Clinical Study 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

This is the second 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"** and 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).

Short title: Immunocompromised Swiss Cohorts Based Trial Platform

Acronym: COVERALL (COrona VaccinE tRiAL pLatform)

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 Prof. Heiner C. Bucher MD MPH Basel Institute for Clinical Epidemiology & Biostatistics University Hospital Basel Spitalstrasse 12 4056 Basel Switzerland Phone: +41 (0)61 328 61 01 Email: heiner.bucher@usb.ch
Investigational Product:	BNT162b2 licensed by Pfizer-BioNTech (Comirnaty) and mRNA-1273 licensed by Moderna (Spikevax)
Protocol Version and Date:	**Version 1.0; 12. 11. 2021**

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.

Clinical Study 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

Site	University Hospital Basel Basel Institute for Clinical Epidemiology & Biostatistics Spitalstrasse 12 4031 Basel
Sponsor-Investigator	Prof. Heiner C. Bucher

Basel, 23.11.2021

Place/Date

Signature

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

Authors of the study protocol:

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Prof. Andri Rauch MD PhD
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Daniel Smith

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.

Clinical Study 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

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

Basel, 23-Nov-2021

Place/Date

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Clinical Study 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

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

Universitätsspital Basel
Pneumologie
Prof. Michael Tamm
Petersgraben 4
CH-4031 Basel

Basel 22/11/2021 M Tamm

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.

Clinical Study 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

Site	Universitätsspital Basel Transplantationsimmunologie & Nephrologie Petersgraben 4 4051 Basel
Principal investigator	Prof. M. Dickenmann

Basel, 22-11-2021

Signature

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Local Principal Investigator at study site*:

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Clinical Study 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

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

Bern, 22/11/2021

Place/Date

Signature

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Local Principal Investigator at study site*:

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Clinical Study 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

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

Zürich, 24.11.2021 H. Günthard

Place/Date Signature

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Local Principal Investigator at study site*:

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Clinical Study 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

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

Zürich / 23. November 2021

Place/Date

Signature

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Local Principal Investigator at study site*:

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Clinical Study 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

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

Zürich, 22/11/2021

Place/Date

Signature

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

UniversitätsSpital Zürich
PD Dr. Macé Schuurmans
Leitender Arzt
Klinik für Pneumologie
8091 Zürich

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.

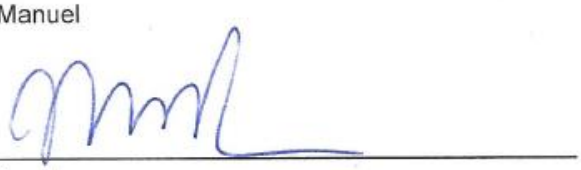
Clinical Study second sub-protocol

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

Site	CHUV Service des maladies infectieuses Rue du Bugnon 46 1011 Lausanne
Principal investigator	Dr. med. Oriol Manuel

Lausanne, 24.11.21

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 ethical 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. In the meantime the first two SARS-CoV-2 vaccines reached market authorisation by Swissmedic. Therefore, we have 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), conducting a head to head comparison of the vaccines by Pfizer/Biontech and Moderna.

In the meantinme, severely immunodeficient persons ≥ 12 years of age who have received two doses of an mRNA vaccine should receive a third dose of Comirnaty® or Spikevax® as part of the basic immunization, regardless of any antibody titer. Among all other immunocompromised patients a booster vaccination with an mRNA vaccine is recommended. These vaccines will be administered to patients from the SHCS and the STCS in the frame of clinical routine. In this second sub-protocol we propose an observational study to collect a blood sample before the third vaccination and 8 weeks after vaccination, to assess the additional benefit of a third SARS-CoV-2 vaccine in these immunocompromised patients.

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
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
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)*
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
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

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

Brief Title: Immunocompromised Swiss Cohorts Based Trial Platform,

Acronym: COVERALL (COrona VaccinE tRiAL pLatform)

Rationale: A new highly contagious corona virus SARS-CoV-2 has emerged in late 2019 in Wuhan, China, and caused in a two-month period a pandemic with the highest disease burden in elderly and people with pre-existing medical conditions. After nearly one year into the epidemic over 0.5 milllion infections, over 21'000 hospitalisations, and over 82000 deaths due to Sars-CoV-2 have been recorded in Switzerland (January 21, 2021).

Since January 12, 2021 two mRNA vaccines against Sars-CoV-2 by Pfizer / BioNTech (Comirnaty®) and COVID-19 mRNA Vaccine Moderna® by 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. Switzerland has already started to give third "booster" vaccines.

The aim of the proposed observational extension is the collection of blood samples to assess the additional benefits and potential risks of a third SARS-CoV-2 vaccination with BNT162b2 or mRNA-1273 among immunocompromised patients. The third vaccine dose will be administered as recommended and as part of the clinical routine.

Objectives and Endpoints:

To conduct an observational study with a head-to-head comparison of a third BNT162b2 or mRNA-1273 vaccination dose with respect to the immune response (binary outcome).

The original randomized trial population will be enlarged to gain precision in assessing the effect of individual factors (including vaccine type) on the immunological response (titers) to a third dose of mRNA vaccine.

Feasibility endpoints:

We refer to the master protocol

Immunological endpoints

- Primary endpoint: 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 Diagnostics (1). An antibody response will be considered as positive using the threshold ≥ 100 units/ml, predicting a protective immune response as indicated by Hall et al. (2), and Khoury and colleagues (3)

Secondary immunological endpoints:

- 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.
- The proportion of patients with a positive antibody response using antibody response using the Antibody CORonavirus Assay (ABCORA) 2 that assesses seropositivity by measuring specific IgG, IgA and IgM responses to SARS-CoV-2 receptor binding domains, S1, S2 and N

16.
- The proportion of patients with neutralizing neutralization activity against the vaccine strain Wuhan-Hu-1 in sera, defined as having an ABCORA sum S1 (sum of S1 signal over cut-off values of IgG, IgA, IgM) above the threshold of 17.
- Immune response (pan-Ig antibodies against the receptor binding domain (RBD) in the S1 subunit of the spike protein (pan-Ig anti–S1-RBD) of SARS-CoV-2.
- Mean immune response of IgM, IgA and IgG to the subunit S1 using ABCORA.
- Newly PCR-confirmed asymptomatic SARS-CoV-2 infection.

Clinical Endpoints:

- Newly PCR-confirmed SARS-CoV-2 infection
- Newly PCR-confirmed asymptomatic SARS-CoV-2 infection
- Newly PCR-confirmed symptomatic SARS-CoV-2 infection
- Severe COVID-19 infection, hospitalization due to COVID-19 or death
- Patient reported asymptomatic or symptomatic infections of household members.
- Follow up on adverse events from vaccines as defined in subprotocol 1

Safety endpoints

- Serious Events

Overall Design:
Observational study extension of a multicenter randomised controlled, open-label, 2-arm platform trial nested in two national cohorts (see master-protocol and first sub-protocol).

Number of Participants enrolled:
The 430 participants from the already completed COVERALL study (352 from the SHCS and 78 from the STCS) will be included. Since our trial platform is nested within two national cohort studies, we have the possibility to supplement the randomized study population by including additional cohort patients who already received two doses of a mRNA SARS-CoV-2 vaccine outside of the COVERALL RCT. To increase the precision in estimating the effect of patient's characteristics on the antibody response (titers) to a third dose vaccine, we plan to enrol additional cohort participants from the SHCS and the STCS, (i.e. who have already received two SARS-CoV-2 vaccinations) reaching a sample size of up to 700 participants.

Biological Sample and health related data Collection and Duration:

Participants of the Swiss HIV Cohort and Swiss Transplant Cohort Studies 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. 8 weeks later (± 2 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

	Eligibility	**Baseline assessment (before third vaccination)**	**Study specific follow-up**	**Continuous follow-up in the frame of the cohort**
Time point	**Approximately -14 to 0 days**	**Day 0**	**8 weeks (±2 weeks)**	
Eligibility screen	X			
Informed consent	X[a]			
Baseline blood samples		X[b]		
Assessment of baseline characteristics		X		
[c]Third SARS-CoV-2 vaccine in the frame of clinical routine (mRNA-1273 by Moderna or BNT162b2 by Pfizer-BioNTntech)		X[c]		
Immunological endpoints			X	
Clinical endpoints			X	X
- Adverse events from vaccines			X	
Safety (Serious Events)			X	X

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

[b] If available it is also possible to use a blood sample that were routinely collected in the frame of the cohort studies.

[c] Will be administered in the frame of clinical routine based on recommendation from treating physician (i.e. outside of this study).

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 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.

1.6 DATA SAFETY MONITORING COMMITTEE

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

1.7 ANY OTHER RELEVANT COMMITTEE, PERSON, ORGANISATION, INSTITUTION

Not applicable.

1.8 AUTHOR CONTRIBUTIONS

Benjamin Speich (BS); Heiner C. Bucher (HCB); Michael Koller (MK); Matthias Briel (MB); Frédérique Chammartin (FC); Irene A. Abela (IAA); and Huldyrch Günthard (HG) designed the study. Nicolas Müller (NM); Andri Rauch (AR); and Katharina Kusejko (KK) gave scientific input. BS wrote the first draft of the sub-protocol. All authors critically revised and approved the final version of the study protocol. BS and HB acquired funding for the trial.

2. ETHICAL AND REGULATORY ASPECTS

We refer to the master protocol.

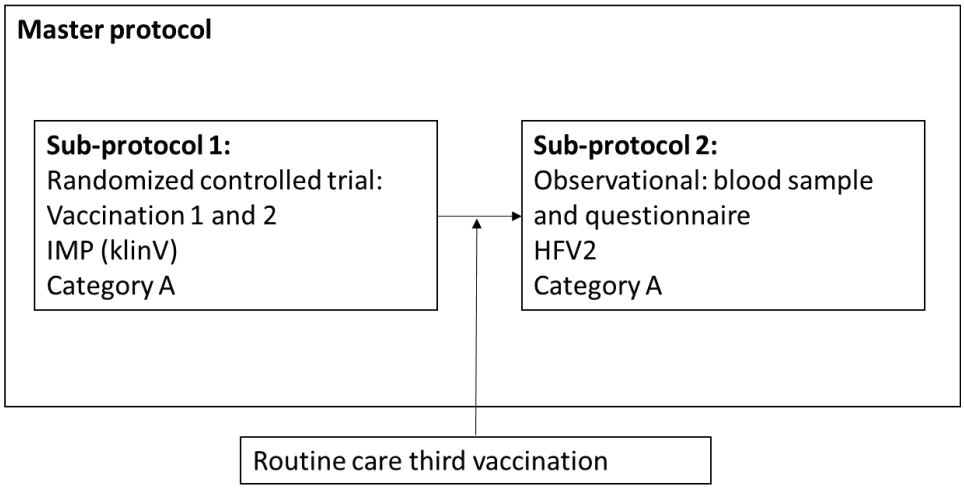
2.1 STUDY REGISTRATION

The pilot trial 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. The pilot-trial will also be registered with the Koordinationsstelle Forschung am Mensch (kofam).

2.2 CATEGORISATION OF STUDY

This substudy is an observational extention (HFV2) in the Category A. This sub-study will assess patients blood sample after routine vaccination for immune response against SARS-CoV-2.

Figure 2: Master protocol, sub-protocol and categorisation of observational study (HFV2)



2.3 COMPETENT ETHICS COMMITTEE (CEC)

We refer to the master protocol.

2.4 COMPETENT AUTHORITIES (CA)

We refer to the master protocol.

2.5 ETHICAL CONDUCT OF THE STUDY

We refer to the master protocol.

2.6 DECLARATION OF INTEREST

We refer to the master protocol.

2.7 PATIENT INFORMATION AND INFORMED CONSENT

We refer to the master protocol.

2.8 PARTICIPANT PRIVACY AND CONFIDENTIALITY

We refer to the master protocol.

2.9 EARLY TERMINATION OF THE STUDY

The Sponsor-Investigator may terminate the sub-study 2 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,

2.10 PROTOCOL AMENDMENTS

We refer to the master protocol.

3. BACKGROUND AND RATIONALE

3.1 BACKGROUND AND RATIONALE

A new highly contagious corona virus SARS-CoV-2 has emerged in late 2019 in Wuhan, China, and caused in a two month period a pandemic with the highest disease burden in elderly and people with pre-existing medical conditions (4-6). After nearly one year into the epidemic over 0.5 million infections, over 21'000 hospitalisations, and over 8`200 deaths due to SARS-CoV-2 have been recorded in Switzerland (January 21, 2021). The highest burden of severe Covid-19 infections and deaths is in the elderly and in individuals with comorbidities known to present risk factors for a severe infection. Since January 12, 2021 two mRNA vaccines against Sars-CoV-2 by Pfizer / BioNTech (Comirnaty®) and COVID-19 mRNA Vaccine Moderna® by Moderna have been licensed in Switzerland and role-out of vaccines has started (7, 8).

In phase III licensing trials of both vaccines which were both submitted as emergency use authorisation (EUA) to FDA with parallel submission to Swissmedic, vaccine efficacy of 95% and 94% were found and both vaccines appeared to be safe. However, estimates of vaccine efficacy were imprecise and with large confidence intervals in the subgroups of individuals most at risk of complications from SARS-CoV-2 infection like the elderly and persons with comorbidities. Likewise, data on immune response overall and in subgroups was not available when the vaccines (i.e. first two doses) were approved (9, 10). In particular very few individuals in both trials with HIV infection were included (and no solid organ recipients were allowed in the trials). In the first COVERALL sub-study (see sub-protocol 1) we could show that HIV patients had an immune response 8 weeks after the second SARS-CoV-2 vaccine, while a large proportionof solid organ transplant recipients had no immune response (Speich et al., *currently under review*). Studies have shown, that a third SARS-CoV-2 vaccine in transplant patients increases the proportion of individuals with an immune response (2). Hence, on strongly immune suppressed indivudials, the thirs SARS-CoV-2 vaccine is highly recommended(11). In the frame of clinical routine a third SARS-CoV-2 vaccine will be offered to all patients from the STCS and the SHCS in the near future.

Data from a head-to-head conparison on vaccine efficacy of the third SARS-CoV-2 vaccine, induced immune response and safety in immunosuppressed individuals with chronic HIV infection or solid organ transplantation is missing. We intend to close this information gap with a trial extension which represents the second sub-study trial of the established trial platform that is linked and nested into the existing

prospectively collected data structure of the two most prominent cohort studies in Switzerland, the Swiss HIV Cohort Study (SHCS) and the Swiss Transplant Cohort Study (STCS) (12, 13).

4. INVESTIGATIONAL PRODUCT (TREATMENT, DEVICE) AND INDICATION

4.1 PRECLINICAL EVIDENCE

We refer to the first sub-protocol for preclinical evidence on the SARS-CoV-2 vaccine by Pfizer-BioNTech (BNT162b2; Comirnaty) and Moderna (mRNA-1273; Spikevax).

4.2 CLINICAL EVIDENCE TO DATE

(ICH/E6 6.2.2; SPIRIT #6a)
ICH: A summary of findings from Phase III clinical trials submitted to regulators.

For clinical evidence information on the first two SARS-CoV-2 vaccines of BNT162b2 and mRNA-1273 we refer to the master-protocol and the first sub-protocol. Here we summarise the clinical evidence of the third SARS-CoV-2 vaccine.

Our results from the first COVERALL sub-study 1 were in line with the findings from a published observational study reporting that immune response in solid organ transplant recipients was detectable in 54% of patients (357/658) (14). An RCT conducted by Hall et al. has shown that solid organ transplant recipients have a higher immune response after a third SARS-CoV-2 vaccination, hence a booster should be considered in this population (2). Two recently published case reports in 14 and 12 virologically suppressed patients living with HIV found high antibody titers after the second vaccination with mRNA-1273 (15, 16). In an observational study conducted in Israel in more than 4 million individuals, SARS-CoV-2 infection rates were ten times lower in individuals who received a third SARS-CoV-2 vaccine compared to the population who did not receive the third “booster” vaccine (17). Due to this high evidence all patients from the STCS and also from the SHCS will be invited in the frame of the clinical routine to receive the third SARS-CoV-2 vaccine.

4.3 RISKS / BENEFITS

Patients gain information on there immune status following booster vacination. There are only minimal risks associated with the sampling of blood (18). 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 base for this particular population and potentially improving vaccination strategies.

4.4 JUSTIFICATION OF CHOICE OF STUDY POPULATION

According to the Swiss Federal Office of Public Health immunocompromised patients are of high priority of vaccinations (19). Whereas for the general population a third vaccine is not recommended before six months after the second vaccine, people with a compromised immunesystem can receive the third vaccine already 28 days after the second vaccination (11). The rationale behind this is that in immunocompromised patients the third vaccine is classified as a primo-vaccination (“Grundimmunisierung”) while for the general population it is regarded as a booster vaccination (“Auffrischimpfung”). According to the treating physicians from the STCS and the SHCS administering third vaccination doses within the clinical routine has already started to some extent (STCS) or will start within the near future. More information on the choice of study population is included within the first sub-

protocol.

5. STUDY OBJECTIVES

5.1 OVERALL OBJECTIVE

To examine the blood samples through which the impact of a third vaccination with BNT162b2 or mRNA-1273 SARS-CoV-2 vaccine on a wide range of immunological response parameters and safety in immunocompromised patients (HIV patients and transplant recipients) can be assessed.

5.2 OBJECTIVES RELATED TO PLATFORM TRIAL SET-UP AND FEASIBILITY OF COHORT BASED PATIENT RECRUIT, TRIAL INCLUSION AND DATA COLLECTION

We refer to the master protocol.

5.3 OBJECTIVES RELATED TO A PLATFORM BASED NESTED EXTENSION STUDY TO INVESTIGATE THE COMPARATIVE EFFECTIVENESS OF A THIRD DOSE OF A MRNA VACCINE (BNT162B2 VS MRNA-1273) AGAINST SARS-COV-2

The study seeks to determine the following SARS-CoV-2 related objectives (for detailed definitions see under 5.6 immunological endpoints and 5.7 study endpoints):

- Immune response (pan-Ig antibodies against the receptor-binding domain (RBD) in the S1 subunit of the spike protein (pan-Ig anti–S1-RBD) of SARS-CoV-2.
- Newly PCR-confirmed asymptomatic SARS-CoV-2 infection,
- Newly PCR-confirmed symptomatic SARS-CoV-2 infection
- Severe COVID-19 infection,
- Patient reported asymptomatic or symptomatic infections of household members.
- Adverse events
- Safety parameters
    - Serious events

5.4 SAFETY OBJECTIVES

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[1].

5.5 STUDY OUTCOMES

For the feasibility outcomes we refer to the master protocol.

[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

c. is life-threatening or results in death.

5.6 IMMUNOLOGICAL OUTCOMES

Immunological endpoints

- Primary endpoint: 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 Diagnostics (1). An antibody response will be considered as positive using the threshold ≥ 100 units/ml, predicting a protective immune response as indicated by Hall et al. (2), and Khoury and colleagues (3)

Secondary immunological endpoints:

- 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.
- The proportion of patients with a positive antibody response using antibody response using the Antibody CORonavirus Assay (ABCORA) 2 that assesses seropositivity by measuring specific IgG, IgA and IgM responses to SARS-CoV-2 receptor binding domains, S1, S2 and N 16.
- The proportion of patients with neutralizing neutralization activity against the vaccine strain Wuhan-Hu-1 in sera, defined as having an ABCORA sum S1 (sum of S1 signal over cut-off values of IgG, IgA, IgM) above the threshold of 17.
- Immune response (pan-Ig antibodies against the receptor binding domain (RBD) in the S1 subunit of the spike protein (pan-Ig anti–S1-RBD) of SARS-CoV-2.
- Mean immune response of IgM, IgA and IgG to the subunit S1 using ABCORA.
- Newly PCR-confirmed asymptomatic SARS-CoV-2 infection.

5.7 CLINICAL OUTCOMES

- Newly PCR-confirmed SARS-CoV-2 infection
- Newly PCR-confirmed asymptomatic SARS-CoV-2 infection
- Newly PCR-confirmed symptomatic SARS-CoV-2 infection
- Severe COVID-19 infection, hospitalization due to COVID-19 or death
- Patient reported asymptomatic or symptomatic infections of household members.
- any local symptom (redness or swelling or prolonged pain at injection side) limiting continuation of normal daily activities during the first 7 days after vaccination
- any systemic symptom (fever, generalized muscle or joint pain) limiting continuation of normal daily activities during the first 7 days after vaccination
- any vaccine related symptom leading to contacting a physician during the first 7 days after vaccination

All clinical outcomes will be measured in the trial database at a follow up 8 weeks (±2 weeks) after the third SARS-CoV-2 vaccine was administered.

5.8 OTHER OUTCOMES OF INTEREST

None.

5.9 SAFETY OUTCOMES

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[2].

[2] 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:

6. STUDY DESIGN

6.1 GENERAL STUDY DESIGN AND JUSTIFICATION OF DESIGN

Nested within the Swiss HIV Cohort study (SHCS)(13) and the Swiss Transplant Cohort Study (STCS)(12) 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 were supported by a competitive grant from the Swiss National Science Foundation (20).

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 the proposed extension, we plan to 1) assess non-inferiority of a third mRNA-1273 vaccination compared to a third BNT162b2 vaccination with respect to immune response (binary outcome), and 2) assess the effect of patients' characteristics on the antibody titer after a third SARS-CoV-2 vaccine in immunocompromised individuals who received vaccination within routine practice, following current guidelines. Patients from the first sub-study will receive a third dose of SARS-CoV-2 vaccine according to their randomisation group. In addition, we will include up to 300 additional patients from both cohorts (at least 100 additional from the STCS) who have already received two doses of SARS-CoV-2 vaccine in an observational extension of the COVERALL study to further explore the main drivers of immune response to a third dose in immunocompromised patients, and to examine the benefits and potential risks of a third vaccination with BNT162b2 or mRNA-1273.

6.2 METHODS OF MINIMISING BIAS

6.2.1 Randomisation

Not applicable in observational study

6.2.2 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.

6.2.3 Other methods of minimising bias

6.3 UNBLINDING PROCEDURES (CODE BREAK)

Not applicable.

6.4 STUDY POPULATION

This is a multi-centre study recruiting patients from 3 of the 7 study centres of the SHCS and 2 of the 6

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.

study centres of the STCS (i.e. University Hospital Basel, University Hospital Zürich, University Hospital Bern [only SHCS]). Both cohorts are representative for individuals living with HIV and solid organ transplants:

SHCS study centres:

- Department of Infectious Diseases, Bern University Hospital, 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
- Universitätsspital Basel, Pneumologie
- Universitätsspital Basel, Transplantationsimmunologie & Nephrologie,

The cohorts are described in more detail elsewhere (12, 13, 21, 22). 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:

- All patients with either a chronic HIV infection or recipients of solid organs registered with informed consent from the SHCS and STCS cohorts aged ≥18 years
- Patients with solid organ transplantation of lungs or kidneys at least one month post-transplantation with a prednisone dose of 20mg or less.
- Additional consent for participation in trial extension
- Third covid-19 vaccination recommended by treating physician and administered in the frame of clinical routine

Exclusion criteria:

- Pregnancy
- Acute symptomatic SARS-CoV-2 infection, influenza or other acute respiratory tract infection
- Known allergy or contra-indications for vaccines or any vaccine components
- Any emergency condition requiring immediate hospitalization for any condition
- Patients with solid organ transplantation (lung or kidney) with the following conditions:
  - Solid organ transplant recipients less than one month post-transplantation
  - Solid organ transplant recipients with the use of T-cell depleting agents in the last 3 months (i. e induction treatment in standard risk or high-risk immunological situation or rejection treatment).
  - Solid organ transplant recipients with the need of pulse corticosteroids (>100mg prednisone or equivalent) in the last 1 month or rituximab in the last 6 months
  - Solid organ transplant recipients with the need of any kind of chemotherapy treatment for cancer

6.5 RECRUITMENT AND SCREENING

Patients who participated in the COVERALL-study (first sub-protocol): Patient who should receive a third SARS-CoV-2 vaccine in the frame of clinical routine (based on judgment of the treating physician) will be contacted by the treating physician or a representative. Patients will be invited to participate to the COVERALL-observational extension study (sub-protocol 2) .

Newly recruited patients 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 (figure 2 and separately submitted electronic Case Report Form). 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 to inform and invite them in this study.

6.6 ASSIGNMENT TO STUDY GROUPS

Since this is an observational study extension, we will not do any active assignement. Participants will receive the third vaccine which they are given during routine practice.

6.7 CRITERIA FOR WITHDRAWAL / DISCONTINUATION OF PARTICIPANTS

We refer to the master protocol.

6.8 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.

6.9 TRIAL SPECIFIC PREVENTIVE MEASURES

(ICH/E6 6.6.2; SPIRIT #11d)
ICH: Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

All patients included into the trial-extension will continue all medication taken for the treatment of their chronic conditions. No drugs are prohibited that would exempt participation from the trial except use of ATG or rituximab within 6 months and pulse corticosteroids within 1 months prior to first vaccination for solid organ transplant patients. 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.

6.10 CONCOMITANT INTERVENTIONS (TREATMENTS)

ICH/E6 6.6.2; SPIRIT #11d)
ICH: Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

All concomitant drugs for patients included into the trial-extension are recorded within the routine cohort based data collection structure (see master protocol). 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.

7. 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 and 8 weeks after vaccination.

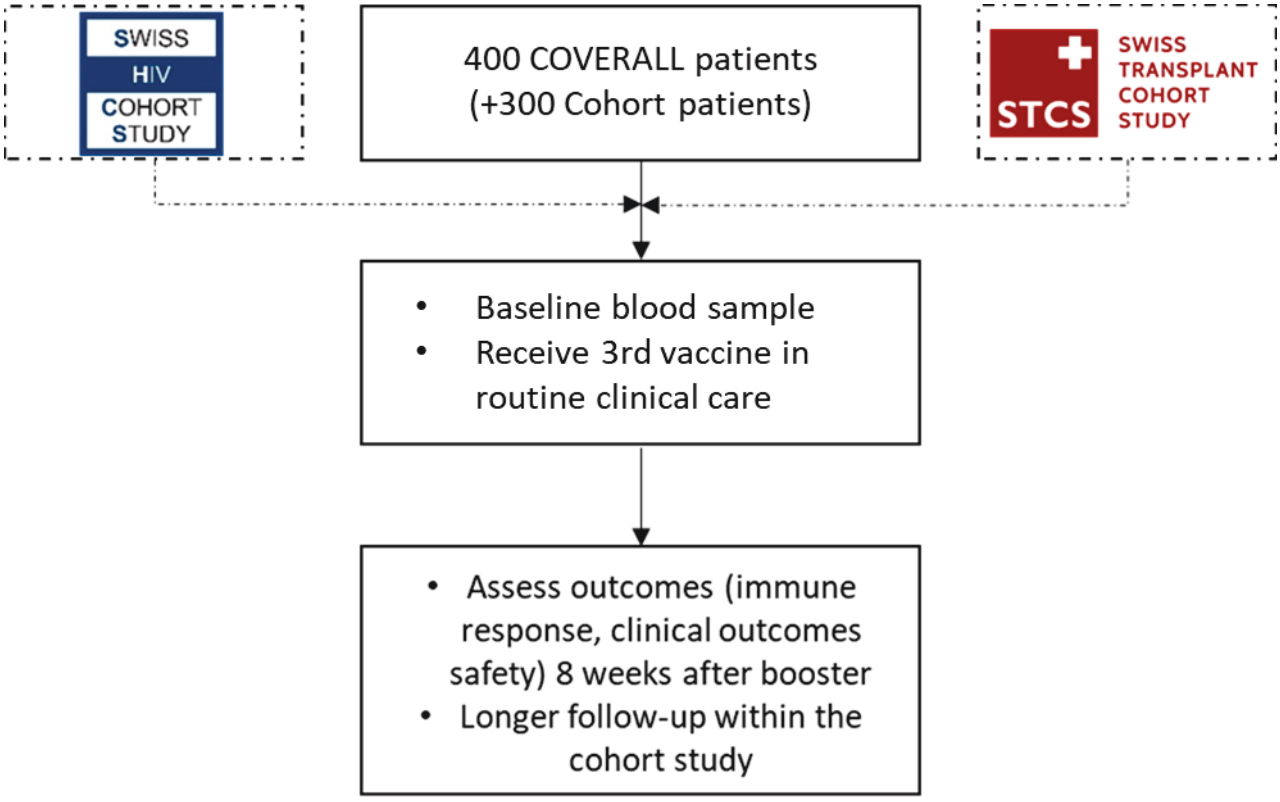
8. RETURN OR DESTRUCTION OF STUDY DRUG / MEDICAL DEVICE

Does not apply, since the vaccines will not be given in the frame of the extension study.

9. STUDY ASSESSMENTS

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

Figure 1: Study flow chart: Observational Study Extension



9.1 ASSESSMENTS OF OUTCOMES

9.1.1 Assessment of feasibility outcomes

We refer to the master protocol.

9.1.2 Assessment of immunological endpoints

We will assess pan-IgG anti S (RBD) (quantitative) and anti- N antibodies (qualitative) with the commercial Elecsys® Anti-SARS-CoV-2 tests at baseline and at 8 weeks following randomisation and vaccination (primary immunological endpoint). We assume that some patients may have received already the third SARS-CoV-2 vaccine, hence we will not have a baseline blood sample from those patients.

We will assess SARS-CoV-2-binding antibody responses of the participants by analyzing the IgM, IgA and IgG responses to a wider range of SARS-CoV-2 proteins (S1, S2, RBD and N using an in-house method (ABCORA 2.0) established at the Institute of Medical Virology (IMV), UZH (secondary immunological endpoint). The ABCORA 2.0 test allows for a parallel assessment of IgG, IgM and IgA reactivity to multiple antigens enabling a high-dimensional temporal resolution of antibody responses and a dissection between humoral responses to an infection and vaccination. We expect that the ABCORA2.0 antibody test will be more sensitive than the Elecsys® Anti-SARS-CoV-2 S antibody test.

Patients will be invited to see their treating physician or a representative 8 weeks after the third vaccine (see Study schedule). A blood sample will be taken (EDTA blood (2 x 7.5 ml)) at baseline and 8 week follow-up visit and assessed for the above listed antibodies:

- 1ml for Elecsys® Anti-SARS-CoV-2 N and S tests (performed locally at each laboratory)
- 2ml EDTA Plasma for ABCORA 2.0 test (performed at IMV, UZH)

EDTA blood should be processed within 24h and EDTA plasma should be stored at -20°C. For ABCORA 2.0 antibody measurements plasma samples will be collected at each center and a collective shipment will be sent after baseline and at 12 weeks after randomisation and vaccination to the IMV, UZH. One sample will be stored according to SHCS and STCS protocols for later eventual analyses at the centers of University Hospital Zurich.

9.1.3 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 8 weeks (±2 weeks), and in addition during future cohort visits,.

- Newly PCR-confirmed asymptomatic Covid-19 infection (identified by the presence of anti–SARS-CoV-2 nucleocapsid antibodies ,or PCR or rapid antigen test) and no related 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 (study specific at 8 weeks, as well as cohort visits) 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 (study specific at 8 weeks, as well as cohort visits) 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 with respiratory failure, evidence of shock (as diagnosed by a treating physician), clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death at any time during the 48 weeks of follow-up.

- Patient reported asymptomatic or symptomatic infections of household members.

Patients will be asked at the 8-week visit if a household member was diagnosed with COVID-19.

9.1.4 Assessment of safety outcomes

9.1.4.1 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.

9.1.4.2 Laboratory parameters

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

9.1.4.3 Vital signs

Not relevant for purpose of this trial.

9.1.5 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.

9.1.6 Assessments in participants who prematurely stop the study

We refer to the master protocol

10. PROCEDURES AT EACH VISIT

10.1.1 Eligibility

All patients who participated already in the first sub-study from COVERALL will prospectively be assessed for eligibility based on the cohort study based trial platform. Eligible patients will be either contacted ahead by cohort centres and informed about the trial-extension and availability of vaccines or directly informed during in between visits or cohort study visits. Eligibility of newly enrolled patients from STCS and SHCS will be will prospectively be assessed for eligibility based on the cohort study based trial platform. Treating physicians from the cohort centres will contact patients and inform them about the study. It will be mentioned that the third vaccine will be administered in the frame of clinical routine and is not part of this study. In case they wish to to receive the third vaccine outside of this study, they have the option to particate 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 (i.e. first and second vaccination) to make sure that the same compound can be used for the third vaccination. In case there are any reasons that justify to change to the other vaccine (e.g. first and second vaccination with BNT162b2, third vaccination with mRNA-1273) this will be allowed following the judgment of the treating physician.

10.1.2 Baseline assessment (before third 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 at the local study centre. After this they will go to the vaccination centre and

receive the third SARS-CoV-2 vaccine in the frame of clinical routine.

10.1.3 Study specific follow-up

Patients will be asked about SARS-CoV-2 infections, adverse events. Further, patients will provide a blood sample (8 weekes) to assess the immunological outcomes.

10.1.4 Continuous follow-up in the frame of the cohort

Clinical endpoints (i.e. SARS-CoV-2 infections) and serious adverse events will be assessed in the frame of the routine cohort visits.

11. 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.

12. STATISTICAL METHODS

Hypothesis

To compare the effectiveness in term of serological immune response of approved SARS-CoV-2 vaccines in immunocompromised patients, we aim to demonstrate that the second vaccine available in the market is no worse than the comparator by more than 10%. Therefore, we formulate the null hypothesis H0: $\pi 1 \geq \pi 2 + 10$ versus the alternative hypothesis H1: $\pi 1 - 10 < \pi 2$. The choice of a non-inferiority margin of 10% relies on expert opinion/clinical judgment.

12.1 DETERMINATION OF SAMPLE SIZE

Within our previous RCT (first sub-protocol) assessing antibody response in immunocompromised patients after the administration of SARS-CoV-2 vaccines, we found that the proportion of patients with an immune response 12 weeks after the first SARS-CoV-2 vaccination and 8 weeks after the second vaccination was 86.67% (95% confidence interval (CI): 82.07%-91.26%) in the BNT162b2 arm and 86.14% (95% CI: 81.37-90.90) in the mRNA-1273 arm (positive immune response according to the Roche Elecsys anti SARS-CoV-2 S with a cut-off at 100 Unit/ml). After a third dose vaccine, we expect a positive antibody response for 50% of transplanted patients (2) and nearly 100% of HIV patients, respectively. Thus, we assume vaccine reactivity of 90% in both vaccine groups and power our non-inferiority trial such that a 95% two-sided confidence interval excludes a difference in favour of the reference group of more than 10%. A sample size of 380 (190 in each treatment arm) is required for a statistical power of 90% and a type I error of 0.025. We believe that a target sample of 380 patients participants is feasible, since we have 412 randomized patients from our first RCT that achieved complete follow-up and drop-out rate from our previous RCT was 4%. Sample size was calculated using the “ssc_propcomp” function of the R statistical software package “SampleSize4ClinicalTrials’ (23).

12.2 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.

12.3 PLANNED ANALYSES

12.3.1 Datasets to be analysed, analysis populations

We refer to the master protocol

12.3.2 Analyses of immunological and clinical outcomes

We will report frequency and percentage of positive serological immune response for both vaccine arms among different pre-specified subgroups of patients most prone to complicated infections with SARS-CoV-2. These are for HIV positive individuals with less and more than 200 CD4 cells/µl, with a suppressed and unsuppressed HIV viral load (i.e. >50 copies/ml), for transplanted patients under intense (triple or quadruple immunosuppressive regimen) or less intense immunosuppressive therapy (dual immunosuppressive regimen) and for allstudy participants according to sex (male/female), age group (below 60, 60 to 69, 70 older) and history of cardiovascular diseases or metabolic syndrome.

Clinical outcomes related to COVID-19 infection and patient reported COVID-19 infection of household members will be reported as frequency with percentage for the different treatment arms.

Randomised comparison from COVERALL (only including patients from randomised COVERALL trial):

Immunological outcomes at baseline and 8-week follow-up will be reported as frequency and percentage of positive serologic immune response for both vaccine arms. The primary objective is to assess the non-inferiority of the second licensed vaccine *versus* the first licensed vaccine in regards to the presence of pan-IgG antibody, as measured by the Elecsys® Anti-SARS-CoV-2 S immunoassay. Difference in primary outcome among the two vaccine arms will be assessed by a two-sided 95% confidence interval, showing a credible range for the true difference between the second licensed vaccine and the first licensed vaccine. Non-inferiority will be established at the α significance level, if the lower limit of a 95% two-sided Wald confidence interval for the difference in antibody response proportion between participants receiving mRNA-1273 and BNT162bs vaccines is above –10%, where 10% is the pre-defined non-inferiority margin.

Randomised comparison from COVERALL (only including patients from randomised COVERALL trial): Patients will be primarily analysed according to their allocated randomization group (intention ot treat (ITT)). We will also perform analyses according to a per-protocol principle that is defined as restricting the analysis to participants who receive the three vaccine doses they were allocated to and an additional "strict" per-protocol analysis that is further restricted to individuals who provide available outcome data at week 8 ± 2 week after the 3rd vaccine. We will address sensitivity to previous natural infection with a sensitivity analyses that excludes participants with positive antibody response to the nucleocapsid protein at baseline as indicated by the Elecsys Anti-SARS-CoV-2 test Elecsys N test.

Observational analysis of all COVERALL extension participants:

Linear regression models will be used to identify the most important patient's characeristics associated to the neutralization titers (ABCORA sum of S1 signal over cut-off values of IgG, IgA, IgM). Patients' characteristics not recorded within the trial will be retrieved from the routine cohorts' follow-up visits. Factors considered for analysis of HIV patients will include the type of vaccine, age, sex, CD4 cell count at vaccination, CD4/CD8 cell count at vaccination as a proxy of immunosenescence, viral load at vaccination, CD4 nadir, history of chronic infection (tuberculosis, chronic hepatitis C), history of immune reconstitution inflammatory syndrome, presence of co-morbidities (cardiovascular disease or metabolic syndrome, autoimmune disease and cancer), smoking, immunosuppressive co-medication at vaccination, and specific antiretroviral regimen (protease inhibitor-based regimen, integrase strand transfer inhibitor (INSTI)-based regimen and tenofovir-based regimen). For transplanted patients, factors considered will be the type of vaccine, the type of transplant (kidney or lung), age, sex, cardiovascular history or metabolic syndrome, smoking status at vaccination, immunosuppression therapy (intense *versus* less intense), co-medication (induction therapy, glucocorticoids, mycophenolate mofetil (MMF), azathioprine (AZA), cyclosporine (CSA) and tacrolimus (FK)). Linear regression will be performed according to a per-protocol analysis and robustness to temporal titer variation will be addressed within a "strict" per-protocol analysis.

12.3.3 Interim analyses

No interim analysis will be done

12.3.4 Safety analysis

We expect safety issue to be small and do not believe that we will have enough power to demonstrate

any statistical difference between the treatment arms.

12.3.5 Deviation(s) from the original statistical plan

We refer to the master protocol.

12.4 HANDLING OF MISSING DATA AND DROP-OUTS

We refer to the master protocol.

12.5 QUALITY ASSURANCE AND CONTROL

12.6 DATA HANDLING AND RECORD KEEPING / ARCHIVING

We refer to the master protocol.

13. DATA MANAGEMENT

We refer to the master protocol.

14. MONITORING

We refer to the master protocol.

15. AUDITS AND INSPECTIONS

We refer to the master protocol.

16. CONFIDENTIALITY, DATA PROTECTION

We refer to the master protocol.

17. STORAGE OF BIOLOGICAL MATERIAL AND RELATED HEALTH DATA

Samples used for diagnostic will be stored for 5 years.

Samples for the ABCORA2.0 and Elecsys® Anti-SARS-CoV-2 S and N tests will be locally stored at the University Hospital virology laboratories and will be shipped by two shipments for all samples collected at baseline after completion of recruitment and after completion of the 3 months follow-up in all patient for all samples collected at three-month follow-up. Samples will be sent to the Institute of Medical Virology, University of Zurich and will be evaluated centrally. No samples will be shared with the funder of the trial (i.e. Moderna).

18. 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).

19. FUNDING AND SUPPORT

This trial extension is funded by Moderna. The set-up of the trial platform was funded by the Swiss National Science Foundation (grant # 31CA30_196245). The Swiss HIV Cohort Study (SHCS) and the Swiss Transplant Cohort Study (STCS) are funded by the Swiss National Science Foundation (SHCS: grant # 177499 and # 201369, STCS: grant # 33CS30_177522). Moderna had the possibility to read and approve the study protocol before the study was started. Otherwise, the funders will have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

20. INSURANCE

We refer to the master protocol.

21. REFERENCES

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22. APPENDICES

Not applicable