PROTOCOL SYNOPSIS

Study title		**Post-authorization Phase IV effectiveness and safety multicentric study of COVID-19 vaccines – CoVigi**	
Protocol code	CoVigi	**EudraCT No.**	2021-000566-14
Sponsor		Masaryk University Žerotínovo náměstí 617/9 601 77 Brno	
Investigational medicinal product, dosage forms		COVID-19 vaccines (ATC group J07BX03): • COMIRNATY (dispersion for injection), • COVID-19 Vaccine Moderna (dispersion for injection), • COVID-19 Vaccine VAXZEVRIA (suspension for injection), • COVID-19 Vaccine Janssen (suspension for injection).	
Route of administration		Intramuscular use	
Phase		IV	
Purpose of clinical trial		Purpose of the trial is to evaluate the efficacy (including immune response) and safety of registered vaccines that are indicated to prevent undergoing the disease caused by SARS-CoV-2 virus (COVID-19) under real clinical conditions.	
Risks and benefits for the subjects		Subjects will benefit from the study by gaining information about development of the level of antibodies in time which is not commonly being done. Subjects will greatly support research on COVID-19 vaccines. The only risk lays in more numerous bloode draws than is usually being done.	
STUDY OBJECTIVES			
Primary objectives		1) Post-authorization monitoring of adverse events and effects (data collection based on a questionnaire survey and evaluation by study physician) • Severity, expectations, intensity, relationship to vaccination • Nature of adverse event, duration 2) Evaluation of the immune response of vaccinated subjects by determining the level of antibodies and cellular immunity over time 3) Incidence of COVID-19 disease in vaccinated subjects based on information on a positive test for SARS-CoV-2 (clinically symptomatic and asymptomatic disease)	
Exploratory objectives		In a subgroup of cancer patients: • Monitoring and evaluation of objectives and parameters mentioned as primary • Evaluation of the circulating immune profile • Evaluation of objectives and parameters in connection with the type of cancer treatment administered	
STUDY POPULATION			
Definiton of population		Primarily, medical employees of the Hospital Brno and employees of the Masaryk University will be offered to be enrolled in the study, as well as oncological patients with solid tumors. Also, any other volunteer that will be interested will be offered the enrollment.	
Inclusion criteria		1) Age ≥ 18 years 2) Willingness to participate in the study expressed by signing the informed consent form	

	A subject may be included in the cohort of newly enrolled subjects with a fully applied vaccination schedule according to the SmPC if he/she also meets the following criteria: 1) Patient under the care of the Internal Hematology and Oncology Clinic of the University Hospital Brno 2) Planned booster vaccination (3rd dose in the original two-dose regimen, or 2nd dose in the single-dose regimen)
Exclusion critera	1) Pregnancy, breastfeeding 2) Inadequacy of patient classification based on the individual assessment of the study physician
Early withdrawal of patients from the study	• Discontinuation from the study is requested by the patient for any reason, • Discontinuation from the study is requested by the investigator upon medical judgment (for example because of a potentional health risk to the subject), • Lost contact with the subject, • Termination of the study upon decision of the regulatory authorities, ethics commitiee or sponsor.
Number of subjects	565
STUDY DESIGN	
Design	Multicentric prospective open Phase IV clinical study will monitor for adverse events and effects, incidence of COVID-19 disease and evaluation of the immune response of vaccinated subjects. Study is not to be randomized. Indication for vaccination will be deciced upon strategy of the Czech government and Ministry of Health. The vaccination itself may be done at a different place from the one where the study is being executed, as long as the vaccination place is stated in a list made by Czech government and Ministry of Health. Sponsor will not provide the vaccines, those will be provided as described above. Sponsor assumes that vaccination will be done in compliance with SmPC of the individual vaccines.
Study duration	Study will start in February 2021 and enrollment of subjects will last 10 months with a two year follow-up. Anticipated date of final assessment of the study is the end of 2023. For newly emerged cohort, follow-up will last from 0,5 to 1,5 years.
Duration of subject´s involvement in the study	According to the vaccine type – 24 to 25 months for the original cohort and 6 to 18 months for subjects enrolled in the newly emerged cohort.
Statistical methods	The evaluation will use common methods of descriptive statistics according to the nature of the data, i.e. numbers and percentages for categorical characteristics and median and interquartile range (IQR) or average and standard deviation (SD) for continuous characteristics. Comparison of antibody levels and cellular immunity parameters in relation to input values will be performed using a paired t-test or a Wilcoxon test according to the normality assumption. The evaluation will be carried out separately for each subgroup. To compare a subgroup of oncological patients with a subgroup of healthy (without active oncological treatment) individuals, statistical tests such as fisher's accurate test or chi-

	quadrant test for comparison of categorical variables and non-parametric Mann-Whitney test or Kruskal-Wallis test for comparison of continuous variables or their parametric alternatives will be used according to the data type, provided that data normality is met. All statistical tests and confiscation intervals will be calculated at a significance level of 5 %. Information on statistical analyses will be specified in the Statistical Analysis Plan (SAP). SAP will be finalised no later than at the time of closure of the eCRF database. After at least 300 subjects have undertaken visit 4, resp. visit 6, interim analysis will be carried out.

DESIGN OF STUDY VISITS

Visit	1	2	3	4	5	6	7	8
Day	***Day 0*** *0–14 days before 1.dose*[1]	*14–21/28 days after 1. dose*[2]	*28–58 days after 1. dose*[3]	*3 months ± 2 weeks after 1. dose*	*6 months ± 2 weeks after 1. dose*	*12 months ± 2 weeks after 1. dose*	*18 months ± 2 weeks after 1. dose*	*24 months ± 2 weeks after 1. dose*
Informed consent	X							
Demographic data[4]	X							
Personal anamnesis[5]	X							
Concomitant anamnesis[6]	X	X	X	X	X	X	X	X
Type of vaccine administered[7]		X	X	X	X	X	X	
Occurrence of COVID-19[8]	X	X	X	X	X	X	X	X
Blood draw – antibodies[9]	X[10]	X	X	X	X	X	X	X
Blood draw – cellular response[11]	X[10]	X	X	X	X	X	X	X
Blood draw – circulating immune profile[12]	X[10]		X		X			
AE questionnaire[13]		X	X	X				

[1] In case the vaccination and enrollment in the study is planned for the same day, the study interventions of Day 0 including the blood draws must happen before 1. vaccine dose administration
[2] 14–21 days apply for COMIRNATY, if there is 21 days planned between 1. and 2. dose; 14–28 days apply for other cases. Blood draws must take place before administration of the 2. vaccine dose (if not single dose vaccine).
[3] Visit 3 is to take place 7-16 days after 2. vaccine dose, i.e:

- There is 21 days between 1. and 2. dose – date of visit will be 28–37 days after 1. dose,
- There is 28 days between 1. and 2. dose – date of visit will be 35–44 days after 1. dose,
- There is 42 days between 1. and 2. dose – date of visit will be 49–58 days after 1. dose,
- exception: VAXZEVRIA – visit 3 is valid, even though participants will not yet be vaccinated with 2. dose – date of visit will be 35–58 days after 1. dose,
- single dose vaccine – date of visit will be 35–58 days after vaccine dose.
- Visit 2 and 3 can not take place at the same day.

[4] Demographic data – age, sex
[5] Personal anamnesis – chronic comorbidities, allergies, acute diseases, and a performance status in a subgroup of oncological patients
[6] In the general population, a record of any pharmacotherapy; in the subgroup of oncological patients with solid tumors in active treatment, the type and date of administration of anticancer treatment, or changes in treatment and the date of termination of anticancer treatment
[7] Type of vaccine administered – trade name of the medicinal product
[8] Occurence of COVID-19 – anamnestic inquiry for a positive test (PCR, antigenic) for SARS-CoV-2 regardless of the presence of disease symptoms (in the case of Visit 1 it is an inquiry for positivity / past disease), testing for SARS-CoV-2 is not required.
[9] For all participants
[10] Blood draw old no longer than 14 days before vaccination
[11] For all participants
[12] Only for subgroup of oncological patients
[13] Survey (questionnaire is filled out by participant)

DESIGN OF STUDY VISITS (new cohort)

Visit	1	2	3
Day	***Day 0*** *0–5 days before booster*[1]	*18 months* *± 2 weeks after 1. dose*	*24 months* *± 2 weeks after 1. dose*
Informed consent	X		
Demographic data[2]	X		
Anamnesis[3]	X		
Concomitant medication[4]	X	X	X
Type of vaccine administered[5]	X	X	
Occurence of COVID-19[6]	X	X	X
Blood draw – antibodies	X	X	X
Blood draw – cellular response	X	X	X

[1] In case the vaccination and enrollment in the study is planned for the same day, the study interventions of Day 0 including the blood draws must happen before booster dose administration
[2] Demographic data – age, sex
[3] Anamnesis – chronic comorbidities, allergies, acute diseases, and a performance status in a subgroup of oncological patients
[4] In the general population, a record of any pharmacotherapy; in the subgroup of oncological patients with solid tumors in active treatment, the type and date of administration of anticancer treatment, or changes in treatment and the date of termination of anticancer treatment
[5] Type of vaccine administered – trade name of the medicinal product, at visit 1 – basic vaccionation, at visit 2 – *booster*
[6] Occurence of COVID-19 – anamnestic inquiry for a positive test (PCR, antigenic) for SARS-CoV-2 regardless of the presence of disease symptoms (in the case of Visit 1 it is an inquiry for positivity / past disease), testing for SARS-CoV-2 is not required.