Clinical Study first sub-protocol

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®

This is the first sub-protocol linked to the mast 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"** (submitted to ethical committee: 15.12.2020, provisional approval: 01.04.2021; 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:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Category A
Study Registration:	Clinicaltrials.gov: NCT04805125Planned: kofam
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:	mRNA vaccines Comirnaty® and Covid-19 mRNA Vaccine Moderna®
Protocol Version and Date:	**Version 1.1; 07. 04. 2021**

CONFIDENTIAL

The information contained in this document is explicitly not confidential. We will make all study protocols (including master protocol, sub-protocols, as well as amendments) publicly available on Open Science Framework (https://osf.io/)

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 first sub-protocol

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®

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

Basel 10.3.2021

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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Local Principal Investigator at study site*:

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Clinical Study first sub-protocol

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®

Site	University Hospital Basel Dep. of Infectious Diseases and Hospital Hygiene Petersgraben 4 4031 Basel
Principal investigator	Dr. Marcel P. Stoeckle

Universitätsspital Basel
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Dr. Marcel Stöckle
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Basel, 09.03.21

Place/Date

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Clinical Study first sub-protocol

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®

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

Zürich, 8 April 2021 — Place/Date

H. Günthard — Signature

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Clinical Study Master-protocol

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

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

Bern, 8/02/21

Place/Date

Signature

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Clinical Study first sub-protocol

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®

Site	Universitätsspital Zürich Klinik für Pneumologie Rämistrasse 100 8091 Zürich
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Zürich, 11/2/2021

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Clinical Study first sub-protocol

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®

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

Lausanne, 8.2.2021

Place/Date

Signature

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Local Principal Investigator at study site*:

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Clinical Study first sub-protocol

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®

Site	CHUV Service des maladies infectieuses Rue du Bugnon 46 1011 Lausanne
Principal investigator	Prof. Matthias Cavassini

Lausanne, le 8.2.2021 _____

Place/Date Signature

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Clinical Study first sub-protocol

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®

Site	Universitätsspital Zürich
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	Rämistrasse 100
	8091 Zürich
Principal investigator	Prof. Thomas Müller

Zürich, 03/02/21
Place/Date

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Clinical Study first sub-protocol

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®

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

8/2/2021 Basel

Place/Date

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Clinical Study first sub-protocol

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®

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

Basel 9/2/21 | Place/Date

| Signature

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In the master protocol (submitted to ethical committee on the 15. December 2020; EC ID 2021-000593) we described the platform and the outline for our pilot trial which will randomise patients from the Swiss Transplant Cohort Study (STCS) and the Swiss HIV Cohort Study (SHCS) to the two SARS-CoV-2 vaccines that are first approved in Switzerland. In the meantime the first two SARS-CoV-2 vaccines reached market authorisation by Swissmedic. Therefore, we present here in the first sub-protocol of a head to head comparison of the vaccines by Pfizer/Biontech and Moderna for use in immune- compromised patient and provide the following iinformation that could not be specified in the master protocol, because interventions were not yet approved:

- Updated Study schedule
- Current available evidence for the two selected study interventions comparison
- Updated inclusion and exclusion criteria
- Specific description of the interventions (i.e. application, dosage, storage conditions, concomitant treatment).

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: First sub-protocol for a pilot trial comparing the mRNA vaccines Comirnaty® and Covid-19 mRNA Vaccine Moderna®

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.

In phase III licensing trials of both vaccines, vaccine efficacy of 95% and 94% were found and both vaccines appeared to be save. However, few individuals with HIV infection were included in both trials and no solid organ recipients were enrolled in the trials.

Data on vaccine efficacy, induced immune response and safety in immunocompromised individuals with chronic HIV infection or solid organ transplantation is missing. We intend to close this information gap with a pilot trial, which represents the first-sub-study trial of the established trial platform that is linked and nested into the existing prospectively collected data structure of the Swiss HIV Cohort Study (SHCS) and the Swiss Transplant Cohort Study (STCS).

Objectives and Endpoints:
To investigate the operability of a platform trial that is nested into two existing cohort studies and compare immune response, safety and clinical efficacy of the first two mRNA vaccines (Comirnaty® by Pfizer / BioNTech and COVID-19 mRNA Vaccine Moderna®, by Moderna) in immune compromised patients in the Swiss HIV and Swiss Transplant Cohort studies.

Feasibility endpoints:

We refer to the master protocol

Immunological endpoints (primary endpoint)

- 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

Clinical Endpoints

- Newly PCR-confirmed symptomatic SARS-CoV-2 infection
- Severe COVID-19 infection, hospitalization due to COVID-19 or death
- COVID-19 burden of diseases (BOD)
- Patient reported asymptomatic or symptomatic infections of household members.

Safety endpoints

- Adverse events from vaccines and
- Serious adverse events

Overall Design:
Multicenter randomised controlled, open-label, 2-arm sub-study pilot trial of a platform trial nested in two national cohorts

Number of Participants enrolled:
Eligible individuals are screened and flagged in both cohorts according to priority vaccination recommendations by the BAG. We will randomise 380 patients from both cohorts (recruitment of

patients from the Swiss Transplant Cohort Study will be limited to kidney and lung transplant recipients. These patients will be randomised to vaccination with Comirnaty® or the COVID-19 mRNA Vaccine Moderna®.

Intervention Groups and Duration:

Participants of the Swiss HIV Cohort and Swiss Transplant Cohort Studies with informed consent and no exclusion criteria will be centrally randomised via the trial platform to vaccination with mRNA vaccines COVID-19 mRNA Vaccine Moderna® or Comirnaty® (Pfizer / BioNTech) at day 0 with booster vaccines at day 21 and day 28, respectively. Antibodies against Sars-Cov-2 will be measured at baseline and 12 weeks with the Elecsys® anti-SARS_CoV_2 S and N (Roche Rotkreuz Siwtzerland) and ABCORA2.0 (IMV) assays. Vaccine related AE will be assessed at 12 weeks. SAE and asymptomatic or symptomatic Sars-Cov-2 infection (PCR confirmed) and hospitalisation, ICU admission, or death from any cause will be recorded at 48 weeks within the clinical trial platform and by routine cohort data collection.

STUDY SCHEDULE

		STUDY PERIOD				
	Eligibility	**Enrolment, randomisation & vaccination**	**Post-randomisation**			
TIMEPOINT	**Approximately -12 weeks**	**Day 0**	**Week 4**	**Week 12 (±7 days)**	**Week 48 (±7 days)**	**Continuous follow-up in the frame of the cohort**
ENROLMENT:						
Eligibility screen[a]	X[a]					
Eligibility assessment	X					
Informed consent		X[a]				
Allocation		X[b]				
INTERVENTIONS:						
Intervention COVID-19mRNA Vaccine Moderna®		X	X			
Control Comirnaty® (Pfizer/BioNTntech vaccine)		X	X			
ASSESSMENTS:						
BASELINE VARIABLES (will be exported from routine cohort data) Baseline blood sample	X					
IGG neutralizing antibodies post randomisation but prior to vaccination		X				
CLINICAL OUTCOMES:	X[e]	X[e]				
- Immune response IgG neutralizing antibodies		X		x[c]		
- Newly confirmed asymptomatic SARS-CoV-2 infection				x[c]	x[c,d]	x[d]
-Newly confirmed symptomatic SARS-CoV-2 infection				x[c]	x[c,d]	x[d]
- Severe COVID-19 infection with respiratory failure, evidence of shock, organ failure, admission to ICU, or death				x[c]	x[c,d]	x[d]
- Adverse events from vaccines				x[c]		
-Serious adverse events			x[c,d]	x[c]	x[c,d]	x[d]
- PCR confirmed symptomatic infections of household members				x[c]	x[c,d]	x[d]

[a]Continuous assessment and selection from routinely collected cohort data

[b]Enrolment and concealed allocation of patients with informed consent will be performed during the same visit when the study is explained to the patient, or, if preferred, during a separate arranged study visit.

[c]Assessed in separate data entry form for the trial

[d] Assessed by routine data collection from cohort data base

[e]Baseline blood samples will be taken from previous cohort visits (no longer than 6 months) or during cohort and randomisation visits at day 0.

1. STUDY ADMINISTRATIVE STRUCTURE

A safety committee consisting of two infectiologists not otherwise involved in the trial and a biostatistician will be formed to oversee patient enrolment and efficacy and safety issues with respect to vaccines used during the pilot trial.

1.1 Sponsor-Investigator

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1.6 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 for the sub-study pilot trial.

1.7 Data Safety Monitoring Committee

An independent data safety monitoring board (IDSMB) will be established which will be advisory to the Trial Committee that constitutes of the PI and the co-investigators. The IDSMB will be regularly informed about any safety aspects and on serious adverse events from vaccinations from the first sub-study protocol and it will provide the primary investigator and the co-investigators with recommendations about the further conduct of the trial.

For further details we refer to the master protocol.

1.8 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

1.9 Authors contributions

Heiner Bucher (HB); Michael Koller (MK); Matthias Briel (MB); Lars Hemkens (LG); Frédérique Chammartin (FC); and Benjamin Speich (BS) designed the study. Nicolas Müller (NM); Huldyrch Günthard (HG); Andri Rauch (AR); Daniel Smith (DS) and Katharina Kusejko (KK) gave scientific input. HB wrote the first draft of the sub-protocol. All authors critically revised and approved the final version of the study protocol. 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 pilot-trial will also be registered with the Koordinationsstelle Forschung am Mensch (kofam).

2.2 Categorisation of study

Category A. This sub-study pilot trial will use vaccines against SARS-CoV-2, which have been licensed by Swissmedic in accordance with the prescribing information approved by Swissmedic, and which - by guidelines from the BAG and Kommission für Impffragen - may be used in immune suppressed individuals when considering the individual benefits and risks.

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 pilot trial sub-study 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 a clinical trial unwise,
- evidence of harm from investigated vaccines

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 (1-3). 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 (4, 5).

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 those with comorbidities. Likewise, data on immune response overall and in subgroups is not yet available (6, 7).

In particular very few individuals in both trials with HIV infection were included (with no information on the CD4 cell count at the time point of vaccination and no solid organ recipients were allowed in the trials).

Data on vaccine efficacy, 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 pilot trial which represents the first sub-study trial of the established trial platform that is linked and nested into the existing prospectively collected data structure the two most prominent cohort studies in Switzerland, the Swiss HIV Cohort Study (SHCS) and the Swiss Transplant Cohort Study (STCS) (8, 9).

3.2 Investigational Product (treatment, device) and Indication

3.3 Preclinical Evidence

We summarize and cite from the published study and online submission documents handed-in to FDA and only cite relevant early safety and efficacy data. For all preclinical data we refer to the summaries in the online submission documents (10, 11).

Pfizer / BioNTech conducted several pilot studies to test the **immunogenicity and safety of BNT162-01**. All these studies are ongoing. BNT162-01 is an ongoing dose finding escalating study with investigation of immunogenicity in 60 adults aged 18-55 years (Phase I). C4591001 is an ongoing phase I II III observer blind placebo controlled trial where in phase I 90 individuals are randomised in a 4 to 1 ratio within each dose and age group of adults aged 18-55 and 65 -85 years and vaccine doses of 10, 20, and 30 µg. Phase II randomised 360 individuals 1:1 to vaccine (30 µg) vs placebo in two age groups 18-55 and 65-85 years of age. Phase III randomised approximately 44'000 participants and includes all phase II participants in a 1:1 ratio vaccine (30 µg) vs placebo in three age groups 12-15 years, 16-55 years and >55 years of age.

Study BNT162-01 by Pfizer / BioNTech is the ongoing, **Phase 1 dose level-finding study**, in which healthy adults 18 to 55 years of age all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. The data for BNT162b2 30 µg were available from 58 participants completed BNT162b2 dosing in the Phase 1 part of the study. The reasons for study discontinuation by each of 2 participants were AE (10 µg group) and participant withdrawal (1 µg group).

After administration of Dose 1 and prior to administration of Dose 2, BNT162b2 showed modest increases in SARS-CoV-2 neutralizing geometric mean titers (GMTs) over baseline, followed by a boost effect after dose 2 that was most pronounced at the 30 µg dose level. At Day 50 post first vaccination, the neutralizing GMT in the 10 µg and 30 µg BNT162b2 participants remained above the GMT in the human convalescent serum (HCS). Further evaluation of antibody persistence is ongoing.

In the **C4591001 Phase 1 study** BNT162b2 was administered to 45 younger participants among whom 42% were male and 58% were female, 87% were White, 4% were Hispanic/Latino, with a median 37 years of age. BNT162b2 was administered to 45 older participants among whom 38% were male and 62% were female, 100% were White, none were Hispanic/Latino, with a median 68 years of age. All participants received both vaccine doses and none discontinued the study as of the data cutoff date of 14 November 2020, after approximately 4 months of follow-up.

In the *Phase 1 portion of Study C4591001*, after administration of Dose 1 and prior to administration of Dose 2, BNT162b2 showed modest increases in SARS-CoV-2 neutralizing GMTs over baseline across dose levels and younger and older groups. Overall, BNT162b2 elicited higher antigen-binding and neutralizing responses in younger participants than in older participants. The boost effect after receiving Dose 2 was most pronounced at the 30 µg dose level for older participants. GMTs measured at 7 days after Dose 2 for BNT162b2 at the 30 µg dose were 360.9 in the younger group and 155.7 in the older group. When compared to an HCS panel GMT of 94, the GMT for the younger group was approximately 3.8-times that of HCS and for the older group was approximately 1.7-times that of HCS.18 By 1 month after Dose 2, GMTs were generally stable and remained approximately 1.6- to 1.9-times that of HCS.

In summary, based on immunogenicity results from Phase 1 participants in Study C4591001, BNT162b2 elicited robust SARS-CoV-2 neutralization and S1-binding IgG antibody levels in younger healthy adults 18 to 55 years of age, and in older healthy adults 65 to 85 years of age. Immune responses were generally stronger in the younger group than in the older group. SARS-CoV-2 neutralizing titers GMTs were higher than those observed in an HCS18 panel from people recovered from COVID-19. Responses were evident after the first dose and substantially boosted after the second dose, supporting the need for a 2-dose vaccination series.

Most participants who received both doses of BNT162b2 had strong SARS-CoV-2 S protein-specific CD4+ (39/39, 100%) and CD8+ (35/39, 89.7%) T cell responses. These T cell responses were directed against different parts of the antigen including epitopes in the receptor-binding domain (RBD), indicating the induction of multi-epitope responses by BNT162b2.

Dosing twice with BNT162b2 led to a substantial increase in the incidence and magnitude of T cell responses. Overall, the mean fraction of S-specific CD4+ and CD8+ T cells was substantially higher (eg, S protein sub-pool 1 IFNγ CD8+ response of 30 µg dosed participants was 12.5-fold above) than that observed in 18 individuals who recovered from COVID-19.

Fore safety data on phase I studies see below.

The mRNA-1273 vaccine manufactured by Moderna, encodes the S-2P antigen, consisting of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1–S2 cleavage site. S-2P is stabilized in its prefusion conformation by two consecutive proline substitutions at amino acid positions 986 and 987, at the top of the central helix in the S2 subunit. The lipid nanoparticle capsule composed of four lipids is formulated in a fixed ratio of mRNA and lipid.

The vaccine was tested in a **phase 1 dose finding open labeled study** in 45 healthy adults, 18 to 55 years of age, who received two vaccinations, 28 days apart, with mRNA-1273 in a dose of 25 µg, 100 µg, or 250 µg. There were 15 participants in each dose group. The vaccine was administered as a 0.5-ml injection in the deltoid muscle on days 1 and 29; follow-up visits were scheduled for 7 and 14 days after each vaccination and on days 57, 119, 209, and 394. The dose-escalation plan specified the staggered enrollment of patients in the three dose groups allowing for additional enrolement when no halting rules were met. Participants recorded local and systemic reactions, using a memory aid, for 7 days after each vaccination.

No serious adverse events were noted, and no prespecified trial halting rules were met. One participant in the 25-µg group was withdrawn because of an unsolicited adverse event, transient urticaria, judged to be related to the first vaccination. After the first vaccination, solicited systemic adverse events were reported by 5 participants (33%) in the 25-µg group, 10 (67%) in the 100-µg group, and 8 (53%) in the 250-µg group; all were mild or moderate in severity. Solicited systemic adverse events were more common after the second vaccination and occurred in 7 of 13 participants (54%) in the 25-µg group, all 15 in the 100-µg group, and all 14 in the 250-µg group, with 3 of those participants (21%) reporting one or more severe events. After the second vaccination, no participants in the 25-µg group, 6 (40%) in the 100-µg group, and 8 (57%) in the 250-µg group reported fever; one of the events (maximum temperature, 39.6°C) in the 250-µg group was graded severe. Local adverse events, when present, were nearly all mild or moderate, and pain at the injection site was common

Binding antibody responses were assessed against S-2P and the isolated receptor-binding domain, located in the S1 subunit by ELISA. Vaccine-induced neutralizing activity was assessed by a pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA) and by live wild-type SARS-CoV-2 plaque-reduction neutralization testing (PRNT) assay. ELISA and PsVNA were performed on specimens collected from all participants on days 1, 15, 29, 36, 43, and 57. For the PsVNA results were only available for the day 1 and day 43 time points in the 25-µg and 100-µg dose groups. For comparison of the participants' immune responses with those induced by SARS-CoV-2 infection, 41 convalescent serum specimens were also tested.

T-cell responses against the spike protein were assessed by an intracellular cytokine–staining assay, performed on specimens collected at days 1, 29, and 43. Results were available only for the 25-µg and 100-µg dose groups.

Binding antibody IgG geometric mean titers (GMTs) to S-2P increased rapidly after the first vaccination and all participants seroconverted by day 15 Dose-dependent responses to the first and second vaccinations were found. Receptor-binding domain–specific antibody responses were similar in pattern and magnitude. For both assays, the median magnitude of antibody responses after the first vaccination in the 100-µg and 250-µg dose groups was similar to the median magnitude in convalescent serum specimens, and in all dose groups the median magnitude after the second vaccination was in the upper quartile of values in the convalescent serum specimens. The S-2P ELISA GMTs at day 57 (299,751 [95% CI, 206,071 to 436,020] in the 25-µg group, 782,719 [95% CI, 619,310 to 989,244] in the 100-µg group, and 1,192,154 [95% CI, 924,878 to 1,536,669] in the 250-µg group) exceeded that in the convalescent serum specimens (142,140 [95% CI, 81,543 to 247,768]).

No participant had detectable PsVNA responses before vaccination. After the first vaccination, PsVNA responses were detected in less than half the participants, and a dose effect was seen and after the second vaccination PsVNA responses were identified in serum samples from all participants. The lowest responses were in the 25-µg dose group, with a geometric mean ID50 of 112.3 (95% CI, 71.2 to 177.1) at day 43; the higher responses in the 100-µg and 250-µg groups were similar in magnitude (geometric mean ID50, 343.8 [95% CI, 261.2 to 452.7] and 332.2 [95% CI, 266.3 to 414.5], respectively, at day 43). These responses were similar to values in the upper half of the distribution of values for convalescent serum specimens. Before vaccination, no participant had detectable 80% live-virus neutralization at the highest serum concentration tested (1:8 dilution) in the PRNT assay. At day 43, wild-type virus–neutralizing activity capable of reducing SARS-CoV-2 infectivity by 80% or more (PRNT80) was detected in all participants, with geometric mean PRNT80 responses of 339.7 (95% CI, 184.0 to 627.1).

The 25-µg and 100-µg doses elicited CD4 T-cell responses with expression of Th1 cytokines (tumor necrosis factor α > interleukin 2 > interferon γ), and minimal type 2 helper T-cell (Th2) cytokine expression (interleukin 4 and interleukin 13). CD8 T-cell responses to S-2P were detected at low levels after the second vaccination in the 100-µg dose group.

3.4 Clinical Evidence to Date

We summarize and cite from the published study and submission documents handed in to FDA (10, 11).

In response to the global health crisis, **Pfizer and BioNTech** submitted November 20, 2020 an Emergency Use Authorization (EUA) application **(EUA request 27034) for the COVID-19 Vaccine (BNT162b2)** to FDA. The vaccine is based on a SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA formulated in lipid nanoparticles (LNPs). In parallel submission to EMA and Swissmedic were done and Swissmedic licensed the vaccine on December 19, 2020.

The EUA request by Pfizer / BioNTech includes **safety and efficacy** data from approximately 38,000 participants randomised 1:1 to receive either vaccine or placebo with a median of 2 months of follow-up after Dose 2 of the 2-dose vaccine regimen in Study C4591001 show that BNT162b2 at 30 µg was safe and well-tolerated in participants ≥16 years of age (6, 10).

In 37,706 participants, the duration of follow-up was ≥2 months post Dose 2 for 50.6% of participants. Duration of follow up was ≥1 month post Dose 2 for 91.6% of participants. Median age was 52 years and 50.6% of participants were male. The younger and older age groups were 57.8% and 42.2% of participants, respectively. Obese participants made up 35.1% of this safety population. Across both treatment groups, 20.5% had any comorbidity (per the Charlsson Comorbidity Index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and

pulmonary disease (7.8%) and were reported at similar frequencies in each group. More participants had comorbidities in the older population (31.1%) than the younger population (12.8%), including diabetes (14.6% and 3.8%), malignancy (7.4% and 1.0%), and pulmonary disease (8.8% and 7%). Overall, 0.3% of participants were HIV-positive.

Overall, 0.2% of randomised participants did not receive study vaccine. A small percentage of participants discontinued study vaccine after Dose 1 and before Dose 2 (0.6%) overall. The most frequently reported reasons for discontinuation included: no longer meets eligibility criteria (0.3% BNT162b2; 0.4% placebo; the most common reasons were previous clinical or microbiological diagnosis of COVID-19), withdrawal by participant, and AE. Withdrawals due to AE were reported for 0.1% of participants in both treatment groups.

All participants in Phase 1 and a subset of at least 6000 participants in Phase 2/3 were planned to record local reactions, systemic events, and antipyretic/pain medication usage for 7 days, following administration of study intervention using an electronic diary (ediary) from Day 1 through Day 7 after each dose.

For any Phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as AEs.

Phase 2/3 AE data were analyzed for the safety population overall and by: Evidence of prior SARS-CoV-2 infection at baseline per nucleic acid amplification test (NAAT) or N-binding antibody assay and by subgroup factors (ie, age, sex, race, ethnicity).

Immunogenicity was evaluated in Phase 1 using a SARS-CoV-2 serum neutralization assay to determine titers and a SARS-CoV-2 S1 binding IgG direct Luminex immunoassay to determine antibody binding levels. Fold rises were also assessed. Only qualified assays were used.

Immunogenicity data were analyzed and reported using descriptive summary statistics of GMTs/geometric mean concentrations (GMCs) and geometric mean fold-rises (GMFRs) for the evaluable immunogenicity population.

Efficacy was assessed based on confirmed cases of COVID-19, for which the case onset date was the date that symptoms were first experienced by the participant and the cases met evaluable criteria. For participants with multiple confirmed cases, only the first case contributed to the VE calculations. Evaluable cases consisted of a positive virological test plus at least one COVID-19 symptom

First primary efficacy endpoint in the phase III trial was COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2. The second primary endpoint was COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

A pre-specified interim analysis of the first primary efficacy endpoint was conducted after accrual of 94 COVID-19 cases. Among participants included in the evaluable efficacy population at the time of the interim analysis, 32,279 participants overall (16,061 in the BNT162b2 group and 16,218 in the placebo groups) did not have evidence of prior infection with SARS-CoV-2 before and during vaccination regimen.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. The 95% credible interval for the VE was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability given the observed data.

Among participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively. The posterior probability of >99.99% for the true VE greater than 30% met the pre-specified success criterion of >98.6% for this endpoint. The 95% credible interval for the VE was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

In total 37,586 participants were included in the **AE analyses** presented in the sections below.

Results for all enrolled participants (N=43,252 participants) who had variable follow up from Dose 1 to the data cutoff date of 14 November 2020 are also presented below. For the 37,586 participants who had a median of at least 2 months of follow-up after Dose 2 (including those analyzed in Phase 2) the numbers of overall participants who reported at least 1 AE and at least 1 related AE were higher in the BNT162b2 group as compared with the placebo group. This trend continued to be seen through the data cutoff date for all enrolled participants (43,252 participants). Few participants in either group had severe AEs, SAEs, or AEs leading to study withdrawal. The incidences of deaths reported were low and similar in the BNT162b2 (1; 0.0%) and placebo (2; 0.0%) groups.

In the younger age group, the number of participants who reported at least 1 AE from Dose 1 to 1 month after Dose 2 was 3177 (29.3%) and 1427 (13.2%) in the BNT162b2 and placebo groups, respectively. In the older age group, the number of participants who reported at least 1 AE from Dose 1 to 1 month after Dose 2 was 1894 (23.8%) and 929 (11.7%) in the BNT162b2 and placebo groups, respectively. Among the 37,586 participants, no clinically meaningful differences in AEs by category were observed by age, sex, race/ethnicity, or baseline SARS-CoV-2 status subgroups.

The EUA request by **Moderna** includes safety and efficacy data from an ongoing Phase 3 randomised, double-blinded and placebo-controlled trial **of mRNA-1273 in approximately 30,400 participants** (7, 11). The primary efficacy endpoint was the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2. In an interim analysis conducted using a data cut-off of November 7, 2020, a total of 27,817 participants randomised 1:1 to vaccine or placebo with a median 7 weeks of follow-up post-dose 2 were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to vaccination. Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5.0% (95% CI 86.5%, 97.8%) with 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 (11 protocol-defined severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group), in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for some of these outcomes did not allow for firm conclusions. Efficacy data from the final scheduled analysis of the primary efficacy endpoint (data cut-off of November 21, 2020, with a median follow-up of >2 months post-dose 2) demonstrated a VE of 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group and was consistent with results obtained from the interim analysis. The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to < 65 years of age and 86.4% (95%CI: 61.4%, 95.5%) for participants ≥ 65 years of age. A final secondary efficacy analysis also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 cases in the vaccine group.

Safety data from a November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomised 1:1 to vaccine or placebo with a median of 7 weeks of follow-up after the second dose supported a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. These safety data are the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cut-off of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Key safety data from this later submission, including death, other serious adverse events, and unsolicited adverse events of interest were independently verified and confirmed not to change the safety conclusions from the interim safety analysis.

The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and 6 Moderna COVID-19 Vaccine VRBPAC Briefing Document chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ≥65 years of age as compared to younger participants. Among unsolicited

adverse events of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff, lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Lymphadenopathy (axillary swelling and tenderness of the vaccination arm) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients < 65 years of age and in 12.4% of vaccine recipients ≥ 65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5 of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic severe hypersensitivity reactions with close temporal relation to vaccine. Throughout the safety follow-up period there were three reports of facial paralysis (Bell's palsy) in the vaccine and one in the placebo group. There were no other notable patterns of numerical imbalances between treat groups for specific categories of adverse events (including other neurologic, neuroinflammatory, and thrombotic events) that would suggest a causa relationship to mRNA-1273.

The frequency of serious adverse events was low (1.0% in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which was numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

With the exception of more frequent, generally mild to moderate reactogenicity in participants <65 years of age, the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrolment.

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

(ICH/E6 6.2.4; SPIRIT #6a)
ICH: Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

Application of vaccines in the intervention and comparator arm will be done according to the product specifications by the producers and Swissmedic using the dosing and vaccination schedule as by the recommendations by the producer and the Schweizerisches Bundesamt für Gesundheit.

The vaccine COVID-19 mRNA Vaccine Moderna® is licensed to be used in adults (older than 18 years) and is to be applied by intramuscular infections. The proposed dosing is 30 microgram on day 0 and day 28 and the vaccine was licensed January 12, 2021 by Swissmedic (11).

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3.6 Explanation for choice of comparator (or placebo)

(SPIRIT #6b)

The Pfizer / BioNTech COVID-19 vaccine, BNT162b2 (30 µg) Comirnaty®, is administered intramuscularly (IM) as a series of two 30 µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single dose followed by a second dose, waiting at least 21 days later (recommended: 28 days in Switzerland) and the vaccine was licensed by Swissmedic December 19, 2021 (12).

3.7 Risks / Benefits

(ClinO, Appendix 4, 3.5; Art 25d2; ICH/E6 6.2.3; SPIRIT #6a; MD: ISO 14155 Annex A & ISO 14971)
ICH: Summary of the known and potential risks and benefits, if any, to human subjects.

In December 2020 between 80 to 100 individuals in Switzerland died per day from Covid-19. Actual rates are lower following more stringent public health measures with a partial lock-down, but rising mutant infections with higher transmission rates are of concern. Introduction of vaccines is the only valid strategy to confine the pandemic by inducing a sufficiently high herd immunity. At the forefront of

the vaccine strategy by BAG is the vaccination of the elderly and frail population suffering from comorbidity. The current trials addressed the very important issue of vaccine induced immunogenicity and safety data in immune-compromised individuals who were not or only to a very limited extend included into the ongoing phase III vaccine trials by Pfizer / BioNTech and Moderna.

The so far existing evidence for both vaccines to be compared in the current trial show strong immune responses in the short observation periods of roughly 60 days, suggesting that both vaccines confer protection against Covid-19 and complications from Covid-19 infection (10, 11).

The potential risk conferred by the vaccines as judged by the safety profile which indicate mostly mild adverse events and a very low incidence of severe adverse events with no apparent marked differences between the vaccine and placebo groups.

Vaccine efficacy for both vaccines was well above 90% in the pre-planned interim analysis (6, 7).

However, it is not known to what extend the actually available immunogenicity, vaccine efficacy and safety data relate to immune compromised individuals. In both phase III trials of vaccines by Pfizer / BioNTech and Moderna no patients with organ transplants were included. In the trial by Pfizer / BioNTech and Moderna there were 121 and 179 HIV positive individuals included (6, 7). No subgroup data on trial efficacy and safety of these individuals and on the level of immunosuppression in this sub-population was reported. Also no data on immune response in HIV positive patients was reported. The present trial fills in this evidence gap by comparing the first two licensed vaccines in Switzerland against Sars-CoV-2 in immune compromised hosts. Nesting the trial into an existing cohort infrastructure allows for the monitoring of vaccine efficacy and long-term safety in an efficient and cost-saving way

3.8 Justification of choice of study population

According to the recommendation by the Bundesamt für Gesundheit (13) the following conditions define patient groups of high priority of vaccinations which include the primary target groups of this trial i.e. patients with HIV infection, solid organ transplantation and patients with these basic conditions plus additional comorbidities. The guidelines stress that due to the limited evidence on safety and efficacy of vaccines against SARS-CoV-2 patients with acquired immune deficiency and immune-suppressive therapy decision for vaccination has to be taken by the treating clinicians by considering risks and benefits for the individual patient.

Comorbidity / Category organ system	**Priority Grouping 1: High risk BGP** (Detailed definitions)
Heart diseases	- congestive heart failure NYHA II - Symptomatic chron. Ischemic coronary heart disease
Hypertension	- Hypertension with systolic blood pressure > 160 mm HG regardless of antihypertensive therapy - Hypertension with cardiac complications and end organ damage
Pulmonary diseases	- COPD, stage GOLD II or above - Emphysema/severe bronchiectasis - Pneumopathy / Lung fibrosis - lung disease with severe reduction of vital capacity
Kidney diseases	- Severe chronic kidney disease with GFR <30ml/min/174m^2
Diabetes	- Diabetes (Type 1 or 2) with relevant organ damage or HbA1c ≥8%

Obesity	- BMI ≥35 kg/m².
Immunodeficiency*, inborne and acquired diseases and immuno-suppressive therapy	Relevant immunodeficiency with - malignant haematological disease - Neoplasia/cancer under active therapy - immune-mediated inflammatory diseases (e.g.. systemic lupus erythematodes, rheumatoid arthritis, psoriatic disease, chronic inflammatory bowel disease), with immunosuppressive therapy (including prednisolone-equivalent >20 mg/day, steroid-sparing therapy and biologicals). - HIV-Infection with CD4+ T cells < 200 / µL. - Organ transplantation, bone marrow or stem-cell transplantation, individuals on waiting list for transplantation

4. STUDY OBJECTIVES

4.1 Overall Objective

We refer to the master protocol.

4.2 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.

4.3 Objectives related to a platform based nested pilot trial to investigate the comparative effectiveness of vaccines against Sars-CoV-2

The study seeks to determine the following SARS-CoV-2 related objectives (for detailed definitions see under 5 study endpoints) which are all developed according to FDA recommendations for phase III Covid-19 vaccine licensing trials (14)):

- 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,
- COVID-19 burden of diseases (BOD)
- Patient reported asymptomatic or symptomatic infections of household members.
- Safety parameters
    - Adverse events from vaccines and
    - Serious adverse events

4.4 Safety Objectives

To evaluate the safety of vaccines in immunocompromised patients and risks for adverse events (AEs) and serious adverse events (SAEs).

5. STUDY OUTCOMES

For the feasibility outcomes we refer to the master protocol.

5.1 Immunological Outcomes

The primary immunological endpoint are antibodies to the SARS-CoV-2 spike (S1) protein receptor binding domain (RBD) in human serum and plasma assessed by the commercial immunoassay

Elecsys® Anti-SARS-CoV-2 S for the in vitro quantitative determination (15). This assay detects pan-Ig antibody response (pan-Ig anti–S1-RBD) and allows for a quantitative assessment of the serological response of the participants at baseline and three months after vaccination. Additionally, we will qualitatively measure anti-Nucleocapsid (N) responses with Elecsys® Anti-SARS-CoV-2 N assay to gain a broader insight on the immune response of the participants.

In addition 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) will be measured. The ABCORA 2.0 test has an advantage over commercial available tests, as it allows 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

5.2 Clinical Outcomes

The clinical effectiveness endpoints are (according to FDA recommendations for phase III Covid-19 vaccine licensing trials (14)) the following:

- Newly PCR-confirmed asymptomatic COVID-19 infection (identified by the presence of anti–SARS-CoV-2 nucleocapsid antibodies or SARS-Cov-2 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 point in within 48 weeks following randomisation.
- 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 point in within 48 weeks following randomisation
- 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; and death at any time point in within 48 weeks following randomisation.
- COVID-19 burden of diseases (BOD), a composite of the above endpoints. The BOD is will be scored as by using 0 for no COVID-19, 1 for non-severe COVID-19, and 2 for severe COVID-19.

An additional clinical effectiveness endpoint is patient reported asymptomatic or symptomatic infections of household members.

All clinical outcomes will be measured in the trial database during a follow-up period of 48 weeks after randomisation and vaccination.

5.3 Other Outcomes of Interest

None.

5.4 Safety Outcomes

5.4.1 Collection of solicited local and systemic adverse events will for feasibility reasons be reduced to:

- 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

6. STUDY DESIGN

6.1 General study design and justification of design

This is a pilot trial which is based on a trial platform that is integrated into the ongoing routine prospective data collection of two national cohorts, the SHCS and STCS. Eligibility of trial participants will be checked from routinely collected cohort data. Baseline data collection is done within cohorts. Randomisation and follow-up data collection of clinical trial endpoint data is done within the trial platform which is linked to the cohort database. The trial platform is overseen and managed by the two data centres of the SHCS and STCS.

A parallel two-arm, open-label randomised controlled pilot trial comparing the first approved SARS-CoV-2 vaccines (Comirnaty® by Pfizer/ BioNTech and COVID-19 mRNA Vaccine Moderna® by Moderna) is planned to compare the immunogenicity, clinical effectiveness and safety of the first two licensed vaccines against Sars-CoV-2.

Enrolment of patients is explained in figure 1 of the master protocol. Cohort data centres will identify eligible patients based on routinely collected cohort data and eligible patients will be flagged according to the priority vaccination criteria by the BAG and contacted for consent for participation prior to randomisation. Randomisation will be performed through minimisation with respect, center, age (<65, ≥65 years old), sex, immune-suppression (<200 CD4 cells/µl in SHCS and uninterrupted prednisone treatment of at least 6 months in addition to standard immunosuppression in STCS) and a random element that reduces randomisation predictability. The minimisation will be conducted for each cohort separately. The trial platform allows to expand the pilot trial and to add further sub-study protocols to evaluate for example vaccine strategies in patients with a first vaccination but insufficient or lacking immune response (Figure 1 master protocol)

6.2 Methods of minimising bias

6.2.1 Randomisation

We refer to the master protocol.

6.2.2 Blinding procedures

We refer to the master protocol.

6.2.3 Other methods of minimising bias

We refer to the master protocol.

6.3 Unblinding Procedures (Code break)

Not applicable.

7. STUDY POPULATION

This is a multi-centre study recruiting patients from 4 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, and CHUV Lausanne). 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, University Hospital Lausanne, University of Lausanne
- 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

- CHUV Lausanne, Service des maladies infectieuses
- CHUV Lausanne, Service de pneumologie
- CHUV Lausanne Service de néphrologie
- Universitätsspital Basel, Pneumologie
- Universitätsspital Basel, Transplantationsimmunologie & Nephrologie,

The cohorts are described in more detail elsewhere (8, 9, 16, 17). The study will be explained to eligible patients during their visit at the cohort centre. These visits will not be scheduled specifically for the purpose of this study.

7.1 Eligibility criteria

Inclusion and exclusion criteria as defined in the master protocol:

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 the pilot trial
- Covid-19 vaccination recommended by treating physician

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 previous PCR documented SARS-CoV-2 infection and, or documented antibodies less than 3 months prior to randomisation
- 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

7.2 Recruitment and screening

We refer to the master protocol.

7.3 Assignment to study groups

We refer to the master protocol.

7.4 Criteria for withdrawal / discontinuation of participants

We refer to the master protocol.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment / medical device)

(ICH/E6 6.2.1, 6.4.2, 6.4.4)

ICH: A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s).

Describe all trial treatments for each arm of the study.

8.1.1 Experimental Intervention (treatment / medical device)

ICH: Name and description of the investigational product(s).

The COVID-19 mRNA Vaccine Moderna® is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose. The COVID-19 mRNA Vaccine Moderna®(100 µg) is administer ed intramuscularly as a series of two doses (0.5 mL each), given 28 days apart. The vaccine is injected in the deltoid muscle.

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

ICH: Name and description of the investigational product(s).

The COVID-19 Vaccine, BNT162b2 (30 µg) commercial name Comirnaty® developed by Pfizer / BioNTech, is administered intramuscularly (IM) as a series of two 30 µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single dose followed by a second dose 28 days later (12). BNT162b2 is supplied as a multiple-dose (5-dose) vial containing a frozen (between -80ºC to -60ºC suspension that is preservative-free. BNT162b2 must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 5 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C and used within 6 hours from the time of dilution..

8.1.3 Packaging, Labelling and Supply (re-supply)

ICH: Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

The COVID-19 mRNA Vaccine Moderna® is a suspension for Intramuscular Injection. 10 multiple-dose vials (each vial contains 10 doses of 0.5 mL). 5 ml dispersion in a vial (type 1 or type 1 equivalent glass) with a stopper (chlorobutyl rubber) and a flip-off plastic cap with seal (aluminium seal). Each vial contains 10 doses of 0.5mL. Pack size: 10 multidose vials. Vials should be protected from light and be stored frozen between -25° to -15°C for a maximum of 30 days. The vaccine may not be stored on dry ice or temperature below -40°C. The vaccine should be prepared and administered by a trained healthcare professional using aseptic techniques to ensure sterility of the dispersion. The vaccine comes ready to use once thawed. One should not shake or dilute vials. Swirl the vial gently after thawing and before each withdrawal. COVID-19 mRNA Vaccine Moderna® vials are multidose. Ten (10) doses (of 0.5mL each) can be withdrawn from each vial. All details are provided in the reference document (https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-epar-product-information_en.pdf).

Comirnaty®(BNT162b2) is supplied as a multiple-dose (5-dose) vial containing a frozen (between -80ºC to -60ºC suspension that is preservative-free. BNT162b2 must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 6 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C and used within 6 hours from the time of dilution. All details are provided in the reference document (https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf).

8.1.4 Storage Conditions

The COVID-19 mRNA Vaccine Moderna® is provided as a frozen suspension [stored between -25º to -15ºC] multi-dose vial containing 10 doses. The vaccine must be thawed prior to administration. After thawing, a maximum of 10 doses (0.5 mL each) can be withdrawn from each vial. Vials can be stored refrigerated between 2° to 8°C for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C and discarded after 6 hours.

Storage, defreezing and preparation of vaccine doses will be done according to the fact sheets provided by Moderna (https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/downloads/storage-summary.pdf).

Storage defreezing and preparation of vaccine doses will be done according to the fact sheets provided by Pfizer/ BioNTech (https://www.comirnatyeducation.ch/files/Checkliste_deutsch.pdf).

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

ICH: Description of and justification of the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

The **COVID-19 mRNA Vaccine Moderna®** (100 µg) is administered intramuscularly as a series of two doses (0.5 mL each), given 28 days apart (12). The vaccine is injected in the deltoid muscle https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/downloads/prep-and-admin-summary.pdf.

Preparation of vaccines (defreezing, dilution of ampules) and syringes for vaccination are done strictly according to the specifications of the producer and the guidelines by the BAG and eidgenössische Kommission für Impffragen (EKIF) https://www.bag.admin.ch/dam/bag/de/dokumente/mt/k-und-i/aktuelle-ausbrueche-pandemien/2019-nCoV/impfempfehlung-covid-19.pdf.download.pdf/Covid-19-Impfempfehlung%20f%C3%BCr%20mRNA-Impfstoffe_120121.pdf.

8.2.2 Control Intervention

ICH: Description of and justification of the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

The **Pfizer / BioNTech COVID-19 Vaccine, BNT162b2 (30 µg**), is administered intramuscularly (IM) as a series of two 30 µg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single dose followed by a second dose 28 days later (12).

BNT162b2 is supplied as a multiple-dose (5-dose) vial containing a frozen (between -80ºC to -60ºC suspension that is preservative-free. BNT162b2 must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 6 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C and used within 6 hours from the time of dilution. Details for storage and preparation are provided in the checkliste by Pfizer / BioNTech (Checkliste für die Lagerung, Handhabung und Zubereitung des COMIRNATY® COVID-19 mRNA-Impfstoffs https://www.comirnatyeducation.ch/files/Checkliste_deutsch.pdf.

Preparation of vaccines (defreezing, dilution of ampules) and syringes for vaccination are done strictly according to the specifications of the producer and the guidelines by the BAG and eidgenössische Kommission für Impffragen (EKIF). https://www.bag.admin.ch/dam/bag/de/dokumente/mt/k-und-i/aktuelle-ausbrueche-pandemien/2019-nCoV/impfempfehlung-covid-19.pdf.download.pdf/Covid-19-Impfempfehlung%20f%C3%BCr%20mRNA-Impfstoffe_120121.pdf

8.3 Dose / Device modifications

(SPIRIT #11b)

Trial participants are vaccinated according to the producers' dosing recommendations. No adaptation of vaccine dosing is planned. In case of a serious adverse event following the application of a first dose, the second dose will not be given.

8.4 Compliance with study intervention

The application of the one-time injection by the treating physician (or a delegated person) will be documented in the trial platform data entry form and the batch number of the vaccine will be entered.

8.5 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.

8.6 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 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.

8.7 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 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.

8.8 Study Drug / Medical Device Accountability

(ICH/E6 6.4.7; SPIRIT 11c)
ICH: Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

Vaccines will be shipped to the pharmacies of the four participating university hospital in cooled containers guaranteeing temperatures during transport of -60 degrees C based on recommendations by the vaccine producers and the Bundesamt für Gesundheit. Vaccines will be shipped by cantonal vaccine storage facilities directly to hospitals for same day use or stored in refrigerators by university hospital pharmacies at the requested temperatures, defrozen and deluted according to prescribed rules of producers and prepared in sterile syringes for vaccination in batches of 6 and 5 vaccinations for the Pfizer / BioNTech and for the Moderna vaccine.

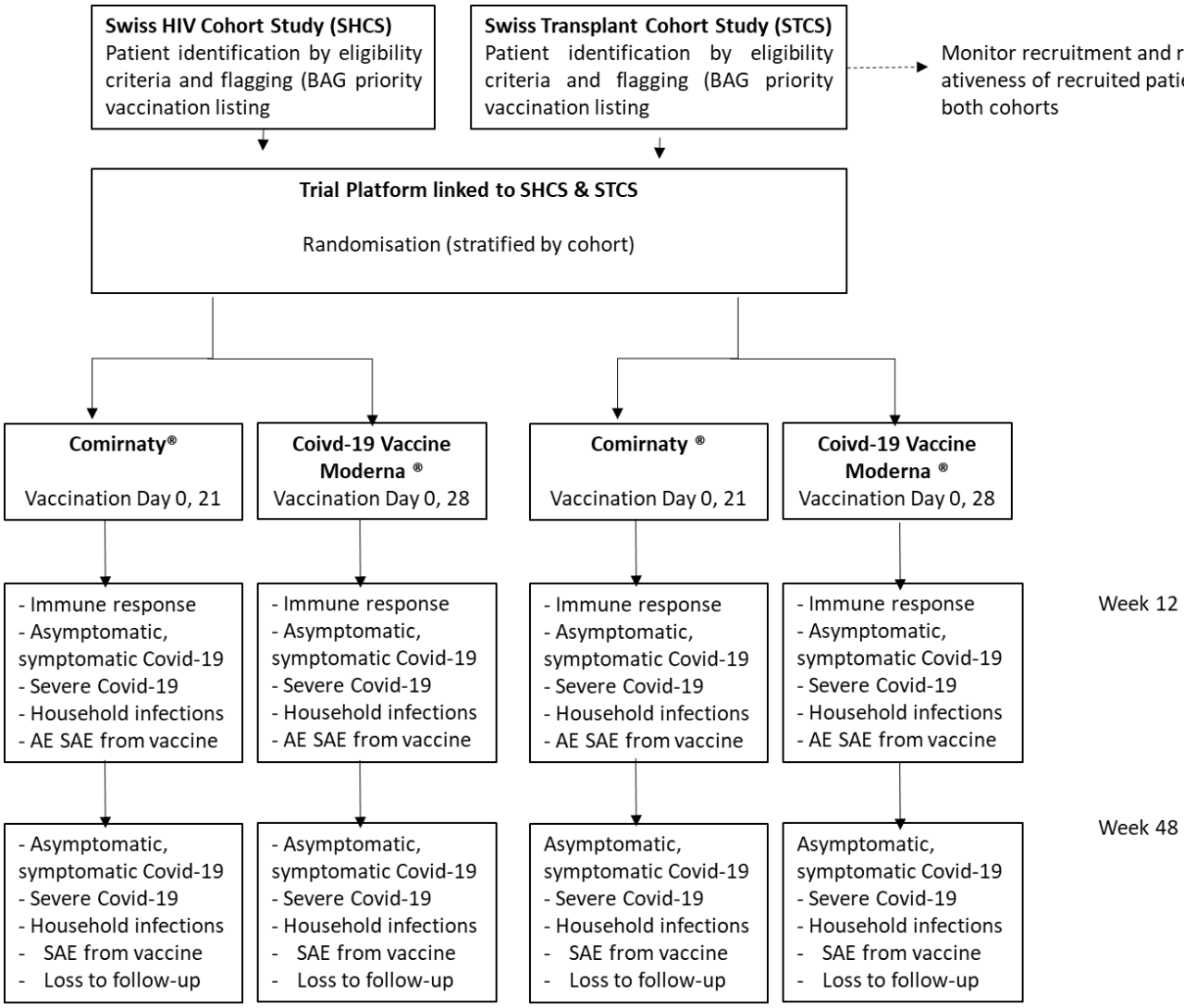
8.9 Return or Destruction of Study Drug / Medical Device

Does not apply. Since the vaccines will be a product which has received marked authorisation in Switzerland, unused vaccines will immediately be used for other patients vaccinated at the respective clinical sites based on the clinical judgement of physicians and according to the priority rules set by the BAG.

9. STUDY ASSESSMENTS

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

Figure 1: Study flow chart.



9.2 Assessments of outcomes

9.2.1 Assessment of feasibility outcomes

We refer to the master protocol.

9.2.2 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 12 weeks following randomisation and vaccination (primary immunological endpoint).

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 (ABCORA2.0) 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 12 weeks after randomisation (see Study schedule). During baseline and follow-up visits this visit a blood sample will be taken (EDTA blood (2 x 7.5 ml)) 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 2.1 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.

9.2.3 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 12 and 48 weeks, and during each cohort visits, that fall in between the trial specific visit dates.

- 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 12 and 48 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 12 and 48 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.

- COVID-19 burden of diseases (BOD), a composite of the above endpoints. The BID is will be scored as by using 0 for no COVID-19, 1 for non-severe COVID-19, and 2 for severe COVID-19.

The burden of diseases endpoint will be assessed by combining the before listed outcomes (i.e. no COVID-infection, non-severe COVID-19 infection

- Patient reported asymptomatic or symptomatic infections of household members.

Patients will be asked at the 12-week and 48-week visit if a household member was diagnosed with COVID-19.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events following vaccination

Any local symptom (redness or swelling or prolonged pain at injection side) continuation of normal daily activities during the first 7 days after vaccination
During the 12-week visit, patients will be asked if they had any local symptoms which limited their 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.

  During the 12-week visit, patients will be asked if they had any systemic symptoms after randomisation which limited their 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

  During the 12-week visit, patients will be asked if they had to contact a physician within 7 days after vaccination.

9.2.4.2 Serious adverse events

For reporting of serious adverse events we will adhere to the ICH E2A guidelines (18) and define a serious adverse event (experience) or reaction 'as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Exemptions will be SARS-CoV-2 related deaths or SARS-CoV-2 related hospitalisations, which are among the assessed clinical outcomes. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe'.

9.2.4.3 Laboratory parameters

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

9.2.4.4 Vital signs

Not relevant for purpose of this trial.

9.2.5 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.

9.2.6 Assessments in participants who prematurely stop the study

We refer to the master protocol

9.3 Procedures at each visit

9.3.1 Eligibility (and eventual enrolment, randomisation)

We refer to the master protocol.

9.3.2 Enrolment and randomisation

We refer to the master protocol.

9.3.3 Follow-up 1 week 12

We refer to the master protocol.

9.3.4 Follow-up 2 week 48

We refer to the master protocol.

10. SAFETY

10.1 Drug studies

10.1.1 Reporting of serious adverse events (SAE) and other safety related events

We refer to the master protocol.

In addition to reporting of all SAE to the sponsor / principle investigators according to the rules set by Swissmedic all study physicians must report SAE via the ElViS (Elektronisches Vigilance-Meldesystem)

to Swissmedic (https://www.swissmedic.ch/swissme-dic/de/home/services/egov-services/elvis.html). All study physicians must register at ElViS.

10.1.2 Follow up of (Serious) Adverse Events

We refer to the master protocol.

11. STATISTICAL METHODS

11.1 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.

11.2 Determination of Sample Size

Phase 1 to Phase 3 trials of COVID-19 mRNA Vaccine Moderna® and Comirnaty® (Pfizer / BioNTech) report immunological response titers that are not comparable due to the different assays that were used. Moderna uses an in-house developed ELISA assay, while Pfizer / BioNTech uses an in-house developed Luminex assay. However, currently available results show that titers are high at 4 weeks post vaccination and the proportion of patients that is reactive to vaccination is close to 100 percent (19, 20). However, no data is available for an immunocompromised population such as the one in our study. By assuming vaccine reactivity of 90% in both vaccine groups, we 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, which represents 32 patients distributed across 6 participating centres. Sample size was calculated using the "ssc_propcomp" function of the R statistical software package "SampleSize4ClinicalTrials' (21).

11.3 Statistical criteria of termination of trial

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

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

We refer to the master protocol

11.4.2 Feasibility analysis

We refer to the master protocol.

11.4.3 Analyses of immunological and clinical outcomes

Immunological outcomes at baseline and 12-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 (second licensed– first licensed) is above –10%, where 10% is the pre-defined non-inferiority margin.

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, patients with less than 200 CD4cell/µL, unsuppressed HI viral load, male gender, age group 60 to 69, 70 older and history of cardiovascular diseases or present metabolic syndrome. For transplanted individuals these are patients with less than 200 CD4cell/µL, intense versus less intense immunosuppressive therapy, male gender, age group 60 to 69, 70 older and

history of cardiovascular diseases or present metabolic syndrome.

A secondary and tertiary analysis will assess the non-inferiority of the second licensed vaccine *versus* the first licensed vaccine in regards to the presence of anti-Nucleocapsid (N), as measured by the Elecsys® Anti-SARS-CoV-2 N assay and the presence of IgM, IgA and IgG as measured by the ABCORA 2.0 assay.

Clinical outcomes related to COVID-19 infection at 48 weeks and patient reported COVID-19 infection of household members will be reported as frequency with percentage for the different treatment arms.

11.4.4 Interim analyses

No interim analysis will be done

11.4.5 Safety analysis

Results from a phase 3 randomised, observer-blinded, placebo-controlled trial conducted at 99 centers across US on 30,420 volunteers reported that no safety concerns were identified, aside from transient local and systemic reactions for the COVID-19 mRNA Vaccine Moderna®. For BNT16b2 vaccine Comirnaty® (Pfizer / BioNTech), a randomised placebo-controlled trial on 43,548 participants showed short-term, mild-to-moderate pain at the injection site, fatigue and headache. The incidence of serious adverse events was low and similar in the vaccine and placebo groups (6). Therefore, 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.

11.4.6 Deviation(s) from the original statistical plan

We refer to the master protocol

11.5 Handling of missing data and drop-outs

We refer to the master protocol.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

We refer to the master protocol.

12.2 Data management

We refer to the master protocol.

12.3 Monitoring

We refer to the master protocol.

12.4 Audits and Inspections

We refer to the master protocol.

12.5 Confidentiality, Data Protection

We refer to the master protocol.

12.6 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.

13. PUBLICATION AND DISSEMINATION POLICY

We refer to the master protocol.

14. FUNDING AND SUPPORT

We refer to the master protocol.

15. INSURANCE

We refer to the master protocol.

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17. APPENDICES

Not applicable