced production instead of PHA, we add the vaccine to the final concentration 0.5-5.0 µg/ml. Samples will be incubated at 37°C for 24 hours, blood cells will be pelleted by centrifugation at 3000G for 10 minutes, the supernatant will be aliquoted and frozen until analysis.

Analysis of the level, functional characteristics and duration of the post-vaccination T-cell response will be carried out by flow cytometry in samples obtained before vaccination (1st day of the study), on the 7th, 21st, 27th and 42nd days of the study, from using the following markers: CD3/CD4/CD8.

The antigen assay, cytokine and interferon stimulation are performed from the supernatant in the stimulated and no stimulated groups of subjects.

8.2.1.5 PCR method for identification of RNA of the coronavirus SARS-CoV-2

The total volume of the reaction mixture is 50 µl, including the sample volume of RNA-25 µl.

Before preparing the reaction mixture, **PCR mixture-1** must be vortexed and the drops discarded by short-term centrifugation.

Operating procedure:

1. Calculate the amount of each reagent required to prepare the reaction mixture. One reaction requires 15µl of PCR-mixture-FL SARS-CoV-2, 10µl of RT-PCR-buffer-R, 1µl of Taq polymerase, 0.5µl of Reverse Transcriptase (M-MLV). Prepare the mixture for the total number of test and control samples plus a margin for one reaction.
2. Thaw the test tube with PCR mixture-FL SARS-CoV-2. Mix the contents of all PCR kit reagents, vortex the drops. Prepare the reaction mixture in a separate test tube. Mix the required amount: PCR-mixture-FL SARS-CoV-2, RT-PCR-buffer-R, Taq polymerase and Reverse Transcriptase (M-MLV), precipitate the drops on a vortex
3. Take the required number of tubes or strips for RT-PCR of RNA of the test and control samples.
4. Add 25µl of the prepared reaction mixture to each tube.
5. Add 25µl of RNA samples obtained as a result of extraction from the test samples to the prepared test tubes.
6. Set control reactions.
 - a) positive control of RNA extraction and RT-PCR (PC) - add 25µl of the sample extracted from SARS-CoV-2 RNA to the test tube with the reaction mixture
 - b) negative control RT-PCR (C-) - add 25 µl K- to the test tube with the reaction mixture
 - c) negative control of extraction (NC) - add 25 µl of the sample extracted from NCS into the test tube with the reaction mixture.

Amplification with real-time detection (Table)

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Table

Step	Temperature	Time	Detection	The number of cycles
1	50°C	30 min		1
2	95°C	15 min		1
3	95°C	15 sec		45
	60°C	30 sec	FAM, JOE	
	72°C	15 sec		

8.2.1.6 Rules for sampling clinical materials for coronavirus SARS-CoV-2 infection analysis

For transportation and storage of upper respiratory tract smears, use registered transport media for molecular genetic studies. It is allowed to use test tubes: "Eppendorf" type with a special transport medium for storage and transportation of respiratory smears - 1 pc. Probe-swab for collection, transportation and storage of biological samples - 2 pcs.

Material intake

1. Smears are taken with dry sterile probe-swab
2. The probe is inserted with a light movement along the outer wall of the nasal cavity to a depth of 2-3 cm to the inferior turbinate.
3. Then the probe is slightly lowered downward, inserted into the lower nasal passage under the lower turbinate and removed along the outer wall of the nasal cavity, making rotational movements (3-4 cm in children and 5-6 cm in adults)
4. Break off the end of the probe so that it allows you to tightly close the lid of the tube
5. Close the tube with the solution and the working part of the probe.

A nasopharyngeal smear and an oropharyngeal smear are placed in one tube for a higher concentration of the virus. The sample taken from the subject of the study is accompanied by a direction containing the maximum information about the patient: Surname, name, patronymic of the patient, IIN, age, date of illness, date of collection and symptoms, city, contact with the patient. In a special thermal container with cooling elements or in a thermos at a temperature of +2°C to +8°C no more than 5 days. If a long-term storage is required, the clinical material should be stored at a temperature of minus 70°C or in liquid nitrogen. Only one freeze/thaw of the material is allowed.

9. Evaluation of safety

9.1 List of the safety parameters

As an indicator of the safety profile of the vaccine, the proportion of persons who have been reported to develop adverse events (AEs) in the four following categories will be determined: Immediate adverse events occurring within two hours after each (or single) vaccination and identified both by the medical staff themselves and according to information provided by the vaccinated person to the study staff.

- Post-vaccination reactions (foreseen clinical manifestations of a local and systemic nature), as a rule, observed as a result of intramuscular vaccination and occurring within two hours and the next 6 days after the injection of any dose of the investigational vaccine preparation and identified both by the medical staff themselves and according to information provided by the vaccinated person to the study staff.
- Adverse events (including unforeseen clinical manifestations) that occur within 7 days after the injection of any dose of the study vaccine and identified both by the medical staff themselves and according to information provided by the vaccinated person to the study staff.

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- All serious adverse events (SAE) occurring up to 3 weeks after each (or single) vaccination, and about the end of the study within 6 months after the first vaccination, identified both by the medical staff themselves and according to information provided by the vaccinated person to the study staff. This also takes into account pathological changes in the laboratory analysis of blood and urine samples collected on the 21st, 42nd, 90th and 180th day of the study.

9.2. Methods and time of evaluation, registration, and analysis of safety parameters

9.2.1. Adverse events occurring after administration of the preparation under examination

9.2.1.1. Immediate adverse events

All study subjects will be closely monitored for two hours after study drug injection to monitor their immediate adverse events. At the same time, all drugs that may be required for emergency care in case of rare Anaphylaxis after vaccination should be ready. Evaluation of immediate adverse events will be carried out by the researching physician or specially trained medical personnel. All cases of immediate adverse events that meet SAE criteria must also be recorded on the SAE Record Form.

If any of the research subjects develop immediate adverse events on the first dose of the drug, the researcher-physician may decide, at his/her discretion, to cancel the injection of the second dose of the study vaccine to this person and exclude him/her from the study.

9.2.1.2 Foreseen local and systemic adverse events

During the period of active observation, subjects may develop post-vaccination local and systemic adverse events characteristic of inactivated vaccines. The classification of these specific adverse events (signs and symptoms) will be carried out by the researching physician based on a standardized rating scale for the findings. The assessment of the level of adverse events, where applicable, will be carried out according to a previously developed scale for assessing the degree of functional impairment and the intensity of adverse events. In the absence of the necessary scale, the severity of the adverse event will be assessed by the effect on the functional activity of the vaccinated person's body, as indicated for the assessment of other AEs. The absence of adverse signs or symptoms is also subject to mandatory registration and is classified as a zero-level ("0") adverse event.

Local adverse events

- Pain at the injection site
- Hyperemia
- Infiltrate
- Injection site temperature
- Others

Systemic adverse events

- Increased body temperature (in the armpit)
- Fever/subjective fever
- Cough (specify wet or dry)
- Labored breathing
- Sore throat
- Disorders of consciousness
- Generalized weakness

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- Spasms/cramps
- Fatigue/malaise
- Joint pain
- Muscle pain
- Rash
- Stomach ache
- Diarrhea
- Emesis

Rash

Abdominal pain

Diarrhea

Vomiting

9.2.2. Adverse events (AE) is defined as any undesirable changes in the state of health of a subject or subject of a clinical trial of a pharmaceutical product, which is not necessarily a consequence of the use of a particular drug. Thus, undesirable phenomenon can be any unfavorable and unforeseen sign (including pathological changes in the laboratory data) , a symptom or disease associated in time with the use of a medical product, regardless of the presence or absence of a causal relationship with the specified drug. Medical staff of the research center should identify cases of development of AE at visits of subjects for control medical examination and at interviews with research subjects who applied to the research center for medical assistance.

In each case of detection of AE, it is necessary to indicate the characteristics of the clinical manifestations, the date of occurrence, severity which is assessed by the doctor-researcher, relationship with the investigational drug (the assessment of this indicator will be carried out only by specialists of the appropriate qualifications, empowered and timed to resolve symptoms of stabilization of the condition).

Each AE is must be evaluated according subject to a scale of severity and its relationship with administered vaccine.

The severity of the adverse event: doctor researcher will assess the severity of all adverse events, including pathological changes in laboratory data in accordance with the gradation established by the protocol. This protocol provides for the use of the US Food and Drug Administration (FDA) Guidelines for the Toxicity Assessment Scale for Healthy Adult and Adolescent Subjects Clinical Trials Investigating Prophylactic Vaccines ”(see. Appendix 1 of this protocol), except for the assessment of febrile conditions (see below). The assessment of the intensity of adverse events not included in the specified grading system will be carried out according to the following parameters O = absence: absence of signs or symptoms: health status is normal.

1= Mild: clinical manifestations require minimal treatment or no treatment is needed; there is no effect on the subject's normal daily activities.

2= Moderate: Clinical manifestations lead to mild complaints or to requiring therapeutic intervention. Moderate clinical manifestations have a noticeable effect on the functional state of the research subject.

3 = Severe : clinical manifestations lead to functional impairment and may necessitate systemic drug therapy. Severe adverse events, as a rule, lead to incapacity (disability).

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4 = Threat to life: any adverse clinical manifestations that, in the opinion of the researcher, immediately pose a threat to the life of the research subject at the moment of their development. (AE, the development of which in more severe forms can cause death, is not subject to grading as a threat to life.)

Gradation of febrile states when measuring temperature in the armpit:

0 = absence: <37 ° C

1 = weak: from 37 ° C to 37 ° C

2 = moderate: from 37,6 ° C to 38,5 ° C

3 = severe: from 38,6 ° C to 40 ° C

4 = life-threatening condition: > 40 ° C

Changes in the severity of AE must be recorded to assess the duration of AE at each intensity level. When AE, characterized by the episode, develop, the onset and duration of each intensity should be recorded.

Relationship with investigational drugs: Registration of all results of the assessment of the relationship between AE and the investigational vaccine obtained by the investigator. It is an integral part of the study documentation and the use of these data only as a factor determining the expediency / in expediency of registration of any study information is not allowed.

If there are any doubts at the qualification of the observed clinical manifestations as AEs, this information should be recorded in the research documents. The association of AEs with the vaccine under study should be assessed using the terms "associated" or "dissociated ". In order to use these terms in a correct way, the investigator should follow these guidelines:

Associated AE - Development of adverse symptom is considered to be a tolerable consequence of the study vaccine. A tolerable consequence implies the presence of factors that indicate a relationship between the vaccine under study and the AE.

Dissociated AE - Development of adverse symptoms is not acceptable consequence of the administration of the investigational vaccine. During investigation assessment and recording of all anticipated and unforeseen AEs that have arisen during this period will be carried out. For the sake of clarity, it should be pointed out that undesirable events of an unforeseen type include all adverse clinical manifestations observed by the research staff during the active observation period of the research subject during the visits to the research center, and moreover all cases of AEs recorded by the subjects in the Self-Observation Diaries and identified in the course of interviewing the subject during the collection of medical history for the interim period or on the basis of clinical examination.

9.2.3. Serious Adverse Events

All cases of AE occurring during the study period will be recorded in the subject's IRC. A serious adverse event (SAE) is defined as an adverse event that meets at least one of the following criteria:

- Leads to death.

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- Risk of the death (life-threatening condition) (the term “life-threatening” in the meaning of “serious adverse event” implies that the research subject is at risk of death immediately at the moment of development of this adverse event; this term does not imply AE, as a result of a more severe course of which, hypothetically, a fatal outcome is possible).
- Requirement to the hospitalization
- Lead to the hereditary anomalies / birth defects (only if the study woman became pregnant after receiving at least one dose of the study vaccine. All pregnancies should be monitored throughout the pregnancy, and information on pregnancy outcome should be referred to the Sponsor and appropriate health services).
- Lead to the persistent or significant disability.
- Leading to any other clinically significant changes in the state of health that do not lead to death, do not pose a threat to life, or do not require hospitalization, but at the same time can be regarded as SAE in cases where, on the basis of an appropriate medical report, such conditions can be a risk factor for the health of the research subject or require medical or intervention to prevent one of the possible consequences of SAE listed above (the decision on the appropriateness of reporting on these cases will be made on the basis of a medical opinion). The responsibility of the investigating physician is to review and assess all cases of SAE that occur within three weeks of each (or single) administration of the investigational vaccine product (the relationship of SAE to the administration of the investigational vaccine should be assessed as described in Section 9.2.2), and each case is recorded in SAE accounting form. In all cases of development of SAE, study subjects should also be under medical supervision until the successful resolution of adverse symptoms or the establishment of a stable patient condition by the investigating physician.

9.2.4. Procedures for detecting pathological changes in laboratory analysis

All acceptable limits for normal clinical laboratory parameters should be established in advance, as far as possible. All pathological changes in laboratory parameters are subject to registration as AE, with the exception of data, the severity of detection of which corresponds to level 1 when the subject of the study is included), and there is no further increase in the severity of the identified indicator. Pathological changes in laboratory parameters can be classified as SAE with an increase in the severity of the indicator to level 4. If the subject does not normalize the indicator by the time of the end of the study (180th day), the researcher is obliged to continue medical observation of this person in accordance with the rules reflected in the SOP "Tactics of administration the subject of the study in case of detection of an AE before the end of the study.

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After the end of the study, the investigator must ensure that the person receives all the necessary medical care.

9.3. Procedures for recording and reporting adverse events and intercurrent diseases

9.3.1. Reporting Adverse Events and Serious Adverse Events

The investigator is responsible for ensuring that all AEs are registered in the CRF, both identified by the investigator and based on information from research subjects. At the registration, investigator must indicate the following parameters:

- Diagnosis or syndrome (s) of AEs (if the development of AEs is established, the presence of signs or symptoms, if not established);
- Date of onset and cessation of manifestations
- Degree of severity;
- Assessment of the relationship with study drug administration;
- Action taken.

The researcher may be asked to provide information on the course of treatment, medical report data and an extract from the medical history or CRF . In the assessment of the relationship of an adverse reaction with the administration of the study drug, the investigator should determine whether the severity of the adverse reaction is sufficient to terminate the subject's participation in the study. The research subject may also voluntarily terminate participation in the research in the event that she (he) made an independent decision about the individual intolerance of the manifestations that have arisen. In case of this occurrence, there is a need to recommend the subject of the study to undergo a control examination at the end of the study (180th day) and to be under medical supervision until the disappearance of adverse symptoms or recover the stable state of health.

The collection and registration of data on SAE cases will be carried out throughout the entire period of the clinical study, starting with the signing of an informed consent to participate in any of these situations, it is urgently necessary to study.

All SAEs, recorded in the Case Report must be submitted to the study sponsor within 24 hours of the discovery or notification of the event. The initial data on the presence of a serious adverse reaction, as well as all changes and additions, must be recorded on the Serious Adverse Reaction Form and sent by fax to the sponsor. The original copy of the DSS Accounting Form, as well as the document confirming the receipt of the fax, should be kept in the researcher's documents.

All deaths, all autopsy reports and associated medical reports must be faxed to the sponsor. To draw up these reporting materials, control examination of the health status of the research subjects must be carried out 30 days or longer after the administration of the last dose of the investigational drug.

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In accordance with the international rules for the registration of a serious adverse reactions, information on the progress of the study in research subjects in whom the development of a serious investigational drug was revealed, which is provided by the researcher to the expert organization and to the Central Commission on Bioethics of the Ministry of Health of the Republic of Kazakhstan, will be open in nature. Further prediction will be based on the documentation prepared by the researcher. After receiving data on the completed DSS, the study sponsor can contact the researcher directly by telephone to obtain any missing, clarifying or additional information.

9.3.2. Medical observation and reporting of adverse events and serious adverse events

In the event of any new significant medical information, relevant data should be provided urgently. This type of information includes, for instance, the appearance of new adverse reaction (s), a change in the qualification of a drug or the occurrence of updated information, that indicates to the need to change the medical interpretation of the observed case of SAE. A change in the causation score to a higher or lower level of the corresponding scale or severity of SAE should also be sent urgently. All results of medical supervision must be sent to the sponsor. Medical surveillance data related to SAEs that have already been reported must also be sent to the sponsor within 24 hours of receipt.

Medical observation data must also be provided in the Serious Adverse Reaction Record Form, noting that this is a treatment report and faxing it to the sponsor. In all cases, the development of a specific SAE in the research subject participating in the research must be orally notified to the above-mentioned specialists of the clinical center.

9.3.3. Suspected Unexpected Serious Adverse Event (SUSAE) Cases Reporting Suspected

Unexpected Serious Adverse Events are defined as SAEs that are not anticipated to occur in the clinical research product information document (Investigator's Brochure).

After identification of the SUSAE, within 24 hours, the researcher is obliged to send the corresponding report to the sponsor by electronic communication in a closed mode. The occurrence of SUSAE must be registered in the SOS Registration Form. The investigator must also register the SUSAE with the CRF.

Notifications of cases of suspected unforeseen SAEs (SUSAE) are sent to the expert organization and the Central Commission on Bioethics of the Ministry of Health of the Republic of Kazakhstan in the form according to Appendix 11 of the Order of the Ministry of Health of the Republic of Kazakhstan dated April 2, 2018 N142 (with amendments and additions as of 06/01/2020) "On approval of the Rules for conducting preclinical (nonclinical) studies, clinical trials, clinical and laboratory tests of medical devices for in vitro diagnostics, as well as requirements for preclinical and clinical bases" "and issuance of an authorization to conduct a clinical research and trial or treating of pharmacological and medical devices".

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9.3.4. Method and duration of observation of subjects after the adverse events occurrence

All research subjects who discontinue participation in a clinical trial will have the right to visit during the entire duration of the study (180 days) in the case of an adverse event or due to the appearance of any symptoms, posing a threat to life (changes in vital signs or in the results of laboratory parameters)

10. Assessment of the safety and efficacy of the investigational drug in laboratory tests

10.1. Assessment of clinical indicators

10.1.1. Definition and classification of adverse events

The secondary objective for this clinical study is to assess the safety of double intramuscular administration of the QazCovid-in vaccine - inactivated vaccine against COVID-19.

Clinical and laboratory parameters that must be assessed to characterize the safety of the drug are listed below. The clinical safety parameters of the drug must be assessed by qualified medical personnel or noted by the subject himself.

10.1.2. Specific clinical signs and symptoms of particular importance

All clinical signs and symptoms should be documented. Nonetheless, the signs and symptoms listed below, as well as the date and time of their onset / onset and resolution, will be identified and recorded for all subjects from the moment of signing the Informed Consent until the end of their participation in the study:

- Pain at the injection site
- Hyperemia
- Infiltrate
- Temperature at the injection site
- Fever / subjective feeling of fever
- Chills
- Cough (specify wet or dry)
- Difficulty breathing
- Sore throat
- Headache
- Confused consciousness
- General weakness
- Spasms / convulsions
- Fatigue / malaise
- Joint pain
- Muscle pain
- Rash
- Abdominal pain
- Diarrhea
- Vomiting

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Clinical assessment by medical staff will be carried out on the Day of vaccination, as well as daily by phone on Days 1-7, 21-27, and at the reception on the 42nd day, 90th day and control for 180- th day of the study. Clinical assessment should be carried out both before and after the administration of the study vaccine or placebo on Day 1 and Day 21. Between 8th and 20th, 28th and 41st, research subjects maintain a self-observation diary and on the 43rd to 89th and from 91st to 179th days of the study, the subject independently monitors his state of the health, in addition, the researchers will make weekly calls to the study subject, whereby it will be explained that in case of appearance of COVID-19 symptoms and further developing any AE, requiring medical attention, there is a need to inform the investigator as soon as possible and seek the necessary medical aid.

10.1.3. Anamnesis

On the first day of the clinical investigation, an anamnesis is taken of the subject's medical conditions and any medications he is currently receiving. All the necessary information about the past diseases and existing at the time of the beginning of the study, and demographic data are recorded in the primary documentation of the subject, and further transferred to the Individual Registration Card (IRC).

10.1.4. Physical examination

Physical examination of the research subjects is carried out by a qualified medical researcher and includes:

- Description of the general appearance of the research subject
- Physical examination of all organs and systems, as well as measurement of the following physiological parameters: height
weight
body temperature (measurement site)
blood pressure
pulse / heart rate
respiratory rate

Physical examination will be performed by the medical staff on Vaccination Day (Study Day 1) and on Days 21, 42, 90 and 180 of Study Day. On Study Day 1, the physical examination should be assessed prior to administration of the dose of the study vaccine.

10.2. Evaluation of laboratory parameters and biological samples

10.2.1. Detection of antibodies to chronic viral infections

Blood samples for HIV status, hepatitis B, C are not carried out for screening but only as a starting point before vaccination and will be carried out using test systems certified in the Republic of Kazakhstan.

- Antibodies to human immunodeficiency virus (HIV) (ELISA) .
- Surface antigen of hepatitis B virus HBV (HBsAg) (ELISA).
- Antibodies to hepatitis C virus (HCV) using a qualitative analysis (ELISA)
- IgM and IgG antibodies to SARS-CoV-2 (IHA).

In this case, the presence of IgM and IgG antibodies to SARS-CoV-2 detected before vaccination by the IHA method serves as a criterion excluding a clinical trial study subject into the phase III.

Participants with unknown HIV status, hepatitis B, C who have been immunized and subsequently tested positive for HIV will receive doctor counseling and will continue to be

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monitored as part of the study. All study participants, including those with unknown HIV status, will be closely monitored for SAEs and symptoms of disease.

Evaluation of the results of serological tests for the presence of chronic viral infections

Serological testing		
HIV	positive	negative
Hepatitis B	positive	negative
Hepatitis C	positive	negative
COVID-19	positive	negative

10.3. Blood samples

Blood sampling is carried out with the aim to conduct a large number of different studies. The blood serum will be used to determine the biochemical parameters, antibodies to HIV, HBV, HCV, COVID-19, setting pH

10.3.1. Blood sampling

In accordance with general safety requirements, blood sampling will be carried out by venipuncture of the forearm into special vacuum tubes. Blood for biochemical analysis, detection of antibodies to chronic viral infections, and determination of anti-coronavirus antibodies should be collected in appropriate tubes for serum separation. Clinical blood in whole blood collection tubes containing potassium EDTA or any other suitable anticoagulant. Until further processing, the blood must remain at room temperature (+ 18 ° C - + 25 ° C). The blood volumes required for various studies, the type of tube and sample collection time are shown in the following table:

Table 5-Blood volumes required for various studies

<i>Analysis name</i>	<i>Tube type</i>	<i>Blood volume</i>	<i>Screening day and 1st day(before vaccination)</i>	<i>21st day</i>	<i>42nd day</i>	<i>90th day</i>	<i>180th day</i>
<i>Clinical blood test with determination of leukocyte formula</i>	<i>anticoagulant</i>	<i>Tube 3 ml</i>	✓	✓	✓	✓	✓

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<i>Biochemical Blood Analysis</i>	<i>for serum separation</i>	<i>Tube 3 ml</i>	✓	✓	✓	✓	✓
<i>Detection of antibodies and antigens to chronic viral infections(HIV, HBV, HCV) and COVID-19</i>	<i>for serum separation</i>	<i>Tube 5 ml</i>	✓				
<i>Whole blood for determination of humoral immunity</i>	<i>for serum separation</i>	<i>Tube 7 ml</i>	✓	✓	✓	✓	✓

10.4. Pregnancy test

In order to detect / confirm pregnancy in a woman, a qualitative determination of human chorionic gonadotropin (HCG) will be performed in morning urine samples. Qualitative analysis will be carried out to determine the hCG hormone in the blood on test strips, the results data will be recorded in a separate document with signatures of the doctors and the subject of the study himself.

Urine samples will be collected on Study Days 1, 21 and 180. The test results of the examined research subjects should be obtained before the introduction of the investigational vaccine or before the end of participation in a clinical trial.

10.5. Biochemical blood test

Blood samples will be analyzed using test systems certified in the Republic of Kazakhstan on an automatic biochemical analyzer according to the following parameters:

- Glucose
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total protein
- Urea
- Creatinine
- Alkaline phosphatase
- Total bilirubin
- Direct bilirubin

Blood samples will be taken in one day in all study subjects on study days 21, 42, 90 and 180. Immediately after blood collection, the sample should be gently inverted 5 times, labeled (subject number, date, sample number) and placed upright at room temperature to clot for at

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least 30 minutes before being transported to the laboratory of the clinical trial center. In the laboratory, all samples will be centrifuged for 10 minutes at 3000 rpm.

Ranges of normal laboratory biochemical parameters of blood, according to the order of the Ministry of Health of the Russian Federation of 14.09.2001 N 364 (as amended on 06.06.2008) "On approval of the procedure for medical examination of a donor of blood and its components"

Indicators	Normal Vlaue	Measurement units
Glucose	3,88-6,1	μmol / L
Alanine aminotransferase (ALT)	up to 50	IU/l
Aspartate aminotransferase (AST)	up to 50	IU/l
Total protein	60-80	g/l
Urea	3,33-8,32	mmol/l
Creatinine	53,0-106,1	μmol / L
Alkaline phosphatase	50-250	IU/l
Total bilirubin	1,7-20,5	μmol / L
Direct bilirubin	0,4-4,3	μmol / L

10.6. Clinical blood test with determination of leukocyte formula

Blood samples will be tested using test systems certified in the Republic of Kazakhstan for the presence of the following indicators:

- Total number of leukocytes, determination of the leukocytes formula(percentage of neutrophils, eosinophils, lymphocytes, monocytes)
- RBC
- Hemoglobin level
- ESR

Blood samples will be collected in one day from all subjects on study days 21, 42, 90 and 180. Immediately after blood collection, the sample should be carefully inverted 7-8 times, marked (subject number, date, sample number) and immediately transferred to the laboratory of the Clinical Research Center for analysis.

Whole blood for a clinical blood test with the definition of a leukocyte formula cannot be separated.

The ranges of normal laboratory biochemical blood parameters have been established according to the order of the Ministry of Health of the Russian Federation dated September 14, 2001 N 364 (as amended on June 6, 2008) "On approval of the procedure for medical examination of a donor of blood and its components."

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Components, elements	Normal Value	Measurement units
Hemoglobin	m 130-16- f 120-140	g/l
Erythrocytes	m 4,0-5,0 f 3,9-4,7	10 ¹² /l
Hematocrit	30,0-46,0	%
Platelets	150,0-400,0	10 ⁹ /l
WBC	4,0-9,0	10 ⁹ /l
Band neutrophils	1-4	%
Segmented neutrophils	47-72	%
Eosinophils	0,5-5,0	%
Basophils	0-1	%
Monocytes	2-9	%
Lymphocytes	18-40	%
ESR	m 2-10 f 2-15	mm/h

10.7. Urinalysis

Midstream specimen of urine samples will be evaluated for the following criteria:

- pH
- Urine specific gravity
- Protein
- Glucose
- Leukocytes
- Erythrocytes
- Epithelium

Urine samples will be collected on one day of the study from all subjects on days 21, 42, 90 and 180 research.

Components, elements	Normal value
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Protein	absent, up to 0.033 g / l
Glucose	absent, up to 0.8 mmol / l
Erythrocytes	up to 3 in the field of view for women ----- single in the field of view for men
WBC	up to 3 in the field of view for women ----- up to 6 in the field of vision for men
Urine specific gravity	within 1012 g / l-1022 g / l
pH	more than 4 and less than 7
Epithelium	up to 10 in the field of vision

11. Statistical aspects of clinical research

11.1. Descriptions of the statistical methods which is predicted to be used, including the timing of each planned interim analysis

Given the exploratory nature, statistical analysis will be carried out by descriptive methods without formally testing statistical hypotheses.

Descriptive statistics will be presented for all demographic and other baseline characteristics, immunogenicity and safety indicators, and their changes (if applicable) during the clinical trial by time points of assessment and by treatment groups. Results will be presented for the following therapeutic groups: Vaccine group and placebo group in study subjects aged 18 and over.

Descriptive statistics for quantitative variables will include mean, standard deviation (SD), minimum and maximum values, and number of valid observations. For quantitative measures of immunogenicity, descriptive statistics will also include geometric mean. Qualitative indicators will be presented in the form of frequencies and percentages. 95% confidence intervals around the point estimate will also be presented (where applicable).

For undefined values, the following algorithm will be applied when calculating the geometric mean antibody titer, the fold increase in the geometric mean antibody titer and the seroconversion level: 1) if the antibody level is below the lower quantification level, half of the lower level will be used, 2) if the antibody level is above the maximum level of detection, the maximum dilution will be used.

11.2. Planned number of subjects. In the case of multicenter studies, the planned number of subjects in each center is determined. Justification of the sample size, including explanations or calculations to justify the statistical power of the study and the clinical rationale of the study

11.2.1. Populations for statistical analysis

Data analysis is carried out in the following populations:

Population of randomized subjects. Population of randomized subjects - consists of subjects who have undergone the procedure of randomization and assigned to one of the study groups. The population will be used to represent the disposition of the subjects.

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Security population. The population will include all randomized subjects to receive at least one dose of the vaccine. All safety analysis will be performed on this population of subjects.

Full data set (Full Analysis Set, FAS). The dataset will include all subjects in the safety population who have at least one serum antibody titer measurement. This population will be used for analysis of immunogenicity data.

Population under the Protocol. The population will include all subjects of the Full Dataset meeting the inclusion / exclusion criteria, who received vaccine doses according to randomization, who provided pre- and post-vaccination data to assess immunogenicity according to the clinical trial design, who did not receive illicit drugs and who completed the study without significant deviations. from the Protocol (PP). This population will be used for the analysis of immunogenicity indicators.

11.2.2. Planned number of subjects

Phase III clinical trial QazCovid-in® - a vaccine inactivated against COVID-19, it is planned to recruit 3,000 healthy subjects aged 18 years and older, a man and a woman, who will be randomized at a 1: 4 ratio for the study drug (2,400 people) and placebo (600 people) with two vaccinations on the 1st and 21st days of the study.

3000 research subjects will be distributed across three clinical sites, with approximately 1000 subjects per clinical site.

11.2.3. Security analysis

The following data will be used in the immunogenicity analysis:

- Content of virus-specific serum IgG and IgM antibodies to SARS-CoV-2 according to ELISA data.
- Content of serum neutralizing antibodies to SARS-CoV-2 virus in the neutralization reaction (PH).
- The level of intracellular cytokine production by antigen-activated T-lymphocytes using flow cytometry.

The following immunogenicity indices will be reported at two-sided 95% confidence intervals by treatment group:

Before and after vaccination (after each dose of study drug):

- Geometric mean values of antibody titers (GTA).
- Level (%) of CD4 + and CD8 + T-cells producing IFN- γ .

After vaccination (after each dose of study drug):

- The proportion of persons with seroconversion (increase in antibody titer by 100 or more times).
- The multiplicity of increase in the mean geometric titer of serum antibodies in comparison with the initial values before vaccination (the ratio of CGTA after and before vaccination).
- Significant increase in post-vaccination level (%) of CD4 + and CD8 + T-cells producing IFN- γ (more than 2 standard deviations from the mean pre-vaccination level).

The fold increase in the geometric mean antibody titer from baseline values before vaccination and the corresponding 95% confidence interval will be estimated based on the logarithmic transformation of the data.

Immunogenicity values will be assessed on the basis of the available data, without the restoration of missing values.

11.2.4. Immunogenicity analysis

The following data will be used in the immunogenicity analysis:

- Content of virus-specific serum IgG antibodies to SARS-CoV-2 according to ELISA data.

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The following immunogenicity indices will be reported at two-sided 95% confidence intervals by treatment group:

Before vaccination and after vaccination (after the introduction of each day study drug):

- Geometric mean values of antibody titers (GTA).

After vaccination (after each dose of study drug):

- The proportion of persons with seroconversion (increase in antibody titer by 100 or more times).
- The multiplicity of increase in the mean geometric titer of serum antibodies in comparison with the initial values before vaccination (the ratio of CGTA after and before vaccination).
- The fold increase in the geometric mean antibody titer from baseline before vaccination and the corresponding 95% confidence interval will be estimated based on the log transformation of the data.

Immunogenicity values will be assessed on the basis of the available data, without the restoration of missing values.

11.2.5. Sample size justification

In this clinical study, the enrollment and randomization for Phase III of 3000 healthy study subjects is contemplated to be assigned to two groups for vaccine administration (2400 subjects) and placebo (600 subjects). To include this number of subjects, it is planned to screen about 7000-8000 people.

The required sample size for solving the primary task of assessing the preventive efficacy of a vaccine preparation was established in accordance with the criteria for assessing the epidemiological situation for COVID-19 coronavirus infection.

11.3. Applied significance level

The section is not applicable. Statistical analysis will be carried out by descriptive methods without formal testing of statistical hypotheses.

11.4. Study Discontinuation Criteria

There are no statistical criteria for termination of the study.

11.5. Accounting procedures for missing, unanalyzed and falsified data

Statistical analysis of all data obtained during the solution of the primary task of assessing the safety of the vaccine, and the conclusions made on their basis will be performed in accordance with the principle of "Intention-to-Treat Analysis" - accounting for the entire contingent of included volunteers, regardless of the randomization to the group of the studied vaccine or placebo. The protocol analysis will be performed for all study participants who received the study vaccine or placebo once or twice and completely completed the examination procedures foreseen for the follow-up visit on Study Day 180.

When assessing the safety and immunogenicity of the QazCovid-in® - inactivated vaccine against COVID-19 clinical trial, the registration of questionable data will be carried out using special statistical tests. To demonstrate the presence of such observations, graphs of individual standardized differences (centered on the mean and normalized to the standard deviation) are provided. Outstanding observations may not be considered when evaluating safety and immunogenicity, provided that it is proven to be reasonable to exclude these findings. Missing volunteer data and non-analyzable indicators will not be included in the final report.

Confirmation of the statistical significance of the found intergroup differences will be carried out using the Mann-Whitney test with an acceptable level of significance $p < 0.05$. The paired Wilcoxon test will be used to confirm intragroup differences before and after vaccination. To

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compare categorical paired and non-paired data, the exact McNemer and Fisher tests, respectively, will be applied. The statistical significance of the differences will be assessed using the GraphPad Prizm computer program (version 6.0).

11.6. Procedures for reporting any deviations from the original statistical plan (all deviations from the original statistical plan are described and justified in the protocol and / or the final study report)

The decision to change the statistical plan reflected in this Protocol is made with the consent of the Sponsor.

All changes in the original statistical plan with their justification are reflected in the Clinical Study Report.

11.7. Principle of selection of subjects for analysis

Research subjects to participate in a clinical trial will need to undergo a screening procedure prior to being included in a trial to assess the prophylactic efficacy, safety and immunogenic activity of the vaccine. An informed consent will be signed by the subject to participate in the vaccine evaluation and medical follow-up study. Then, a screening examination of each study subject will be carried out, including a set of different procedures, collection of medical history, ECG and physical examination, and subjects only seronegative for the SARS-CoV-2 virus will be included in the study. Each research subject participating in the screening survey will be assigned a four-digit screening number. To select the required number of SARS-CoV-2 seronegative subjects, it is planned to examine about 7000-8000 people for a phase III clinical study. The screening results will determine the suitability of the research subject for participation in the research. If a healthy subject is considered eligible for participation in the study and meets all the criteria for inclusion in the study:

1. Availability of signed and dated informed consent of the subject to participate in the study.
2. Healthy male and female subjects aged 18 and over.
3. Ability and voluntary willingness to carry out all the visits provided for in the study for follow-up medical supervision.
4. Volunteer willingness to use methods of reliable contraception throughout the entire period of his participation in the study.
5. Negative results for antibodies IgM, IgG to SARS-CoV-2.
6. No history of COVID-19 coronavirus infection.
7. Lack of close contact in the last 14 days with persons suspected of being infected with SARS-CoV-2, or persons who have a laboratory-confirmed diagnosis of coronavirus infection COVID-19.

An informed consent will be signed by the subject to participate in the vaccine evaluation and medical follow-up study.

12. Direct access to primary data (documentation)

Prior to the start of the study, it will be determined and recorded which documents or fields for recording or data entry completed by the researchers will be considered as source documents. The source documents for this study may be outpatient and inpatient records, laboratory test forms, questionnaires, Self-observation diaries and Sample collection logs. For some data fields, the source document may be a KFM. Fields for recording / entering data in the KFM, for which there is a separate source document, will be carefully filled in with the name of the source document.

Only authorized research personnel and oversight representatives of the Central Bioethics Commission and relevant regulatory authorities can have direct access to the original research

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data. The identification of the research subject is available to the above persons only if necessary.

13. Quality control and quality assurance

The study will be conducted in accordance with the procedures outlined in the protocol. It is the responsibility of the investigator to monitor the subjects' strict adherence to the schedule of visits for the follow-up medical examination and all examination procedures without violating the intervals established between them.

For the personnel participating in the study, special data collection forms will be developed, which will also provide a place for recording all actually performed manipulations (even if these manipulations do not require data registration) in the required sequence. All personnel participating in a study must have completed mandatory training prior to commencing the study.

All researchers will have a specialized education, high professional training and experience of participation in Clinical Research for at least 5 years, allowing them to take responsibility for the proper conduct of the clinical research. Researchers' qualifications will be in compliance with regulatory requirements, and confirmed by their scientific biographies (CV, Curriculum Vitae), postgraduate certificates and GCP certificates, all documents will be submitted to the Research Sponsor and the Central Commission on Bioethics. Investigators will be thoroughly familiarized with the use of the investigational product in accordance with the Protocol, the current Investigator's Brochure, product information and other Research documents provided by the Sponsor.

The clinical center will be monitored to confirm that the rights of the research subject are respected and that the research procedures are in accordance with the protocol, including administration of the investigational vaccine, obtaining clinical data and collection of biological samples.

This clinical trial will be monitored by a suitably qualified trial monitor. The project monitor, whose responsibility is to visit the researchers at the start of the study and at the end of it, and periodically during the course of the study to assess the progress of the study, will perform its functions in the framework of joint working contacts with the researcher. The volume, nature and frequency of these visits will be determined by the objectives of the clinical study, the structure and complexity of the study, as well as the size of the contingent included in the study; the frequency and nature of control actions will be described in the Clinical Study Monitoring Plan. The sponsor may also involve representatives of the N.N. A.A. Smorodintsev of the Ministry of Health of the Russian Federation in all cases of interaction with the research center and monitoring visits in the prescribed manner.

13.1.1. Study readiness control visit

The Study Monitor and / or Sponsor's representatives will visit the Study Center prior to the study start to discuss the study protocol and clinical specimen collection procedures with the Center staff. Before the start of the procedure for selecting subjects for the study, all the necessary regulatory documents must be in place, including the permission of the Central Commission on Bioethics of the Ministry of Health of the Republic of Kazakhstan. Also, a Curriculum vitae (Summary) of the clinical investigator in charge must be prepared. If it is necessary to submit any additional documents, the Sponsor will inform the researchers about it.

13.1.2. Study monitoring visits

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Monitoring will be carried out during a clinical trial, if quarantine measures are taken in connection with a pandemic on the territory of the Republic of Kazakhstan, monitoring will be carried out online. All documents will be forwarded to the e-mail addresses of the monitors.

The personnel responsible for monitoring the study will periodically monitor the progress of the study and should have access to all necessary data to ensure that the study is ethical and safe, and that the data recorded is reliable / valid.

During follow-up visits and contacts, the monitor should:

- Check and evaluate the progress of the research.
- Conduct an analysis of the data collected during the study.
- Verify the initial data.

• Check the correctness of filling in the KFM for all research subjects, in order to ensure the completeness of the data indicated in the KFM and their compliance with the records in the primary documents, as well as the research protocol.

- Verify compliance with the instructions for storage and use of the investigational drug.
- Check the regulatory (normative) files (documents).
- Identify any unresolved issues (problems) and suggest ways to solve them.

The purpose of the follow-up visit is to ensure that:

- Data is true, accurate and complete.
- The safety of research subjects and the observance of their rights are ensured.
- The study is performed in accordance with the approved protocol (including all subsequent amendments) and all relevant regulatory requirements.

As part of a clinical trial, the Principal Investigator agrees to provide the Monitor or Sponsor's representative with direct access to all documents related to the study, and sets aside time (his and the study staff) to discuss with the Monitor the test results and other issues (issues identified) related to the study. to research.

The Principal Investigator also agrees that representatives of the N.N. A.A. Smorodintsev of the Ministry of Health of the Russian Federation, if necessary, can be present during the visit of the current control.

13.1.3. Control visit at the end of the study

Upon completion of the clinical investigation, the Sponsor's Monitor or Representative, in conjunction with the Investigator, should:

- Refinement and / or analysis of data.
- Counting, reconciliation and disposal of used and unused vaccine vials at the research center.
- Checking the completeness of the study documentation.
- Transfer of all research data to the Research Sponsor.

Sponsor reserves the right to temporarily suspend or prematurely terminate this study at any time for reasons related to the safety of the investigational drug. In the event that a study is discontinued or temporarily suspended, the Sponsor will inform the center's principal investigator and regulatory authorities of the decision made and the reasons for stopping or discontinuing the study. The Principal Investigator assists the Sponsor in providing relevant information to the Monitoring Ethics Commission of the Ministry of Health of the Republic of Kazakhstan, indicating the reasons for the suspension or termination of the study. In the event of early termination of the study or closure of the study center, the monitor or the Sponsor's representative will take all the actions specified above.

13.2. Audit and inspection

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In addition to the scheduled monitoring checks, which are described above, audits carried out by other representatives of the sponsor are possible, or inspections by any official authorities that have expressed such a desire (even after the end of the study).

Within the framework of such a visit, the same activities can be carried out as during the monitoring visit, and the data can be re-checked, the control of which has already been carried out by the permanent monitor.

In the event of a request for inspection by a notified body, the investigator should immediately inform the study sponsor.

13.3. Protocol amendments

Any changes or additions to this protocol must be in the form of a written amendment, which must be approved by the sponsor and the investigator prior to the entry into force of these changes and additions.

If the change affects the safety of research subjects, the volume or quality of clinical trials (significant amendments), an official permission of the Central Commission on Bioethics of the Ministry of Health of the Republic of Kazakhstan and the authorized body is required. A copy of the Ethics Commission's written permission must be provided to the Sponsor.

The list of changes that require the issuance of an appropriate permit:

- increasing the dose of the drug used in the study;
- significant changes to the study design (eg use of an additional control group or cancellation of a previously approved control group);
- an increase in the number of invasive procedures used in research subjects;
- use of additional procedures or withdrawal of previously approved procedures for monitoring the safety of the study.

Once approved by the Ethics Commission, the change becomes an integral part of the protocol.

Amendments to the protocol that do not require permission from the Ethics Commission or an expert organization, these structures must be informed without fail.

The above requirements are not intended to prevent the investigator or sponsor from taking urgent action in the interests of the safety of the research subject. If the investigator makes such an emergency change in the protocol, it is necessary to urgently notify the sponsor. Any changes that the researcher qualifies as necessary or desirable, for example, changing the timing of blood sampling, days of observation, the choice of additional parameters, must be made in writing.

13.4. Deviations from the protocol

A protocol deviation is any non-adherence to the clinical trial protocol, GCP, or the Study Procedure Guidelines approved by the study center. Failure to comply with the protocol may be due to the fault of the research subject, investigator, or research personnel. In case of violation of the protocol, the staff of the research center should take all possible measures aimed at correcting this violation. Examples of protocol deviations:

- Irregular or inappropriate use of the investigational drug.
- Unreasonable repetition of any planned procedures or analyzes.
- Changing the intervals between two visits or procedures in excess of the time stipulated in the protocol.
- Incorrect or negligent maintenance of primary documents on research procedures, corresponding forms and journals or CRFs.
- Early termination by the subject of participation in the study, regardless of the reason.

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Changes to research procedures are unacceptable without the consent of the Sponsor. Minor discrepancies with the protocol will be dealt with on a case-by-case basis, taking into account the recorded information on the reason (s) for the changes made.

It is the responsibility of the research center staff to carefully monitor the occurrence of any deviations from the protocol and to promptly notify the Sponsor of such cases.

14. Ethical aspects

14.1. Ethics and Criteria for Good Clinical Practice

The study will be conducted in accordance with the provisions of the latest version of the Declaration of Helsinki, national legislation and the requirements of the current Good Clinical Practice (GCP) Guidelines (CPMP / ICH / 135/95), the current legislation of the Republic of Kazakhstan.

14.2. Information leaflet with informed consent form

The researcher must provide each research subject with written information for the subject and explain the nature of the research, its purpose, the methods used, the planned timing and the potential risks and benefits associated with participating in the research, as well as warn about possible adverse health effects. All research subjects will be informed that their personal data will be strictly confidential, however, in order to carry out the research, not only the attending physician, but also other persons vested with the appropriate powers, have the right to check the medical records of each research subject. Participation in the research will be carried out on a paid basis by concluding individual contracts with each research subject.

Each research subject will be informed that his participation in the research is on a voluntary basis, and he may terminate his participation in it at any time. This decision does not prejudice his right to follow-up treatment.

Informed consent must be in writing in a standardized manner. Before signing the document and specifying the date, the subject of the study should be given time to familiarize himself with the provisions of the document and understand their meaning. The original of the document must be signed in duplicate. One signed copy of the original is handed over to the subject of the study. A second copy of the original should be kept in the investigator's documents for the study.

The research subject becomes the subject of examination and clinical research only after signing an informed consent to participate in the clinical research.

14.3. Inclusion of women, minorities and children

Participation in this clinical study is open to healthy adults of any gender, race or ethnicity. No person can be denied participation on the basis of gender or race or ethnicity. However, the researcher should try to recruit an equal number of men and women. Study enrollment will be completed after 3,000 subjects are recognized (based on screening results) as eligible for participation in the study. This clinical trial is open to the participation of only adult men and women aged 18 and over.

Children and adolescents under the age of majority determined by the legislation of the Republic of Kazakhstan cannot participate in this clinical trial.

14.4. Identification and confidentiality of information about subjects

Personal information, including name, date of birth, gender, residence / address, will be collected from each research subject and entered on the research registration cards. However, there is a potential risk of breaching the confidentiality of this information. To avoid this risk, each person included in the study will be assigned a three-digit individual number of the research subject, by which his further identification will take place, and by which, in accordance with the

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list of numbers of research subjects, it will be possible to determine from which person the data was obtained. research and / or biological samples. In all cases, where appropriate, the individual research subject number assigned to each subject will be used instead of personal data. In the Individual Registration Cards (CRC) of the research subject provided to the Sponsor for processing the data obtained, only the individual number of the research subject assigned to him / her will be indicated to identify the subject. The paper records will be kept in a secure location and will only be accessible to authorized and authorized personnel involved in this study. The computer database files will be available to the personnel participating in the study only if they have special clearance and passwords to enter. None of the research reporting documents will use personal data to identify the research subject. With respect to all research data, including personal data of research subjects and the results of their laboratory tests, the research staff will comply with the confidentiality requirements and prohibit their disclosure to persons who do not have the right to access this data.

Identification of biological samples will be carried out only by the individual number of the research subject; the use of personal data for this purpose is not provided. In the same way, when compiling reports on laboratory tests, the research subject will also be indicated only by his individual number. For the study of biological samples, only the methods provided for by this research protocol and approved by the Central Commission on Bioethics of the Ministry of Health of the Republic of Kazakhstan will be used.

14.5. Informing subjects about research results

Each research subject must be notified of, or have access to, all clinical laboratory test results. The results of special laboratory tests (virological and immunological results) are not provided to the research subjects.

Upon completion of the clinical investigation report, the investigator may provide a summary of the study results to the subject. This information can be presented only orally or in the form of general research results. Printed materials containing research results in general cannot be made available to research subjects. The researcher can choose the form for such exchange of information about the research results with the subjects himself or at the request of the Central Commission on Bioethics of the Ministry of Health of the Republic of Kazakhstan.

14.6. Further use of samples, collected during the study

Biological samples will be kept until the end of the clinical study. This is necessary for all analyzes related to the study. Samples will be stored in RIBSP laboratories. The samples do not have any personally identifiable information. Upon completion of the study, all samples will be destroyed unless written consent has been obtained to store the samples of the study subject for up to 20 years for future use. The samples obtained during the study can be extremely valuable sources for the further development of vaccines against the coronavirus. Written informed consent for such long-term storage of samples from any research subject may be requested and obtained after the research subject signs written informed consent to participate in the vaccine trial. If the research subject consents to the long-term storage of their samples, then only samples collected after the screening procedure can be stored for later use.

However, these samples will not be used for further research unrelated to this study, without appropriate ethical examination, approval of the Central Bioethics Commission of the MH of the RK and the consent of the research subject, if any Ethics Commission / Committee deems it necessary.

15. Work with data and record keeping

15.1. Obligations for data processing

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The researcher guarantees the accuracy, completeness, accuracy (legibility) and timeliness of the data provided. Data collection is the responsibility of the clinical trial staff at the research center under the supervision of the principal investigator.

Each case of AE should be classified, including an assessment of severity and relationship with the investigational drug, and reviewed by the Principal Investigator or designated person.

15.2. Data collection methods

This clinical trial will use a unified electronic data collection (EDC) system across all clinical sites. Each clinical site must ensure that its research team is well trained in the ESD system. It is possible to maintain completely paper documentation.

All information the receipt of which is stipulated by the research protocol is subject to registration in the CRF provided by the sponsor. The CRF will also be filled in in a unified data system or in writing. All entries should be made legibly in accordance with the “Guidelines for Completing a CRF. Any data transfer must be accompanied by an explanation. All records in source documents and CRFs must be made accurately and legibly to ensure accurate interpretation of the recorded data. Black ink must be used for recordings to ensure legibility of reproducible copies. The original entry should be crossed out with a single line, when making changes or amendments, and the date of the change and the initials of the employee who made them should be indicated next to it. ERASURE OF ALL THE ORIGINAL RECORDS, WRITING OVER THE ORIGINAL RECORDS, USING OF CORRECTIVE FLUID OR PRINTING CHANGES IS NOT ALLOWED IN NO CASE. All initial documents and answers about laboratory research should be carefully checked by the executors of clinical and laboratory studies, who must certify the accuracy and completeness of the information entered.

Each CRF must be certified by the signature of the researcher with the date, confirming his responsibility for the quality of all specified data and certifying that all the data provided are reliable and fully reflect all stages of the subject's participation in the study.

Clinical safety data and all laboratory data (virological and immunological) will be transferred to the CRF from the laboratory test report forms. Dates of visits for follow-up examinations and laboratory procedures will be indicated on all forms. Each subject, when included in the study, will be assigned an individual research subject number - this number will be used in all reports and the research database and will indicate from which particular individual the data was obtained. Entering CRF data into the database, checking their accuracy, identifying the study subject by an individual number and processing the entered data will be carried out using special software for working with databases.

The data obtained during the clinical trial will include biographical information, medical history, clinical data (signs and symptoms, prescribed or not prescribed drug therapy), safety data from the results of physical and laboratory studies (hematological and biochemistry data), virological and immunological laboratory study.

15.3. Deadlines for provision of reports

Upon completion of the collection of analyzes within the period specified in this Protocol (90 and 180 days), the results are processed and analyzed, followed by the preparation of reports (intermediate for 90 days and final for 180 days).

15.4. Storage of the study documentations

All data obtained during the clinical study will be transferred to the Sponsor and stored for 25 years after the end of the clinical study. Destruction of any records without the written consent of the sponsor is not permitted. It is not the sponsor's responsibility to inform the Principal Investigator that it is no longer necessary to keep the records of this clinical study.

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16. Funding

In this clinical study, research subjects are paid a fee. Remuneration is paid only to study subjects included in the clinical study, respectively, after signing an informed consent. Payment will be made in one total amount after 180 days of research within 7 working days. Financial obligations towards the research subjects will be regulated by a separate agreement.

Even in the case of early termination by a study subject from a part in a clinical trial, payment will be made after the end of the study.

17. Insurance

All research subjects participating in a clinical study is guaranteed medical insurance in accordance with the current legislation of the RK during the period of participation in the study. The Principal Investigator is obliged to inform the study subject about the provision of health insurance for him in case of health problems related to this study, as well as explain to the study subject that the implementation of other types of treatment and concomitant therapy during the study *on the basis of the insurance policy* during the period of participation in the study (excluding emergency medical care) is only possible with the permission of the Principal Investigator. The subject of the study will be informed that the insurance company may be in the payment of insurance compensation if the health problems that have arisen are not regarded as related to participation in this study.

18. Publications

18.1. Interim and final report of the study, and rights for publishing study materials

Based on the results of the III phase of the clinical study, the analysis of the results obtained will be carried out and an interim report on the clinical study on the 90th day of the study after the unblinding procedure, and will be drawn up and submitted to the expert organization, and the final report will be drawn up after the final visit of the subjects of the study on the 180th day of the study. The reports will contain text and tables including safety and immunogenicity data. The reports will be reviewed, approved and signed by the principal investigators.

Reports should be drawn up in accordance with the ICH recommendations and in the form of the Order of the MH of the RK dated April 2, 2018 № 142 (with amendments and additions as at 1 June 2020) “On approval of the Rules for conducting preclinical (nonclinical) studies, clinical trials, clinical and laboratory studies of medical devices for in vitro diagnostics, as well as requirements for preclinical and clinical bases” and “Issuance of a permit for conducting a clinical trial and (or) testing of pharmacological and medicinal products, medical devices”. If there are minor discrepancies in these rules and recommendations, the priority remains with the legislation of the Republic of Kazakhstan.

After the preparation of the interim and final reports and their submission, the Sponsor may, at its discretion, publish the results of this study in the peer-reviewed scientific journal(s). It is prohibited to publish any data related to or obtained in the course of the Clinical Study, use the Sponsor's name in any advertising or promotional materials without the prior written consent of Sponsor in relation to the content of materials prepared for publication.

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19. Appendices

Appendix 1

Food and Drug Administration (FDA) Guidance for Industry, September 2017 (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

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Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

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For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

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Contains Nonbinding Recommendations

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I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See,

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for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

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II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed

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during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

The document is advisory in nature

A. Tables of pathological clinical manifestations

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

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Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrythmia
Bradycardia - beats per minute	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/ 24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Some interference with activity or repeated use of non-narcotic pain reliever	Significant, prevents daily activity or repeated use of narcotic pain reliever	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization

Systemic illness	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulation)	No interference with activity	Some interference with activity not requiring medical intervention.	Prevents daily activity and requires medical intervention	ER visit or hospitalization

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B. Tables of pathological changes in laboratory parameters

The laboratory indicators presented in the table are methodological in nature and depend on the parameters of the normal indicators used in the institution where the study is conducted. To demonstrate the compliance of the indicators, the range of indicators of the norm used by the institution should be provided.

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Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mEq/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN” is the upper limit of the normal range.

IV. LITERATURE

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (<http://ctep.cancer.gov/reporting/CTC-3.html>)
2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences, August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)
3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (<http://brightoncollaboration.org/en/index/aeft.html>)
4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences, September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)
5. Division of Microbiology and Infectious Diseases Adult Toxicity Table, May 2001. (<http://www.niaid.nih.gov/dmid/clinresearch/dmidadulttoxtable.doc>)