COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

This is the third sub-protocol linked to the master protocol entitled **"Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: A master protocol for the set-up of a Swiss Cohorts Based Trial Platform",** the first sub-protocol entitled "**Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: First sub-protocol for a pilot trial comparing the mRNA vaccines Comirnaty® and Covid-19 mRNA Vaccine Moderna®**", (submitted to ethical committee: 15.12.2020, finally approved: 19.04.2021; ID number 2021-000593), and the second sub-protocol "**Randomised controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Second sub-protocol for an observational trial extension comparing additional benefits and potential risks of a third SARS-CoV-2 vaccination with BNT162b2 or mRNA-1273**" (submitted to ethical committee: 24.11.2021, finally approved: 07.12.2021; ID number 2021-000593).

Short title: Immunocompromised Swiss Cohorts Based Trial Platform

Acronym: COVERALL (COrona VaccinE tRiAL pLatform) bivalent

Study Type:	Extension of a clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Category A
Study Registration:	Clinicaltrials.gov: NCT04805125
Study Identifier:	COVERALL
Sponsor, Sponsor-Investigator or Principal Investigator:	University Hospital Basel Benjamin Speich, PhD CLEAR-Methods Center, Division of Clinical Epidemiology, Department of Clinical Research University Hospital Basel Totengässlein 3 4051 Basel Switzerland Phone: +41 (0)61 328 38 19 Email: benjamin.speich@usb.ch
Investigational Product:	Bivalent booster vaccine m-RNA-1273.214 licensed by Moderna and bivalent booster vaccine Comirnaty Original/Omicron BA.4-5 licensed by Pfizer-BioNTech (both applied in the frame of clinical routine and not within this observation study)
Protocol Version and Date:	**Version 1.0; 28.09.2022**

Signature Page(s)

Sponsor-investigator:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	University Hospital Basel CLEAR-Methods Center, Division of Clinical Epidemiology, Department of Clinical Research University Hospital Basel Totengässlein 3 4051 Basel Switzerland
Sponsor-Investigator	Benjamin Speich, PhD

Basel, 28.9.2022 _____

Place/Date Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	Basel HIV Cohort
	Dep. of Infectious Diseases and Hospital Hygiene
	University Hospital Basel
	Petersgraben 4
Principal investigator	Dr. Marcel P. Stoeckle

Place/Date	Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

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COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	Universitätsspital Basel Pneumologie Petersgraben 4 4051 Basel
Principal investigator	Prof Michael Tamm

Basel 28/9/2022

Place/Date Signature

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Local Principal Investigator at study site*:

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COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	Universitätsspital Basel
	Transplantationsimmunologie & Nephrologie
	Petersgraben 4
	4051 Basel
Principal investigator	PD Dr. med. Patrizia Amico

Basel, 28.09.22
Place/Date

Signature

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Local Principal Investigator at study site*:

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COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	Bern HIV Cohort
	Universitätsklinik für Infektiologie
	Freiburgstrasse 16p, Haus 5, Stock E
	3010 Bern
Principal investigator	Dr. Anna Lena Eichenberger

Place/Date	Signature

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Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	Zürich HIV Cohort Klinik für Infektionskrankheiten und Spitalhygiene UniversitätsSpital Zürich Rämistrasse 100 8091 Zürich
Principal investigator	Prof. Huldrych Günthard

Zürich 28th September 2022 H. Günthard

Place/Date Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	Klinik für Nephrologie UniversitätsSpital Zürich Rämistrasse 100 8091 Zürich
Principal investigator	Prof Thomas Müller

Place/Date	Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	Klinik für Pneumologie Universitätsspital Zürich Rämistrasse 100 8091 Zürich
Principal investigator	PD Dr. Macé Schuurmans

Place/Date	Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

COVERALL: third sub-protocol

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Site	CHUV
	Centre de transplantation d'organes
	Rue du Bugnon 46
	1011 Lausanne
Principal investigator	Prof. Oriol Manuel, MD

Place/Date	Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

In the master protocol (submitted to the ethics committee on the 15. December 2020; EC ID 2021-000593) we described the platform and the outline for our pilot trial which randomised patients from the Swiss Transplant Cohort Study (STCS) and the Swiss HIV Cohort Study (SHCS) to the two SARS-CoV-2 vaccines that were first approved in Switzerland. We conducted a first sub-study (as outlined in the first sub-protocol, submitted to the ethical committee on the 15. December 2020; EC ID 2021-000593), that compared head to head the vaccines by Pfizer/Biontech and Moderna.

Thereafter, a third dose of a SARS-CoV-2 vaccine was recommended for the entire population, priorising severely immunodeficient persons. These vaccines were administered to patients from the SHCS and the STCS in the frame of clinical routine. In a second sub-study (as outlined in the second sub-protocol, submitted to the ethical committee on the 24. November 2021; EC ID 2021-000593) we assessed in an observational study the additional benefit of a third SARS-CoV-2 vaccine in these immunocompromised patients 8 weeks after vaccination.

Recently, new adapted bivalent mRNA SARS-CoV-2 vaccines were developed, showing potent neutralizing antibody response against Omicron subvariants in the general population. As a third sub-protocol embedded in our COVERALL trial platform, we propose to conduct an observational study to assess the immunologic response and safety of the bivalent SARS-CoV-2 vaccines among immunocompromised persons (persons living with HIV or kidney or lung transplant recipients).

Table of Contents

ABBREVIATIONS

AE	Adverse Event
BAG	Bundesamt für Gesundheitswesen
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
BOD	Burden of disease
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CI	Confidence Interval
COVERALL	COrona VaccinE tRiAL pLatform
COVID	Corona virus diseases
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
CONSORT	Consolidated Standards of Reporting Trials
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
Elecsys S	Immunoassay Elecsys Anti-SARS-CoV-2 S Roche Test
FDA	Food and drug administration
GCP	Good Clinical Practice
GMT	Geometric mean titers
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HIV	Human Immunodeficiency Virus
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
ICMJE	International Committee of Medical Journal Editors
IFN-γ	Interferon gamma
Ig	Immunoglobulin
IIT	Investigator-initiated Trial
IMP	Investigational Medicinal Product
IMV	Institut für Medizinische Virologie in Zürich
ISO	International Organisation for Standardisation
ITT	Intention to treat
MD	Medical Device
MedDO	Medical Device Ordinance *(in German: MepV, in French: ODim)*

PI	Principal Investigator
RBD	Receptor binding domain
RECORD	REporting of studies Conducted using Observational Routinely-collected Data
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDV	Source Data Verification
SHCS	Swiss HIV Cohort Study
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STCS	Swiss Transplant Cohort Study
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

STUDY SYNOPSIS

Controlled trials to assess approved SARS-CoV-2 vaccines in immunocompromised patients: Third sub-protocol for an observational study comparing benefits and potential risks of the newly approved bivalent SARS-CoV-2 vaccines

Brief Title: Immunocompromised Swiss Cohorts Based Trial Platform,

Acronym: COVERALL (COrona VaccinE tRiAL pLatform) bivalent

Rationale: Since January 12, 2021 two mRNA based vaccines against SARS-CoV-2 by Pfizer-BioNTech (Comirnaty®) and by Moderna (COVID-19 mRNA Vaccine Moderna®) have been licensed in Switzerland and roll-out of vaccines has started.

We have set up a COrona VaccinE tRiAL pLatform (COVERALL) nested into the existing prospectively collected data structure of the Swiss HIV Cohort Study (SHCS) and the Swiss Transplant Cohort Study (STCS). Within the frame of a first sub-study (see first sub-protocol) we have assessed in a head-to-head comparison the efficacy of BNT162b2 by Pfizer-BioNTech and mRNA-1273 by Moderna in immunocompromised patients form the SHCS and the STCS. In these patients the antibody response of mRNA-1273 was non-inferior to BNT162b2. Patients living with HIV had in general an antibody response, while a high proportion of transplant recipients had no antibody response. The second sub-study found similar results 8 weeks after the 3rd vaccination (i.e. non-inferiority of moderna vaccine; antibody response in patients living with HIV, high proportion of transplant recipients with inadequate antibody response).

Recently smaller phase II-II studies with bivalent SARS-CoV-2 vaccines have shown superior antibody response against variants that are being monitored such as alpha (B.1.1.7 and Q lineages), beta (B.1.351 and descendent lineages), gamma (P.1 and descendent lineages), delta (B.1.617.2 and AY lineages) and the variant of concern omicron (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5 lineages) when compared to the approved monovalent vaccine. We therefore aim to conduct an observational study assessing the immunologic response and safety of the bivalent SARS-CoV-2 vaccines. Currently (23. 9. 2022) the bivalent SARS-CoV-2 vaccine from Moderna (i.e. m-RNA-1273.214) is approved by the Swiss authorities (Swissmedic) and the bivalent SARS-CoV-2 vaccine by Pfizer-BioNTech is under evaluation. Since we do not know when the product from Pfizer-BioNTech will become available, we describe and pre-specify two scenarios for this study.

Scenario 1 (Comparison): In this observational study, we will recruit patients who have received m-RNA-1273.214 by Moderna in the frame of clinical routine. We will start a second arm of our observational study as soon as another bivalent mRNA vaccine (from Pfizer-BioNTech) has been approved by Swissmedic. This will allow for a non-randomized comparison of the 2 bivalent mRNA vaccines.

Scenario 2 (No comparison): In case there is a delay in the approval of the second bivalent mRNA vaccine of more than 3 months after the start of the substudy-3, we will conduct a single arm observational study only (Scenario 2 in Figure 1), because the comparability of the two arms will be increasingly compromised over time.

Objectives and Endpoints:

Aim Scenario 1: To compare immunologic response and safety of the bivalent mRNA-1273.214 vaccine from Moderna among immunocompromised persons (persons living with HIV or kidney or lung transplant recipients) to the immunologic response of immunocompromised persons who received the bivalent mRNA vaccine from Pfizer-BioNTech.

Aim Scenario 2: To assess immunologic response and safety of the bivalent mRNA-1273.214 vaccine among immunocompromised persons (persons living with HIV or kidney or lung transplant recipients).

Objectives:

All objectives and endpoints apply to both scenarios. However, Scenario 1 allows for a comparison of the endpoints between the two vaccines.

1) To assess the efficacy of the bivalent mRNA-1273.214 booster vaccine

2) To evaluate the durability of the bivalent mRNA-1273.214 booster vaccine response: Proportion of participants that show waning of antibody response at 8 weeks and 6 months, respectively, measured by pan-Immunoglobulin (Ig) antibodies
3) To describe the longitudinal T-cell immune response of the bivalent mRNA-1273.214 booster vaccine in a sub-sample of participants: cellular immune response build up and waning
4) To assess the safety of the bivalent mRNA-1273.214 booster vaccine

Endpoints:
Immunological endpoints:

- The proportion of patients with a positive antibody response to SARS-CoV-2 spike (S1) protein receptor binding domain (RBD) in human plasma assessed by the commercial immunoassay Elecsys Anti-SARS-CoV-2 S (Elecsys S) from Roche (1) 4 weeks, 8 weeks, and 6 months after vaccination. An antibody response will be considered to be still sufficient, using the threshold ≥100 units/ml, predicting a protective immune response as indicated by Hall et al. (2), and Khoury and colleagues.(3)
- Geometric mean of quantitative antibodies against RBD at 4 weeks, 8 weeks, and 6 months using Elecsys S test from Roche.
- The proportion of patients with a positive antibody response using SARS-CoV-2 spike (S1) Elecsys S by Roche, using a threshold of ≥0.8 units/ml as defined by the manufacturer at 4 weeks, 8 weeks, and 6 months.
- T-Cell response, using a commercially available Interferon gamma (IFN-γ) release assays (Quant-T-Cell SARS-CoV-2 by Euroimmun and Elecsys® IGRA SARS-CoV-2 by Roche) in a subsample of 60 patients (40 receiving bivalent (Wuhan/BA.1) SARS-CoV-2 mRNA-1273.214 vaccine by Moderna; 20 receiving bivalent (Wuhan/BA.1) SARS-CoV-2 mRNA vaccine by Pfizer-BioNTech) 4 weeks and 6 months after vaccination (sub-sample will be decreased to 40 patients in Scenario 2).

Clinical Endpoints:

- Newly confirmed SARS-CoV-2 infections 4 weeks, 8 weeks, and 6 months after vaccination.
- Newly confirmed symptomatic SARS-COV-2 infection 4 weeks, 8 weeks, and 6 months after vaccination
- Severe COVID-19 infections (requiring hospitalization or leading to death) 4 weeks, 8 weeks, and 6 months after vaccination

Safety endpoints

- Vaccine-related adverse events 4 weeks after vaccination
- Serious adverse events 4 weeks, 8 weeks, and 6 months after vaccination

Overall Design:
Observational study extension conducted within our trial-platform (COVERALL) nested in two national cohorts.

Number of Participants enrolled:
Since our trial platform is nested within two national cohort studies (SHCS and STCS), we have the possibility to identify and invite cohort patients who will receive the new bivalent mRNA Sars-CoV-2 vaccine in the frame of clinical routine. We plan to enrol the following number of individuals:

Scenario 1:

160 patients receiving bivalent (Wuhan/BA.1) SARS-CoV-2 mRNA-1273.214 vaccine by Moderna

- kidney transplant recipients (n=30)
- lung transplant recipients (n=30)
- people living with HIV with CD4 cell counts below 350 cells/µL (n=50)
- people living with HIV with CD4 cell counts of ≥ 350 cells/µL (n=50)

AND

80 patients receiving bivalent (Wuhan/BA.1) SARS-CoV-2 mRNA vaccine by Pfizer-BioNTech

- kidney transplant recipients (n=10)
- lung transplant recipients (n=10)
- people living with HIV with CD4 cell counts below 350 cells/µL (n=30)
- people living with HIV with CD4 cell counts of ≥ 350 cells/µL (n=30)

Sub-sample: A sub-sample of 60 patients will be selected (n=40 bivalent mRNA-1273.214 vaccine by Moderna; n=20 bivalent SARS-CoV-2 mRNA vaccine by Pfizer-BioNTech) for whom we will assess the T-Cell response, measured using the Quant-T-Cell SARS-CoV-2 by Euroimmun and Elecsys® IGRA SARS-CoV-2 by Roche. For this sub-sample we aim to prioritize patients which are at higher risk for a low immune response (i.e. solid organ transplant recipients and people living with HIV wit CD4 counts below 350 cells/µL so that we can include from each of the above groups 10 patients who received bivalent mRNA-1273.214 and 5 who received bivalent SARS-CoV-2 mRNA vaccine by Pfizer-BioNTech).

Scenario 2:

160 patients receiving bivalent (Wuhan/BA.1) SARS-CoV-2 mRNA-1273.214 vaccine by Moderna

- kidney transplant recipients (n=30)
- lung transplant recipients (n=30)
- people living with HIV with CD4 cell counts below 350 cells/µL (n=50)
- people living with HIV with CD4 cell counts of ≥ 350 cells/µL (n=50)

Sub-sample: A sub-sample of 40 patients will be selected for whom we will assess the T-Cell response (10 from each of the groups listed above).

Biological Sample and health related data Collection and Duration:

Participants of the Swiss HIV Cohort Study (SHCS) and Swiss Transplant Cohort Study (STCS) with informed consent and no exclusion criteria will be included. At day 0 patients will provide a baseline blood sample and will receive the third SARS-CoV-2 vaccine in the frame of clinical routine. At 4 weeks (± 1 week), 8 weeks (± 2 weeks), and 6 months (± 4 weeks) participants will have a follow up visit in which they provide a blood sample. Clinical outcomes as well as safety outcomes will be assessed.

Study schedule

Assessment	**Baseline**	**4 weeks** (± 1 week)	**8 weeks** (± 2 weeks)	**6 months** (± 4 weeks)
Eligibility and consent[a]	X			
Baseline assessment	X			
Assessment of monoclonal antibody treatment and flu vaccination	X	X	X	X
Vaccination (mRNA-1273.214 or product by Pfizer-BioNtech) in the frame of clinical routine[b]	X			
Anti-SARS-CoV-2 S and N antibody tests (Elecsys® Roche)	X	X	X	X
T-cell test (IFN-γ release assay): Quant-T-Cell SARS-CoV-2 by Euroimmun and Elecsys® IGRA SARS-CoV-2 by Roche *Only in sub-sample of 60 patients (Scenario 1) or 40 patients (Scenario 2)*	X	X		X
Clinical outcomes		X	X	X
Vaccine specific adverse events		X		
Serious adverse events		X	X	X

[a] Informed consent can also be given at later time point if bivalent vaccine was already administered in the frame of clinical routine and consent is only referring to blood samples and use of data.

[b] Will be administered in the frame of clinical routine based on recommendation from treating physician

1. STUDY ADMINISTRATIVE STRUCTURE

Sponsor-Investigator

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1.2 STATISTICIAN ("BIOSTATISTICIAN")

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1.3 LABORATORY

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1.5 DATA MANAGEMENT

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Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland

2. COMMITTEES AND INVOLVED INSTITUTIONS:

2.1 MONITORING INSTITUTION

Central monitoring of data entry into the trial platform and cohort database will be done within the routine procedures by the central and local cohort data managers and the biostatistician responsible as already implemented in sub-protocol 1 and 2.

2.2 DATA SAFETY MONITORING COMMITTEE

Due to the observational nature of this study extension, no data safety moniroring committee will be used.

2.3 ANY OTHER RELEVANT COMMITTEE, PERSON, ORGANISATION, INSTITUTION

Scientific protocol writing committee: Members of the scientific protocol writing committee, consisting of Alain Amstutz, Benjamin Speich, Heiner C. Bucher, Alexandra Griessbach, Niklaus Labhardt, Irene Abela, Katharina Kusejko, and Matthias Briel, were responsible for designing the study, receiving funding and writing the study protocol.

2.4 AUTHOR CONTRIBUTIONS

Alain Amstutz (AA); Benjamin Speich (BS); Heiner C. Bucher (HCB); Michael Koller (MK); Matthias Briel (MB); Niklaus Labhardt (NL); Frédérique Chammartin (FC); and Irene A. Abela (IAA) designed the study. Katharina Kusejko (KK) gave scientific input. AA and BS wrote the first draft of the sub-protocol 3. All authors critically revised and approved the final version of the study protocol. AA, BS, FC, IAA, MB, NL and HCB acquired funding for the trial.

3. ETHICAL AND REGULATORY ASPECTS

We refer to the master protocol.

3.1 STUDY REGISTRATION

COVERALL is registered with the U.S. National Institutes of Health (www.clinicaltrials.gov) under NCT04805125. The current registration will be adapted to implement the proposed trial extension. All sub-protocols are freely available on https://clinicaltrials.gov/ct2/show/NCT04805125. This extension will also be registered with the Koordinationsstelle Forschung am Mensch (kofam).

3.2 CATEGORISATION OF STUDY

This substudy is an observational extension (HFV2) in the Category A. This sub-study will assess patients blood sample after routine vaccination for immune response against SARS-CoV-2. Of note, the first study within out trial platform (sub-protocol 1) was an interentional study (klinV), while also substudy-2 (sub-protocol 2) was an observational study (HFV2).

3.3 COMPETENT ETHICS COMMITTEE (CEC)

We refer to the master protocol.

3.4 COMPETENT AUTHORITIES (CA)

We refer to the master protocol.

3.5 ETHICAL CONDUCT OF THE STUDY

We refer to the master protocol.

3.6 DECLARATION OF INTEREST

We refer to the master protocol.

3.7 PATIENT INFORMATION AND INFORMED CONSENT

We refer to the master protocol.

3.8 PARTICIPANT PRIVACY AND CONFIDENTIALITY

We refer to the master protocol.

3.9 EARLY TERMINATION OF THE STUDY

The Sponsor-Investigator may terminate the sub-study 3 prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk,

- alterations in accepted clinical practice that make the continuation of this extension study unwise

3.10 PROTOCOL AMENDMENTS

We refer to the master protocol.

4. BACKGROUND AND RATIONALE

4.1 BACKGROUND AND RATIONALE

We have set up a COrona VaccinE tRiAL pLatform (COVERALL) nested into the existing prospectively collected data structure of the Swiss HIV Cohort Study (SHCS) and the Swiss Transplant Cohort Study (STCS), according to an adaptive trial **master protocol** (4). Within the frame of a **first sub-study** we have assessed in a head-to-head comparison the efficacy of BNT162b2 by Pfizer-BioNTech and mRNA-1273 by Moderna in immunocompromised patients form the SHCS and the STCS (5). In these patients the antibody response of mRNA-1273 was non-inferior to BNT162b2. Patients living with HIV had in general an antibody response, while a high proportion of transplant recipients had no antibody response. The **second sub-study** found similar results 8 weeks after the 3rd vaccination (i.e. non-inferiority of moderna vaccine; antibody response in patients living with HIV, high proportion of transplant recipients with inadequate antibody response; *manuscript in preparation*).

The currently used SARS-CoV-2 vaccines were developed targeting the SARS-CoV-2 wild type and show limited efficacy against newer SARS-CoV-2 variants of concern. Hence, Moderna has developed a new bivalent booster vaccine based on variant spike sequences (Wuhan/Omicron BA.1). In a recent study this newly developed bivalent mRNA-1273.214 vaccine showed also a potent neutralizing antibody response against Omicron subvariants and a superior antibody response against alpha, beta, gamma, delta and omicron variants when compared to the approved monovalent vaccine mRNA-1273 Spikevax (6). Similarly, Pfizer-BioNTech has developed a bivalent mRNA vaccine (Wuhan/Omicron BA.1) with promising results (7, 8). Currently, evidence on the efficacy and safety of bivalent mRNA-vaccines in immunocompromised persons is very limited.

Hence, we propose a **third sub-study** of our COVERALL study assessing the humoral and cellular immune response, clinical and safety outcomes of the bivalent mRNA-vaccines (Wuhan/Omicron BA.1) in patients from the SHCS and STCS who have received at least three monovalent m-RNA SARS-CoV-2 vaccinations by either Moderna or Pfizer-BioNTech. Little is known about the cellular (T-cell mediated) immune response for these bivalent vaccines. Evidence from previous mRNA vaccine studies has shown inconsistent patterns between humoral and cellular response, especially among solid organ transplant recipients (9-11).

We propose to conduct an observational study, with two possible scenarios, dependent on how soon the second bivalent mRNA SARS-CoV-2 vaccine from Pfizer-BioNTEch will become available. Independently, we will start the study with the bivalent mRNA vaccine from Moderna which has already been approved by Swissmedic, being the first bivalent mRNA vaccine available in Switzerland. We will start a second observational arm with the bivalent mRNA vaccine from Pfizer-BioNTech, as soon as it has been approved by Swissmedic. This will allow a non-randomized comparison of the 2 bivalent mRNA vaccines (**Scenario 1** in Figure 1). In case the approval of Pfizer-BioNTech's bivalent mRNA vaccine comes later than than 3 months after study start, we will not open this second observational arm because the non-randomized comparability of the two arms will be too compromised due to time difference (**Scenario 2** in Figure 1).

5. INVESTIGATIONAL PRODUCT (TREATMENT, DEVICE) AND INDICATION

5.1 PRECLINICAL EVIDENCE

Moderna's bivalent mRNA-1273.214 vaccine showed a potent neutralizing antibody response against variants that are being monitored such as alpha, beta, gamma, delta and the variant of concern omicron when compared to their approved monovalent vaccine mRNA-1273 Spikevax (6). Similarly, Pfizer-BioNTech has developed a bivalent mRNA vaccine (Wuhan/Omicron BA.1) with promising results (7).

5.2 CLINICAL EVIDENCE TO DATE

In a phase 2–3 study, Moderna compared the 50-µg bivalent vaccine mRNA-1273.214 (25 µg each of ancestral Wuhan-Hu-1 and omicron B.1.1.529 [BA.1] spike messenger RNAs) with their previously authorized 50-µg mRNA-1273 booster among adults who received a two-dose (100-µg) primary series and first booster (50-µg) dose of mRNA-1273 (≥3 months earlier) (6). "*In participants with no previous SARS-CoV-2 infection, the geometric mean titers (GMT) of neutralizing antibodies against the omicron BA.1 variant were 2372.4 (95% confidence interval [CI], 2070.6 to 2718.2) after receipt of the mRNA-1273.214 booster and 1473.5 (95% CI, 1270.8 to 1708.4) after receipt of the mRNA-1273 booster. In addition, 50-µg mRNA-1273.214 and 50-µg mRNA-1273 elicited GMT of 727.4 (95% CI, 632.8 to 836.1) and 492.1 (95% CI, 431.1 to 561.9), respectively, against omicron BA.4 and BA.5 (BA.4/5), and the mRNA-1273.214 booster also elicited higher binding antibody responses against multiple other variants (alpha, beta, gamma, and delta) than the mRNA-1273 booster. Safety and reactogenicity were similar with the two booster vaccines*." (6).

No peer-reviewed publication is currently available for the bivalent SARS-CoV-2 vaccine from Pfizer-BiNTech (19. September 2022) . Hence we cite from the available press releases (7, 8). "*Pfizer/BioNTech's bivalent vaccine contains 15-µg of mRNA encoding the wild-type spike protein of SARS-CoV-2, which is present in the Original Pfizer-BioNTech COVID-19 Vaccine, and 15-µg of mRNA encoding the spike protein of the Omicron BA.4/BA.5 subvariants."* (8). Pfizers' Omicron-adapted vaccine candidates (30 µg and 60 µg) studied in the Phase 2/3 trial in 1,234 participants 56 years of age and older elicited substantially higher neutralizing antibody responses against Omicron BA.1 when compared to the companies' current COVID-19 vaccine (7). "*The pre-specified criterion for superiority was measured by the ratio of neutralizing geometric mean titers (GMR) with the lower bound of the 95% confidence interval >1. The geometric mean ratio for the bivalent 30 µg and 60 µg vaccines compared to the current COVID-19 vaccine were 1.56 (95% CI: 1.17, 2.08) and 1.97 (95% CI: 1.45, 2.68), respectively*" (7). One month after administration, a booster dose of the Omicron-adapted bivalent candidates (30 µg and 60 µg) conferred a 9.1 and 10.9-fold increase in neutralizing GMTs against Omicron BA.1. The vaccine candidates were well-tolerated in participants who received one or the other Omicron-adapted vaccine. In addition, "*a SARS-CoV-2 live virus neutralization assay tested on sera from participants over 56 years of age and older, sera efficiently neutralized BA.4/BA.5 with titers approximately 3-fold lower than BA.1*" (7).

There is no evidence on the efficacy and safety of these bivalent mRNA vaccines in immunocompromised people.

5.3 RISKS / BENEFITS

Participants gain information on their immune status following booster vaccination over time (at 4 weeks, 8 weeks, and 6 months). This knowledge can be important to participants and treating physicians when new boosters might be considered. There are only minimal risks associated with the sampling of blood (12). The study population frequently requires drawing of blood and the study samples can be drawn in the context of other routine blood examinations avoiding any additional risk. Results such as immune response of the patients obtained by the analysis of the blood samples will be communicated to the participant. By taking part in this study the participant will help benefit future patients by adding to the knowledge for this particular population and potentially improving vaccination

strategies.

5.4 JUSTIFICATION OF CHOICE OF STUDY POPULATION

According to the Swiss Federal Office of Public Health immunocompromised patients are of high priority of vaccinations and further research is needed to understand their response to vaccines appropriately. The treating physicians of the STCS and the SHCS will administer the vaccines according to the latest vaccine recommendations (13).

6. STUDY OBJECTIVES

6.1 OVERALL OBJECTIVE

Overall Objective Scenario 1: To compare immunologic response and safety of the bivalent mRNA-1273.214 vaccine from Moderna among immunocompromised persons (persons living with HIV or kidney or lung transplant recipients) to the immunologic response of immunocompromised persons who received the bivalent mRNA vaccine from Pfizer-BioNTech.

Overall Objective Scenario 2: To assess immunologic response and safety of the bivalent mRNA-1273.214 vaccine among immunocompromised persons (persons living with HIV or kidney or lung transplant recipients).

6.2 OBJECTIVES RELATED TO A PLATFORM BASED NESTED EXTENSION STUDY TO INVESTIGATE THE IMMUNOLOGIC RESPONSE AND SAFETY OF THE CURRENT BIVALENT MRNA VACCINES

- To assess the efficacy of the bivalent mRNA vaccines
- To evaluate the durability of the bivalent mRNA vaccine response: Proportion of participants that show waning of antibody response at 8 weeks and 6 months, respectively, measured by pan-IgG antibodies
- To describe the longitudinal T-cell immune response of the bivalent mRNA vaccines in a sub-sample of participants: cellular immune response build up and waning
- To assess the safety of the bivalent mRNA vaccines

6.3 SAFETY OBJECTIVES

We aim to systematically assess vaccine-related adverse events until 4 weeks after vaccination and serious adverse events over the entire study period.

If a serious event occurs, defined as a serious complication during a blood draw, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;

b. results in permanent or significant incapacity or disability; or

We aim to systematically assess vaccine-related adverse events until 4 weeks after vaccination and serious adverse events over the entire study period

6.4 STUDY OUTCOMES

6.4.1 Immunological Outcomes

Immunological endpoints:

- The proportion of patients with a positive antibody response to SARS-CoV-2 spike (S1) protein receptor binding domain in human serum or plasma assessed by the commercial immunoassay Elecsys Anti-SARS-CoV-2 S (Elecsys S) from Roche(1) 4 weeks, 8 weeks, and 6 months after vaccination. An antibody response will be considered to be still sufficient, using the threshold ≥100 units/ml, predicting a protective immune response as indicated by Hall et al.(2), and Khoury and colleagues.(3)
- Geometric mean of quantitative antibodies against RBD at 4 weeks, 8 weeks, and 6 months using Elecsys S test from Roche.
- The proportion of patients with a positive antibody response using SARS-CoV-2 spike (S1) Elecsys S by Roche, using a threshold of ≥0.8 units/ml as defined by the manufacturer at 4 weeks, 8 weeks, and 6 months.
- T-Cell response, using a commercially available IFN-γ release assay (Quant-T-Cell SARS-CoV-2 by Euroimmun and Elecsys® IGRA SARS-CoV-2 by Roche) in a subsample of 60 patients (40 receiving bivalent (Wuhan/BA.1) SARS-CoV-2 mRNA-1273.214 vaccine by Moderna; 20 receiving bivalent (Wuhan/BA.1) SARS-CoV-2 mRNA vaccine by Pfizer-BioNTech) 4 weeks and 6 months after vaccination (sub-sample will be decreased to 40 patients in Scenario 2).

6.4.2 Clinical Outcomes

Clinical Endpoints:

- Newly confirmed SARS-CoV-2 infections 4 weeks, 8 weeks, and 6 months after vaccination.
- Newly confirmed symptomatic SARS-CoV-2 infection 4 weeks, 8 weeks, and 6 months after vaccination
- Severe COVID-19 infections (requiring hospitalization or leading to death) 4 weeks, 8 weeks, and 6 months after vaccination

6.4.3 Other Outcomes of Interest

None.

6.4.4 Safety Outcomes

Safety Endpoints:

- Vaccine-related adverse events 4 weeks after vaccination
- Serious adverse events 4 weeks, 8 weeks, and 6 months after vaccination

c. is life-threatening or results in death.

7. STUDY DESIGN

7.1 GENERAL STUDY DESIGN AND JUSTIFICATION OF DESIGN

Nested within the Swiss HIV Cohort study (SHCS) (14) and the Swiss Transplant Cohort Study (STCS)(15) we have set-up the COrona VaccinE tRiAL pLatform (COVERALL; see also master-protocol and first sub-protocol). This trial platform allowed for rapid patient recruitment, efficient and cost-saving data collection, as well as high flexibility in adapting the study design, which is key given the rapid changing circumstances during the COVID-19 pandemic. The platform set-up and a first pilot trial (first sub-protocol) were supported by a competitive grant from the Swiss National Science Foundation (4).

Within the established trial platform we conducted a first multicentre randomised controlled, open-label, 2-arm randomised controlled trial (**first sub-protocol**) in immunocompromised patients to assess the efficacy of the two mRNA SARS-CoV-2 vaccines (i.e. BNT162b2 by Pfizer / BioNTech and mRNA-1273 by Moderna) that reached market authorisation in Switzerland. The primary clinical outcome was change in pan-Ig antibody response (pan-Ig anti-S1-RBD; baseline vs. 12 weeks after first vaccination; 8 weeks after second vaccination, respectively). We randomised a total of 430 patients (352 from SHCS and 78 from STCS). In a recently conducted observational extension (i.e. **second sub-protocol**), we assessed the non-inferiority of a third mRNA-1273 vaccination compared to a third BNT162b2 vaccination with respect to immune response (*manuscript in preparation*).

Within the here proposed substudy-3 (**third sub-protocol**) we aim to conduct an observational study to assess the antibody response in immunocompromised patients from the SHCS or the STCS after having received the new bivalent SARS-CoV-2 vaccine either from Moderna or Pfizer-BioNtech. We plan to assess the antibody response over time (i.e. at 4 weeks, 8 weeks and 6 months) to be able to assess the durability of the bivalent mRNAbooster vaccine response (16) in immunocompromised patients.

7.2 METHODS OF MINIMISING BIAS

7.2.1 Randomization

Not applicable in observational study

7.2.2 Blinding procedures

All personnel and patients will know which vaccine was given in clinical routine. Outcome assessors conducting laboratory analyses will not be aware which vaccine patients received.

7.2.3 Other methods of minimising bias

7.3 UNBLINDING PROCEDURES (CODE BREAK)

Not applicable.

7.4 STUDY POPULATION

This is a multi-centre study recruiting patients from 3 of the 7 study centres of the SHCS and 3 of the 6 study centres of the STCS (i.e. University Hospital Basel, University Hospital Zürich, Inselspital University Hospital Bern [only SHCS], and University Hospital Lausanne [CHUV; only STCS]). Both cohorts are representative for individuals living with HIV and solid organ transplants:

SHCS study centres:

- Department of Infectious Diseases, Inselspital University Hospital Bern, University of Bern
- Division of Infectious Diseases & Hospital Epidemiology, University Hospital Basel
- Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich

STCS study centres:

- Klinik für Pneumologie, Universitätsspital Zürich
- Klinik für Nephrologie, Universitätsspital Zürich
- Klinik für Pneumologie, Universitätsspital Basel
- Klinik für Transplantationsimmunologie & Nephrologie, Universitätsspital Basel
- Service de pneumologoie, Universitätsspital Lausanne (CHUV)
- Centre de transplantation d'organes, Universitätsspital Lausanne (CHUV)

The cohorts are described in more detail elsewhere (14, 15, 17, 18). The study will be explained to eligible patients during their visit at the cohort centre. Cohort patients will be contacted by phone or letter to inform them about the study.

Inclusion and exclusion criteria:

Inclusion criteria:

- Patients with either a HIV infection or recipients of solid organs registered in the SHCS and STCS cohorts and signed informed consent form
- Patients aged ≥18 years
- Patients receiving a new bivalent (Wuhan/Omicron BA.1) mRNA SARS-CoV-2 vaccine in the frame of clinical routine, according to the treating physician
- Provide consent for the COVERALL observational bivalent booster extension study (third sub-protocol)

Exclusion criteria:

- Acute symptomatic SARS-CoV-2 infection, influenza or other acute respiratory tract infection
- Any emergency condition requiring immediate hospitalization for any condition
- Known allergy or contra-indications for vaccines or any vaccine components or any other contraindication to receive the vaccine according to the treating physician
- Patients who did not receiv the "baseic immunization" SARS-CoV-2 vaccination (e.g. two shots of Spikevax from Moderna, two shots of Comirnaty from Pfizer-BioNtech).

7.5 RECRUITMENT AND SCREENING

Patients recruitment from the SHCS or the STCS: Specific eligibility criteria can be defined and implemented by the trial platform data base which is based on all clinical and laboratory cohort data and managed by the cohort data centres. Both cohorts have developed a clinical information system that summarizes all relevant clinical and laboratory information for patients and widely serves as a clinical management and decision support system. Eligible patients can be flagged within this system. Treating cohort physicians will contact flagged patients either by letter, phone call, or during routine cohort study visits to inform and invite them in this study. Of note: only relatively few people living with HIV have CD4 cell counts below 350 cells/µL (<5%). Therefore local investigator will receive a list, highlighting these patients so that they can priories this patient group at the beginning of the study to ensure that we can reach the required sample size.

7.6 ASSIGNMENT TO STUDY GROUPS

Since this is an observational study extension, we will not do any active assignment. Participants will receive the bivalent vaccine which they are given during routine practice. We will implement monitoring reports so capture how many patients from which sub-group are already participating. When the required sample size is reached for a specific sub-group investigators will be informed to stop recruitment for this sub-group of patients.

7.7 CRITERIA FOR WITHDRAWAL / DISCONTINUATION OF PARTICIPANTS

We refer to the master protocol.

7.8 DATA COLLECTION AND FOLLOW-UP FOR WITHDRAWN PARTICIPANTS

Patients have the right to withdraw the planned follow-up visits. Clinical outcomes for those patients will be assessed from routinely collected cohort data.

7.9 TRIAL SPECIFIC PREVENTIVE MEASURES

All patients included into the trial-extension will continue all medication taken for the treatment of their chronic conditions. For transplanted patients with recent organ transplant receipt and / or more severe immune-suppressant treatment, decision to vaccinate patients and for trial participation is taken by the treating physicians by considering all benefit and potential harms for vaccination against Sars-CoV-2 in a particular patient.

Use of any drugs for the treatment of local or systemic adverse effects of vaccines is according to clinical judgement by clinicians.

7.10 CONCOMITANT INTERVENTIONS (TREATMENTS)

Concomitant drugs for patients included into the trial-extension are recorded within the routine cohort based data collection structure (see master protocol). Within substudy-3 we will systematically assess during all study visits the use of monoclonal antibodies and the flu vaccination (see case report form). Physicians are free in the choice of any concomitant drugs for the treatment of HIV, immunosuppressants for transplanted patients or any other drugs used for the treatment of additional chronic conditions and take decisions for their use according to best clinical judgement and treatment guidelines. There are no particular drugs that are not permitted for their use during vaccination and follow-up.

Use of any drugs for the treatment of local or systemic adverse effects of vaccines is according to clinical judgement by clinicians.

8. STUDY DRUG / MEDICAL DEVICE ACCOUNTABILITY

The vaccines will be administered in the frame of clinical routine at official vaccination centres. These can be located directly at University Hospitals or at other locations (e.g. Messehalle in Basel). We will collect blood at the baseline visit, at 4 weeks, 8 weeks and 6 months after vaccination.

9. RETURN OR DESTRUCTION OF STUDY DRUG / MEDICAL DEVICE

Does not apply, since the vaccines will not be given in the frame of the substudy-3.

10. STUDY ASSESSMENTS

Study flow chart(s) / table of study procedures and assessments

Study schedule

Assessment	Baseline	4 weeks (± 1 week)	8 weeks (± 2 weeks)	6 months (± 4 weeks)
Eligibility and consent[a]	X			
Baseline assessment	X			
Assessment of monoclonal antibody treatment and flu vaccination	X	X	X	X
Vaccination (mRNA-1273.214 or product by Pfizer-BioNtech) in the frame of clinical routine[b]	X			
Anti-SARS-CoV-2 S and N antibody tests (Elecsys® Roche)	X	X	X	X
T-cell test (IFN-γ release assay): Quant-T-Cell SARS-CoV-2 by Euroimmun and Elecsys® IGRA SARS-CoV-2 by Roche *Only in sub-sample of 60 patients (Scenario 1) or 40 patients (Scenario 2)*	X	X		X
Clinical outcomes		X	X	X
Vaccine specific adverse events		X		
Serious adverse events		X	X	X

[a] Informed consent can also be given at later time point if bivalent vaccine was already administered in the frame of clinical routine and consent is only referring to blood samples and use of data.

[b] Will be administered in the frame of clinical routine based on recommendation from treating physician

10.1 ASSESSMENTS OF OUTCOMES

10.1.1 Assessment of immunological endpoints

We will assess the proportion of patients with a positive antibody response to SARS-CoV-2 spike (S1) protein receptor binding domain in human serum or plasma assessed by the commercial immunoassay Elecsys Anti-SARS-CoV-2 S (Elecsys S) from Roche (1) 4 weeks, 8 weeks, and 6 months after vaccination. An antibody response will be considered to be still sufficient, using the threshold ≥100 units/ml, predicting a protective immune response as indicated by Hall et al. (2), and Khoury and colleagues (3). We will also assess antibody response at baseline (i.e. before vaccination with bivalent SARS-CoV-2 vaccine). However, we assume that some patients may have received already the bivalent SARS-CoV-2 vaccine before the start of this study, hence we will not have a baseline blood sample from those patients. Furthermore we will measure the geometric mean of quantitative antibodies against RBD at 4 weeks, 8 weeks, and 6 months using Elecsys S test from Roche and the proportion of patients with a positive antibody response using SARS-CoV-2 spike (S1) Elecsys S by Roche, using a threshold of ≥0.8 units/ml as defined by the manufacturer at 4 weeks, 8 weeks, and 6 months.

Therefore, a blood sample will be taken during each study visit (EDTA blood sample (1 x 3 ml)):

Participating centres can decide if they want to conduct Elecsys® Anti-SARS-CoV-2 N and S tests locally at their own routine laboratory, or if they want to send the blood samples in large batches for the analyses to the Institut für Medizinische Virologie (IMV), in Zürich

In a sub-sample of 40 patients who receive the bivalent mRNA SARS-CoV-2 vaccine from Moderna and 20 who receive bivalent vaccine from Pfizer-BioNTech, we will assess the T-Cell response using a commercially available IFN-γ release assay (Quant-T-Cell test by Euroimmun (19)) at baseline, 4 weeks and 6 months. We will use the same blood sample to conduct an additional T-Cell test by Roche (Elecsys® IGRA SARS-CoV-2 (20)) to compare the performance of the two diagnostic tests.

For this purpose we will collect 1 heparin blood sample (8 ml) from patients selected for this sub-sample. As these blood samples have to be processed within the same day we will only select patients from the study center Zürich and Basel for this blood sample. Heparin blood sample collected in Basel will be sent on the same day by bike carrier to the IMV in Zürich to assure that they are processed within the same day as they were collected.

10.1.2 Assessment of clinical endpoints

Patients are informed to contact center physicians in case an asymptomatic or symptomatic SARS-CoV-2 infections was diagnosed outside the settings of participating cohort centers. Clinical endpoints will be assessed at 4 weeks (±1 week), 8 weeks (±2 weeks) and 6 months (±4 weeks).

- Newly PCR-confirmed Covid-19 infection (identified by the presence of anti–SARS-CoV-2 nucleocapsid antibodies, or PCR or rapid antigen test)

During all visits at the trial centres (a PCR SARS-CoV-2 test will only be conducted if the treating physician would also conduct such a test during clinical routine (e.g. exposure to infected individual). PCR tests done in between independently will be recorded with dates and results. In case of a positive test result, physicians will check for symptoms and patients will be followed-up according to clinical routine and physicians' judgement.

- Newly PCR-confirmed symptomatic Covid-19 infection with at least one of the following symptoms (i.e. fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose nausea or vomiting, and diarrhea) at any time during the 48 weeks of follow-up

During all visits at the trial centres a PCR SARS-CoV-2 test will only be conducted if the treating physician would also conduct such a test during clinical routine (e.g. COVID-19 related symptoms; exposure to infected individual). In case of a positive test result, physicians will check for symptoms and patients will be followed-up according to clinical routine and physicians' judgement.

- Severe COVID-19 infection requiring hospitalization or leading to death

10.1.3 Assessment of safety outcomes

10.1.3.1 Vaccine specific adverse events

Patients will be asked at the 4 week study visit about the following specific vaccine related adverse events:

- Any symptoms at injection site (redness, swelling or pain) limiting continuation of normal daily activities during the first 7 days following the booster vaccination?
- Any systemic symptoms (fever, muscle pain, joint pain) limiting continuation of normal daily activities during the first 7 days following the booster vaccination?
- Any vaccine related symptoms leading to physician contact during the first 7 days following the booster vaccination?

10.1.3.2 Serious adverse events

Eventhough this is an observational study, we will systematically assess any serious adverse events that lead to hospitalization or death at 4 weeks, 8 weeks and 6 months follow up. Patients will be asked at these study visits about hospitalisations after having received the bivalent SARS-CoV-2 vaccines. In

addition, the information system from the hospital will be checked for information about hospitalisations or death of the patient.

10.1.3.3 Serious Events (SEs)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21.

The project is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

10.1.3.4 Laboratory parameters

Laboratory parameters besides immune response parameters will be assessed at bi-annually cohort visits according to the cohort protocols.

10.1.3.5 Vital signs

Not relevant for purpose of this trial.

10.1.4 Assessments in participants who prematurely stop the study

All clinical outcomes will be assessed from routinely collected cohort data which will also be available if patients decide to prematurely stop participating in the clinical trial.

10.1.5 Assessments in participants who prematurely stop the study

We refer to the master protocol

10.1.6 Other assessments

In case a new SARS-CoV-2 vaccine shot will be recommended before the last 6 months follow-up visit is conducted we will add a case report form to assess the additional SARS-CoV-2 vaccines applied after the first bivalent mRNA vaccine shot.

11. PROCEDURES AT EACH VISIT

11.1.1 Eligibility

Potentially eligible patients will be either contacted ahead by cohort centres and informed about the substudy-3 and availability of bivalent vaccines or directly informed during cohort study visits. Eligibility of newly enrolled patients from STCS and SHCS will be prospectively assessed for eligibility based on the cohort stud- based trial platform. Treating physicians from the cohort centres will contact patients and inform them about the study. It will be mentioned that the new bivalent vaccines will be administered in the frame of clinical routine (as soon as the guidelines are adapted) and is not part of this study. In case they wish to receive the bivalent SARS-CoV-2 mRNA vaccine outside of this study, they have the option to participate in this observational study which only consists of additional blood samples being drawn and analysed to assess the immune response of the patient. It will be assessed which SARS-CoV-2 vaccines they received previously (i.e. first, second, and third vaccination). In case there are any reasons that justify to change to vaccine from different producers during their vaccination history this will be allowed following the judgment of the treating physician.

11.1.2 Baseline assessment (before application of bivalent SARS-CoV-2 vaccination)

Patient will return the signed consent form which will also be signed by the treating physician. Patients will provide a blood sample of EDTA blood at the local study centre. After this they will go to the vaccination centre and receive the bivalent mRNA SARS-CoV-2 vaccine (either by Moderna or Pfizer-BioNTech) in the frame of clinical routine. Patients will also be asked about their previous vaccine history (i.e. which vaccines they received and when [months and year]) and if they have received monoclonal antibodies.

11.1.3 Study specific follow-up

4 weeks, 8 weeks and 6 months: Patients will be asked about SARS-CoV-2 infections and about adverse events. Further, patients will provide a blood sample of EDTA blood to assess the immunological outcomes. During all study visits patients will be asked if they received monoclonal antibodies.

Sub sample of patients for T-Cell tests (baseline, 4 weeks and 6 months): Patients will provide at least 8ml heparin blood which is immediately transferred to the IMV in Zürich for processing on the same day.

12. SAFETY

The PI (and if applicable the sponsor) is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

13. STATISTICAL METHODS

Hypothesis

All analysese conducted will be of exploratory nature. For scenario 1, we expect to observe similar immunological outcomes for the two bivalent vaccines in our study popuation.

13.1 DETERMINATION OF SAMPLE SIZE

Not applicable. The present study does not aim to test an hypothesis and a convenience sample of 240 participants for scenario 1 and 160 for scenario 2 has been chosen to better understand immunological response to bivalent vaccines in an immunocompromised population.

13.2 STATISTICAL CRITERIA OF TERMINATION OF TRIAL

Not applicable. No interim analysis is planned during the trial extension and termination will not be based on any statistical criteria.

13.3 PLANNED ANALYSES

13.3.1 Datasets to be analysed, analysis populations

We refer to the master protocol

13.3.2 Analyses of immunological and clinical outcomes

Descriptive statistics will be used to present immunological and safety outcomes. We will report frequency and percentage with 95% Wald confidene interval (CI) of positive immune response and

geometric mean titer (GMT) with 95% CI. GMT are defiened as the anit-logs of the means and addressed anticipated right-skewness of the data. Safety outcomes will be reported as frequency and percentage with 95% CI. For scenario 1, we will additionally report mean difference in positive response and ratio of GMT between the two bivalent vaccines with 95%CI .

Baseline and demographic characteristics will be summarised overall and -for scenario 1 – by vaccine received.

13.3.3 Interim analyses

No interim analysis will be done

13.3.4 Safety analysis

Safety issue is expected to be small and will be describe using number, frequency and 95% CI.

13.3.5 Deviation(s) from the original statistical plan

We refer to the master protocol.

13.4 HANDLING OF MISSING DATA AND DROP-OUTS

We refer to the master protocol.

13.5 QUALITY ASSURANCE AND CONTROL

13.6 DATA HANDLING AND RECORD KEEPING / ARCHIVING

We refer to the master protocol.

14. DATA MANAGEMENT

We refer to the master protocol.

15. MONITORING

We refer to the master protocol.

16. AUDITS AND INSPECTIONS

We refer to the master protocol.

17. CONFIDENTIALITY, DATA PROTECTION

We refer to the master protocol.

18. STORAGE OF BIOLOGICAL MATERIAL AND RELATED HEALTH DATA

Samples used for diagnostic at the IMV in Zürich will be stored for 5 years.

19. PUBLICATION AND DISSEMINATION POLICY

All trials that are set-up within the trial platform and results from sub-studies will be published (also negative results or if a trial has to be discontinued) in peer-reviewed journal publications. We intend to make this sub-protocol available on clinicaltrials.gov. Authorship to publications will be granted according to the rules of the International Committee of Medical Journal Editors (ICMJE).

20. FUNDING AND SUPPORT

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21. INSURANCE

We refer to the master protocol.

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23. APPENDICES

Not applicable