Study Protocol

Version 3.2

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Preventive strategies against SARS-CoV-2 in kidney transplant recipients:

Intervention A – vaccination: Single blinded randomized controlled trial on BNT162b2 or mRNA-1273 (mRNA) vs Ad26COVS1 or ChAdOx1-S (viral vector) for third vaccination as well as pilot trial on fourth vaccination in kidney transplant recipients without SARS-CoV-2 spike protein antibodies following full vaccination (BOOST-TX)

Intervention B – **monoclonal** antibodies: Recombinant SARS-CoV-2-antibodies in kidney transplant recipients without neutralizing antibody response following full vaccination (RESCUE-TX)

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I. List of abbreviations

COVID-19… Corona Virus Disease 2019

CNI… Calcineurin inhibitor

CRF… Case Report Form

EMA… European Medicines Agency

GCP… Good Clinical Practice

i.m. … intramuscular

mRNA… messenger Ribonucleic Acid

SAE… Serious Adverse Event

SARS-CoV-2… Severe Acute Respiratory Syndrome Coronavirus type 2

SUSAR… Suspected Unexpected Serious Adverse Reaction

II. Table of Contents

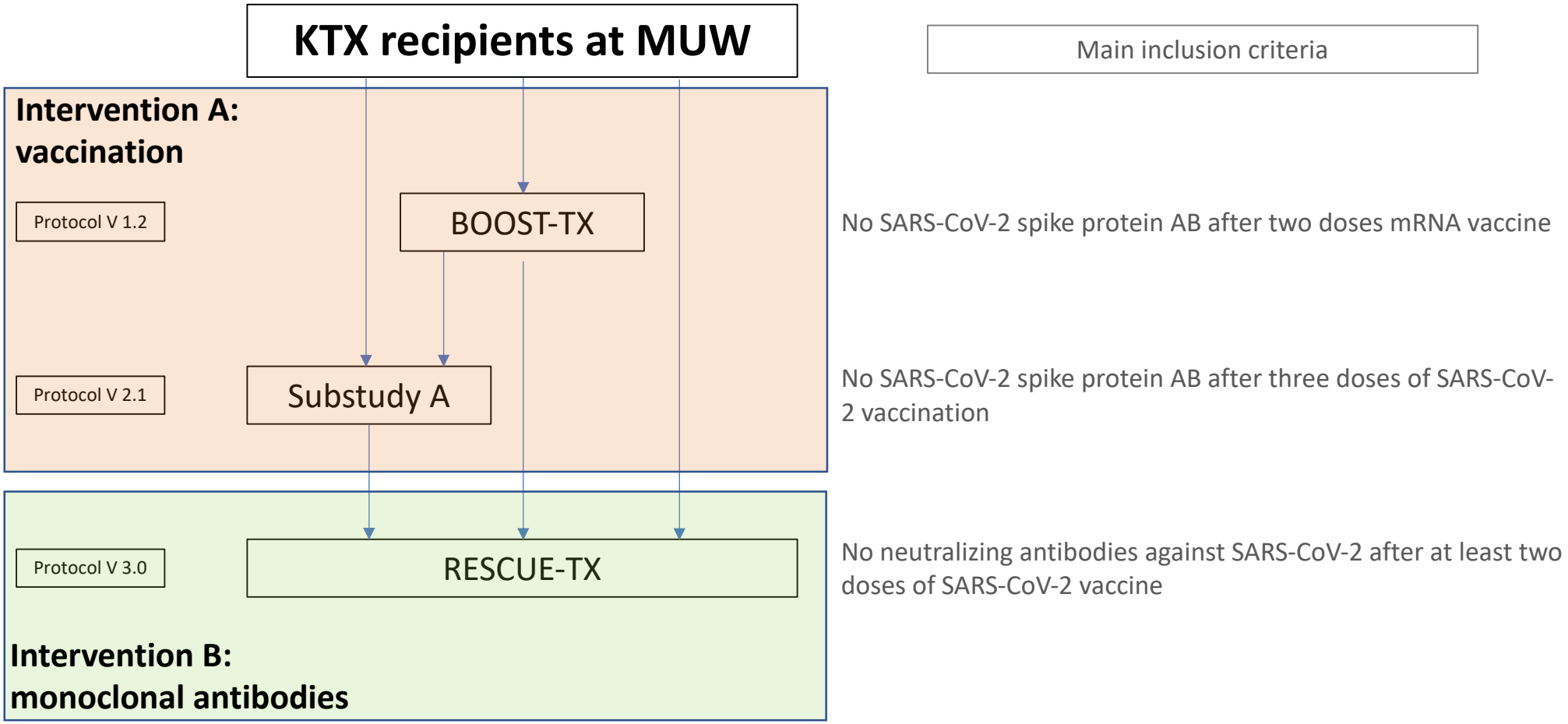

Figure 1. Concept of study design

KTX… kidney transpant recipients
MUW … Medical University of Vienna

Periods	Name	Screening	Treatment	Follow-up				
Visits	Number	1	2	3	4	5	6	7
	Name	Screening	Treatment	Follow up 1	Follow up 2	Follow up 3	Follow up 4	Follow up 5
	Time	within 28 days prior to vaccination	Day 1	Day 29-42 (4 weeks after treatment)	Day 57-70 (8 weeks after treatment)	Day 85-98 (12 weeks after treatment)	Day 168-196 (24 weeks after treatment)	Day 336-364 (48 weeks after treatment)
Informed consent		x						
Inclusion / Exclusion Criteria		x						
Medical History		x						
Concomitant medication		x						
SARS-CoV-2 Antibodies		x		x	x	x	x	x
T-cell response		x		x				
Pregnancy test		x	x					
Adverse events			x	x	x	x	x	x

Table 1. BOOST-TX Visits and Assessments scheduled

Periods	Name	Screening	Treatment			Follow-up			
Visits	Number	1	2	3	4	5	6	7	8
	Name	Screening_SUB_A	Start_intervention_ SUB_A	4th vaccination	Stop_intervention_ SUB_A / FUP1_SUB_A	FUP2_SUB_A	FUP3_SUB_A	FUP4_SUB_A	FUP5_SUB_A
	Time	at least 28 days after 3rd vaccination	Day 1	Day 8	Day 15	Day 35-42	Day 92-105	Day 175-203	Day 343-371
Informed consent		x							
Inclusion / Exclusion Criteria		x							
Pregnancy test		x		x					
Adverse events					x	x	x	x	x
Lab (creatinine, proteinuria		x		x	x	x	x	x	x
Special lab tests (donor specific antibodies, torque teno virus, PBMCs)		x				x			x

Table 2. Substudy A: Visits and Assessments scheduled

Periods	Name	Screening	Treatment	Follow-up						
Visits	Number	1_RESCUE	2_RESCUE	3_RESCUE	4_RESCUE	5_RESCUE	6_RESCUE	7_RESCUE	8_RESUCE	9_RESCUE
	Name	Screening	Treatment	Follow up 1	Follow up 2	Follow up 3	Follow up 4	Follow up 5	Follow up 6	Follow up 7
	Time	within 56 days prior to study drug administration	Day 1	Day 15-22 (2 weeks after treatment)	Day 29-42 (4 weeks after treatment)	Day 57-70 (8 weeks after treatment)	Day 85-98 (12 weeks after treatment)	Day 168-196 (24 weeks after treatment)	Day 252-280 (36 weeks after treatment)	Day 336-364 (48 weeks after treatment)
Informed consent		x								
Inclusion / Exclusion Criteria		x								
Medical History		x								
Concomitant medication		x								
AZD7442 concentration				x	x	x	x	x	x	x
Neutralizing antibodies		x		x	x	x	x	x	x	x
SARS-CoV-2 Antibodies		x		x	x	x	x	x	x	x
Pregnancy test		x	x							
Adverse events			x	x	x	x	x	x	x	x

Table 3. RESCUE-TX Visits and Assessments scheduled

III. Preamble

The overall objective of this study is to assess treatment strategies to prevent COVID-19 in kidney transplant recipients who do not respond to standard vaccination regimen (i.e two doses of mRNA vaccine). Treatment options that will be evaluated include repetitive and heterologous vaccination and immunosuppression modulation (BOOST-TX and Substudy A; intervention A) as well as long-acting monoclonal antibodies against the spike protein that represent a passive immunization strategy (intervention B). The study concept is visualized in Figure 1 and subsequent modules build upon risk factor that have been identified in the previous study interventions (immunosuppression as risk factor for non-response in the BOOST-TX trial -> Immunosuppression reduction in the Substudy A) as well as availability of novel treatment concepts since the first initiation of the study (long-acting antibody cocktail against SARS-CoV-2 -> RESCUE-TX in vaccine non-responders). The modular design reflects a patient focused treatment concept that aims at preventing a COVID-19 infection in kidney transplant recipients.

Intervention A comprises a randomized controlled trial on heterologous vaccination (mRNA vs vector boost as third dose) as well as a pilot trial on immunosuppression reduction (peri-vaccination withdrawal of mycophenolate) to increase vaccine efficacy.

Intervention B is considered a rescue strategy in individuals who do not develop protective immunity following vaccination and is set up as a prospective observational study to assess pharmacokinetics of the monoclonal antibody cocktail AZD7442.

1 Intervention A: Vaccination

1.1 Background

Kidney transplant recipients are at high risk for a severe COVID-19 disease course and therefore prioritized to receive early vaccination against SARS-CoV-2 (1, 2). In general, the immune response to vaccination is reduced in immunosuppressed individuals including kidney transplant recipients. A recent study from Israel confirmed that only 37.5% of kidney transplant recipients developed detectable antibodies against the spike protein following full vaccination with BNT162b2 (Pfizer-BioNTech) (3). The type of maintenance immunosuppression may have a significant impact on the immune response in kidney transplant recipients. Patients treated with co-stimulation blockade (Belatacept) as maintenance immunosuppression showed even lower immunization rates of only 5.7 % (4).

Several strategies have been proposed to improve response to SARS-CoV-2 vaccination including additional dosing and mixing different vaccine types to broaden the presented antigen repertoire (heterologous vaccination or “mix-and-match strategy”) (5). Recent data show a higher reactogenicity of heterologous boosting in the general population (6). In the European Union there are currently two different classes of SARS-CoV-2 vaccines available: a) mRNA (mRNA-1273 [Moderna Biotech] and BNT162b2 [Pfizer-BioNTech]) and b) viral vector-based vaccines (ChAdOx1 [AstraZeneca] and Ad26COVS1 [Jansen]). Of these Ad26COVS1 is the only vaccine that has been shown to induce a protective immune response after a single dose (7). Kidney transplant recipients in Austria have primarily been vaccinated with mRNA-based vaccines.

1.2 Study rationale

More than half of all kidney transplant recipients do not develop SARS-CoV-2 antibodies following full vaccination with a mRNA-based SARS-CoV-2 vaccine. However, there is currently no data available to guide immunization strategies in these patients. A “mix and match” strategy combining different types of vaccines has been proposed to improve immune response following vaccination, but efficacy of such a strategy in kidney transplant recipients has not yet been evaluated.

Substudy A: Triple immunosuppression and especially mycophenolate mofetil (as antiproliferative treatment) has been identified as risk factor for vaccine non-response in kidney transplant recipients (3). Peri-interventional stopping of Mycophenolate or azathioprine may therefor increase response rate to a 4th SARS-CoV-2 vaccination in individuals without immune response to three doses of SARS-CoV-2 vaccine. Drug half-life time is up to 17 hours and 24 hours for mycophenolate and azathioprine, respectively. Cessation of the medication for 7 days will ensure adequate clearance of the drug before vaccination. Discontinuation until seven 7 days after the fourth dose will ensure uninhibited T-cell function following vaccination. A case series from patients with rheumatological disease (n=24) suggests a benefit of temporary hold of mycophenolate treatment to increase the response to SARS-CoV-2 vaccination. The response rate for patients who discontinued mycophenolate was 92% compared to 65% in a larger cohort of patients with rheumatic disease (8). Overall risk profiles and immunosuppressive treatment regimen in patients with rheumatic disease are different to solid organ transplant recipients and warrant further investigation on safety and efficacy.

1.3 Study objective:

The primary objective of this study is to test if a “mix and match” strategy (using a viral vector-based vaccine) results in a better antibody response against the SARS-CoV-2 spike protein compared to an additional dose of mRNA vaccine (“more-of-the-same”) in patients who did not develop antibodies following full vaccination with a mRNA vaccine.

Substudy A: In kidney transplant recipients without any immune response to a third vaccination we will evaluate safety and efficacy of immunosuppression reduction to achieve seroconversion following a fourth vaccination (pilot study).

1.3.1 Primary objective (Hypotehsis)

We specifically hypothesize that a single dose of the viral vector-based vaccine Ad26COVS1 [Jansen] or ChAdOx1-S [AstraZeneca] results in a higher rate of antibody response compared to a third dose of the previously used mRNA vaccine (mRNA-1273 [Moderna Biotech] or BNT162b2 [Pfizer-BioNTech]).

Substudy A: Reduction of immunosuppression peri-vaccination (i.e. stopping of mycophenolate or azathioprine) will facilitate seroconversion in patients not responding to three doses of an SARS-CoV-2 vaccine.

1.3.2 Primary Endpoint

- Number of patients presenting a positive humoral immune response (antibody), assessed with the Roche ELISA test using the manufacturer recommended cutoff of 0.8U/ml, to theSARS-CoV-2 vaccine at 4 weeks after the 3rd vaccination. The decision to perform a responder analysis is motivated by the fact that currently the exact

relationship between anti-SARS-CoV-2 antibody concentration and protective immunity is not known.

Substudy A: Number of patients presenting a positive humoral immune response (antibody), assessed with the Roche ELISA test using the manufacturer recommended cutoff of 0.8U/ml, to theSARS-CoV-2 vaccine at 4 weeks (i.e. day 35-42) after the 4th vaccination.

1.3.3 Secondary endpoints

- Number of patients presenting a positive humoral immune response (antibody), assessed with the Roche ELISA test using the manufacturer recommended cutoff of 0.8U/ml, to the SARS-CoV-2 vaccine at 8, 12, 24, 48 weeks after the 3rd vaccination.
- Number of detectable antibodies (U/ml measured by the Roche ELISA test) at 4, 8, 12,24 and 48 weeks after vaccination.
- Number of patients presenting a positive cellular immune response defined as doubling of extracellular IFNg concentration in the plasma after ex-vivo re-stimulation with a SARS-CoV-2 spike protein peptide pool at 4 weeks after the vaccination.
- Strength of the cellular response to SARS-CoV-2 spike protein peptides measured in terms of the extracellular IFNg concentration after ex-vivo re-stimulation with a peptide pool at 4 weeks after the vaccination.
- incidence of COVID-19 disease within 24 and 48 months after vaccination
- **Substudy A:** Number of patients presenting a positive humoral immune response (antibody), assessed with the Roche ELISA test using the manufacturer recommended cutoff of 0.8U/ml, to the SARS-CoV-2 vaccine at 7 days after the 4th vaccination.

- **Substudy A:** Number of detectable antibodies (U/ml measured by the Roche ELISA test) at 4 weeks after vaccination the 4th vaccination.
- **Substudy A:** Antigen-specific T-cell response against SARS-CoV-2 (ELISPOT assay) and Immunophenotyping of lymphocytes (before and after mycophenolate withdrawl)

1.4 Study design

This is a single center, single blinded, randomized study. Only the patient will be blinded for the type of vaccine administered. Based on sample-size calculations (see below) a total of 200 patients will be enrolled into the study.

Substudy A is a pilot and feasibility study in up to 60 patients who did not develop SARS-CoV-2 spike protein antibodies four weeks after three vaccine doses (this includes patients from the main vaccination trial who did not develop SARS-CoV-2 spike protein antibodies and up to 30 additional patients who will be specifically recruited for the substudy A).

1.4.1 Study population

The study population comprises kidney transplant recipients without detectable SARS-CoV-2 spike protein antibodies at least 4 weeks after the second dose of a mRNA based vaccine.

Substudy A: Patients who did not develop SARS-CoV-2 spike protein antibodies at least four weeks after the third vaccine dose.

1.4.2 Inclusion criteria

- patient has received a kidney transplantation

- full SARS-CoV-2 vaccination with mRNA vaccine (two doses) at least 4 weeks before screening
- > 18 years of age
- no SARS-CoV-2 spike protein antibodies at least 4 weeks after the second dose of an mRNA vaccine
- **Substudy A:** no SARS-CoV-2 spike protein antibodies four weeks after the third dose
- **Substudy A:** Maintenance immunosuppression with mycophenolate or azathioprine
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1.4.3 Exclusion criteria

- acute illness with fever
- Prior documented infection with SARS-CoV-2
- triple anticoagulation therapy
- Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug trial(s), or subject is receiving other investigational agent(s)
- Subject has known sensitivity or intolerance to any of the products to be administered for the purpose of this study
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with the study procedures
- Subject is pregnant or breast feeding
- **Substudy A:** SARS-CoV-2 spike protein antibodies four weeks after the 3rd vaccination > 0.8 U/mL

1.5 Methodology

1.5.1 Subject enrollment:

All subjects must personally sign and date the consent form before any screening procedures are performed. Patients are eligible for enrollment when they have satisfied all of the inclusion/exclusion criteria. Following enrollment patients will be randomized to one of the treatment groups. All participants who enter into the screening period for the study (after signing the informed consent) will receive a personal identification number. This number will be used to identify the subject throughout the trial and must be used on all study documentation related to the subject. The subject identification number must remain constant throughout the entire trial.

Substudy A: Patients who did not develop SARS-CoV-2 spike protein antibodies four weeks after the third vaccination (<0.8 u/mL) and satisfy all inclusion / exclusion criteria are eligible to participate in substudy A.

1.5.2 Patient screening

Patients followed at the transplant clinic of the Medical University of Vienna who received two doses of mRNA-based SARS-CoV-2 vaccine will be invited to the study. In the screening phase kidney transplant recipients that are followed at the kidney transplant clinic of the Medical University of Vienna that fulfill the mentioned inclusion criteria will be identified. Following informed consent, patients will be tested for SARS-CoV-2 spike protein and nucleocapsid antibodies. Screening has to be performed within 4 weeks prior to vaccination.

Substudy A: Patient who did not develop SARS-CoV-2 spike protein antibodies at four weeks after a 3rd vaccination who fulfill the inclusion criteria will be invited to participate in the substudy A of the BOOST-TX trial.

1.5.3 Randomization and study arm allocation

Randomization will be performed as soon as the SARS-CoV-2 antibody status is available.

- Patients included in the study will be randomized 1:1 to receive a third dose of the previously administered mRNA vaccine (mRNA-1273 or BNT162b2) or a single dose of a vector based vaccine (Ad26COVS1 or ChAdOx1-S [this is based on availability of the vaccine]).
- Randomization will be stratified by the maintenance immunosuppressive regimen calcineurin inhibitor (CNI) vs co-stimulation blockade (Beletacept)
- To ensure that comparison groups will be of approximately the same size a block randomization will be used in order to balance subjects randomized to each group (https://www.meduniwien.ac.at/randomizer/).

Substudy A:

- **Substudy** A is a non-randomized pilot trial. Immunosuppression reduction will be assessed on a case-by-case basis by a transplant nephrologist and the patient weighing the individual immunological risk for an alloimmune response and the risk for SARS-CoV-2 infection.

1.5.4 Blinding

Patients will be blinded for the treatment.

Substudy A: no blinding

1.5.5 Prohibited medication

The exclusion criteria describe triple anticoagulation as prohibited medication in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up phase

1.5.6 Treatment

Patients will receive a single dose of the study drug intra muscular (i.m.) within 28 days after screening. Patients will receive a time slot for vaccination following randomization. Vaccination will be performed at the outpatient clinic of the Division of Nephrology and Dialysis at the Medical University of Vienna (chronic hemodialysis unit and pre-transplant clinic).

Substudy A: Patients will stop their maintenance therapy with mycophenolate or azathioprine seven days before the scheduled 4th vaccination (Substudy A: day 1) or continue on the prescribed dose. At day 8 (Substudy A) patients will receive the 4th vaccination (BNT162b2 or mRNA-1273; specific type of vaccine is dependent on availability).

1.6 Study medication, Dosage and Administration

Study medication will be provided by the central pharmacy of the Medical University of Vienna.

1.6.1 Treatment arm 1 (“more of the same”):

active substance: mRNA-1273

trade name: COVID-19 Vaccine Moderna

Manufacturer: ROVI PHARMA INDUSTRIAL SERVICES S.A.

Route of administration: i.m.

Duration: once

Dose: 0.5 ml

or

active substance: BNT162b2

trade name: COMIRNATY COV-19 VAC

Manufacturer: BIONTECH MANUFACTURING GMBH

Route of administration: i.m.

Duration: once

Dose: 0.3 ml

1.6.2 Treatment arm 2 (“mix and match”):

active substance: Ad26COVS1

trade name: COVID-19 Vaccine Janssen

Manufacturer: JANSSEN BIOLOGICS B.V.

Route of administration: i.m.

Duration: once

Dose: 0.5 ml

or

active substance: ChAdOx1

trade name: Vaxzevria

Manufacturer: MEDIMMUNE PHARMA B.V.

Route of administration: i.m.

Duration: once

Substudy A:

Patients will discontinue mycophenolate or azathioprine treatment 7 days before the 4th vaccination and re-start medication 7 days after the 4th vaccination. Patient will receive vaccination with either BNT162b2 or mRNA-1273 (type of vaccine is dependent on availability).

1.6.3 Study-drug delivery and drug storage conditions

The vaccines are prepared and dispensed by the central pharmacy of the General Hospital of Vienna. All trial substances will be handled and administered according to manufacturer's recommendations.

1.7 Follow-up:

Follow up visits will be scheduled 4, 8, 12,24 and 48 weeks after vaccination at the kidney transplant outpatient clinic to assess the immune response to the vaccination (blood draw for antibody and T-cell measurement). Independent from study visits, patients are routinely followed at the transplant clinic of the Nephrology Department of the Medical University of Vienna at regular intervals including blood draws (creatinine, immunosuppression levels).

Substudy A: Patients enrolled in substudy A will be followed-up on day 8, day 15 as well as day 35-42 (primary endpoint substudy A), day 92-105, day 175-203 and day 343-371.

1.7.1 Study duration

The response to the vaccination will be evaluated at day 29-42 (visit 3, primary endpoint) as well as day 57-70, day 85-98, day 168-198 and day 336-364 (visit 4, 5, 6 and 7, secondary endpoints).

1.7.2 End of study

The end of the trial is the last visit of the last patient.

1.8 Withdrawal of subject

Subjects may prematurely discontinue from the study at any time. Subjects must be withdrawn under the following circumstances:

- at their own request
- if the Investigator feels it would not be in the best interest of the subject to continue
- if the subject violates conditions laid out in the consent form / information sheet or disregards instructions by the study personal

In all cases, the reason why subjects are withdrawn must be recorded in detail in the CRF Should the study be discontinued prematurely, all study materials (completed, partially completed and empty CRFs) will be retained.

1.9 Additional study related procedures

Table 1 shows summarizes Study visits and Assessments.

1.9.1 Laboratory testing

- SARS-CoV-2 spike protein and nucleocapsid antibodies at Visit 1, Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7 (9ml blood)
- SARS-CoV-2 specific T- cell response at Visit 1 and Visit 3 (3x8 ml blood)

Antibodies will be measured by the Department of Laboratory Medicine using clinically validated ELISA tests (Roche, Switzerland). SARS-CoV-2 specific T-cell responses will be assessed by QuantiFERON assays with SARS-CoV-2 specific peptides at the research laboratory of the Division of Nephrology (Quiagen, Netherlands).

Table 2 shows additional study visits for individuals enrolled in substudy A. Additional laboratory testing includes creatinine, proteinuria and development of donor specific antibodies.

Additional visits are scheduled at days 1, 8, 15 and 35-42 of the substudy A.

1.9.2 Clinical data

- Baseline clinical data will be recorded at visit 1 (current medication including maintenance immunosuppression, medical history including date of transplantation) using the CRF document.
- Adverse events will be assessed at visits 2, 3, 4 and 5

1.10 Benefit and risk assessment

Patients with immunosuppression are considered to be at great risk for a severe disease course of COVID-19 an additional vaccination will increase their chance to develop a

protective immune response. The risk for adverse events following a third vaccination is low compared to the risk associated with a SARS-CoV-2 infection in this population. All study drugs have been approved by the European Medicines Agency (EMA).

Substudy A: Patients not responding to a 3rd dose of SARS-CoV-2 vaccine are considered at highest risk for immunological none-response to vaccination. On the other hand, the risk for acute rejection is considered low in short time reduction of mycophenolate. Nevertheless, patients will be monitored closely during immunosuppression reduction.

1.11 Adverse event reporting

1.11.1 Definitions

1.11.1.1 Adverse Events

An adverse event is by definition “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (International Conference on Harmonisation [ICH] Guideline for Good Clinical Practice).

- Worsening of a pre-existing medical condition (e.g., cancer, diabetes, migraine headaches, gout) should be considered an adverse event if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.
- Interventions for pretreatment conditions (e.g., elective surgery) or medical procedures that were planned before study enrollment are not considered adverse events.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events. However, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

1.11.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (e.g., emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

1.11.2 Reporting procedures for all Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined above) observed by the investigator or reported by subjects are properly captured in the subjects' medical records.

In addition, the investigator is responsible for ensuring that, for those subjects randomized into the study, all adverse events captured on the subjects' medical records (as specified above) are reported on the case report form. This collection period will be from the time of administration of the study drug until the end of the study.

The following adverse event attributes must be assigned by the investigator:

- adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known)
- event description (with detail appropriate to the event)
- dates of onset and resolution
- severity
- assessment of relatedness to investigational product
- action taken

The relationship of the adverse event to the investigational product will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?" The investigator should respond to this question with either Yes or No.

Medically significant adverse events considered related to the investigational product by the investigator will be followed until resolved or considered stable.

Adverse events will be reported in the publication arising from this study.

1.11.3 Serious Adverse Event reporting procedures

Serious adverse events will be collected and recorded from the date the informed consent is signed through the end of the study. If a serious adverse event occurs before administration of the investigation product, the relationship of the adverse event to study screening is to be assessed. If a subject is permanently withdrawn from treatment because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the Case Report Forms.

A SAE that is a known and previously described side effect of the treatment will be reported to the Austrian Federal Office for Safety in Health Care as well as the responsible ethics committee once a year in the form of a Development Safety Update Report (DSUR). Events that are suspected unexpected serious adverse reactions (SUSARs) will be reported to the responsible ethics committee and the European Medicines Agency. Fatal SUSARs will be reported as soon as possible, but latest within 7 days and non-fatal SUSARs within 15 days.

1.11.4 Summary of known and potential risks of the study drug

All three study medications are approved by the EMA for vaccination against SARS-CoV-2 in individuals over 16 years of age. Overall safety profiles are excellent with over a billion

doses administered worldwide as of May 19,2021 (ourworldindata.org). An overview of undesirable effects and respective frequencies for each study drug are reported below:

1.11.4.1 COVID-19 Vaccine Moderna [mRNA-1273, Moderna]:

System organ class	undesirable effect	Frequency
Blood and lymphatic system disorders	Lymphadenopathy	very common
Immune system disorders	Anaphylaxis, Hypersensitivity	unknown
Nervous system disorders	Cephalea	very common
	Acute Peripheral facial palsy	rare
Gastrointestinal disorders	Nausea/Emesis	very common
Skin and subcutaneous tissue disorders	Rash	common
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia	very common
General disorders and administration site conditions	Pain at Injection site, Tiredness, Chills, Fever, Swelling at injection site	very common
	Erythema at Injection site, Urticaria at injection site, Rash at injection site	common

	Itching at injection site	uncommon
	Facial swelling	rare

1.11.4.2 **Comirnaty [BNT162b2, PfizerBioNTech]**

System organ class	undesirable effect	Frequency
Blood and lymphatic system disorders	Lymphadenopathy	uncommon
Immune system disorders	Anaphylaxis, Hypersensitivity	unknown
Psychiatric disorders	Sleeplessness	uncommon
Nervous system disorders	Cephalea	very common
Gastrointestinal disorders	Nausea	common
Skin and subcutaneous tissue disorders	Arthralgia, Myalgia	very common
	Pain in the extremities	uncommon
General disorders and administration site conditions	Paint at the injection site, tiredness, chills, fever, swelling at the injection site	very common
	Redness at injection site	common
	Malaise, itching at injection site	uncommon

1.11.4.3 **COVID-19 Vaccine Janssen [Ad26.COV2-S, Johnson&Johnson]**

System organ class	undesirable effect	Frequency
Immune system disorders	Hypersensitivity, Urticaria	rare
Nervous system disorders	Anaphylaxis	not known

	Headache	very common
	Tremor	uncommon
Respiratory, thoracic and mediastinal	Cough	common
	Sneezing, oropharyngeal pain	uncommon
Gastrointestinal disorders	Nausea	common
Skin and subcutaneous tissue disorders	Rash	uncommon
Musculoskeletal and connective tissue disorders	Myalgia	very common
	Arthralgia	common
	Muscular weakness, back pain, limb pain	uncommon
General disorders and administration site conditions	Tiredness, pain at injection site	very common
	Fever, erythema at injection site, swelling at injection site, chills	common
	Asthenia, malaise	uncommon

1.11.4.4 **Vaxzevria [ChAdOx1-S, AstraZeneca]**

System organ class		
Blood and lymphatic system disorders	Thrombocytpenia	common
	Lymphadenopathia	uncommon
Metabolism and nutritional disorders	reduced appetite	uncommon
Nervous system disorders	Cephalea	very common
	Vertigo, tiredness	uncommon

Vascular disease	Thrombosis associated with thrombocytopenia	very rare
Gastrointestinal disorders	Nausea	verycommon
	Diarrhea, emesis	common
Skin and subcutaneous tissue disorders	Hyperhidrosis, pruritus, rash	uncommon
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia	very common
General disorders and administration site conditions	Pain at injection site, Itching at injection site, Hematoma at injection site, tiredness, feeling unwell, chills	very common
	Swelling at injection site, erythema at injection site, fever	common

Very common: ≥1/10

Common: ≥1/100 to <1/10

Uncommon: ≥1/1,000 to <1/100

Rare: ≥1/10,000 to <1/1,000

Very rare: <1/10,000

Not known: cannot be estimated from the available data

1.12 Statistical analysis

1.12.1 Sample size calculation

For testing the primary study endpoint (positive antibody to the SARS-CoV-2 vaccine) we assume a response rate of 30% and 50% in the mRNA and the viral vector-based vaccine treatment arms and expect a dropout rate of a maximum of 5%. Currently, no data on a third vaccination in kidney transplant recipients exist. The 30% response rate for the homologous vaccination group has been chosen expecting a slightly lower response rate to the third vaccination in kidney transplant recipients who did not respond to the standard 2-dose vaccination regime compared to the initial response rate of kidney transplant recipients to the standard 2-dose vaccination regime (37% response rate). The 50% response rate estimate for the heterologous vaccination groups is based on early data from studies investigating heterologous vaccination which showed a higher reactogenicity after the heterologous vaccination. Enrollment of 100 patients per group will provide 80% power (alpha-error: 5%) to detect a difference in response between the two treatment groups.**Substudy A** is a pilot trial to assess feasibility of immunosuppression reduction. There is only limited data on efficacy of a fourth vaccination in non-responders after three doses of SARS-CoV-2 vaccine and no data on efficacy of immunosuppression reduction.

1.12.2 Endpoint analysis

For all endpoints a per protocol analysis will be carried out.

For the primary endpoint (positive humoral immune response to SARS-CoV-2 vaccination at 4 weeks after the vaccination) SARS-CoV-2 S IgG antibody test results will be recorded and counts and percentages of patients exceeding the manufacturer defined cutoff of 0.8U/ml in

each treatment arm will be reported. A chi-squared test will be employed to test for statistically significant differences in the number of responders (antibody concentration exceeds the manufacturer defined cutoff of 0.8U/ml) between the treatment arms.

1.12.2.1 Secondary endpoint analysis

All secondary endpoint analysis will be conducted in an exploratory fashion and no adjustment for multiple testing will be performed.

- Number of patients presenting a positive humoral immune response at 8, 12, 24 and 48 weeks after vaccination will be analyzed in the same fashion as the primary endpoint.
- For the analysis of number of detectable antibodies at 4, 8, 12, 24 and 48 weeks after vaccination ELISA readouts (U/ml) will be recorded. At each time point their median and interquartile range in each treatment arm will be determined and a t-test will be performed to determine if there is a statistically significant difference between the means of the logarithmized ELISA readouts (U/ml) of the two treatment arms.
- For the analysis of number of patients presenting a positive cellular immune response to SARS-CoV-2 vaccination at 4 weeks after the vaccination the extracellular IFNg concentration in a negative control sample and after ex-vivo re-stimulation with a SARS-CoV-2 spike protein peptide pool will be recorded for all patients. Doubling of IFNg concentration after re-stimulation will be considered as positive cellular response to the vaccination. Counts and percentages of patients with positive response will be reported for each treatment arm. A chi-squared test will be employed to test for statistically significant differences in the number of responders between the two treatment arms.

- For the analysis of the strength of the cellular immune response at 4 weeks after vaccination the extracellular IFNg concentration in negative control sample and after ex-vivo re-stimulation with a SARS-CoV-2 spike protein peptide pool will be recorded for all patients. IFNg concentration from the patient specific negative control samples will be subtracted from the re-stimulated samples to normalize for patient specific differences in cellular activation. Median and interquartile range of the normalized IFNg concentrations after re-stimulation will be calculated for both treatment arms and a t-test will be performed to determine if there is a statistically significant difference between the two treatment arms with respect to the means of the logarithmized IFNg concentration after re-stimulation.
- For the analysis of SARS-CoV-2 infection after a third vaccination, counts and percentages of individuals with SARTS-CoV-2 infection by weeks 24 and 48 will be determined

Before carrying out any endpoint analysis the number of study participants either on co-stimulation blockade or CNI as well as the number of patients who were initially vaccinated with either mRNA-1273 or BNT162b2 will be determined. In case of sufficient number of study subjects with different immunosuppressants or initially received vaccines the statistically analysis plan will be updated to introduce additional stratification.

Substudy A:

Primary endpoint: Number and percentage of responders at day 35-42 after the 4th dose (i.e. 4 weeks after 4th vaccination).

Secondary endpoint: Number and percentage of patients presenting a positive humoral immune response at day 15 (i.e. 7 days after the 4th vaccination).

2 Intervention B – monoclonal antibodies

2.1 Background

Results from the interim-analysis of the BOOST-TX trial showed that a third booster dose of a COVID19 vaccine results in the development of SARS-CoV-2 antibodies in 39% of study participants. Importantly, only one in five patients with a positive antibody response also had neutralizing antibodies and only 9% showed SARS-CoV-2 spike protein specific T-cells suggesting that a large number of kidney transplant recipients remains without protective immunity even after three doses of a SARS-CoV-2 vaccine.

Long-lived monoclonal antibodies against SARS-CoV-2 such as AZD7442 provide a promising strategy to prevent infection in individuals who do not develop protective immunity following vaccination. AZD7442 is a combination of two monoclonal antibodies (AZD8895 [tixagevimab] and AZD1061 [cilgavimab]) that simultaneously bind to distinct non-overlapping epitopes on the spike protein receptor binding domain to neutralize SARS-CoV-2. Similar antibody cocktails have shown efficacy to reduce risk of infection and severe disease course (9). Recently, results from the PROVENT Phase III trial showed a 77% reduction in the risk to develop symptomatic COVID-19 following treatment with AZD7442. Plasma levels of AZD7442 > 2.1µl/ml were associated with neutralizing capacity against SARS-CoV-2 (minimum effective concentration against SARS-CoV-2 Delta variant, unpublished data from the manufacturer [AstraZeneca]).

2.2 Study rationale

Treatment with long-acting antibody combinations such as AZD7442 provides a novel treatment strategy to induce protective immunity against SARS-CoV-2 infection and severe COVID-19 disease in patients who cannot be immunized using vaccines.

2.3 Study objective:

The primary objective of this study is to test if a single dose of the long-acting antibody AZD7442 is sufficient to reach protective AZD7442 antibody levels (>2.1 µl/ml) that result in neutralizing capacity in the serum against SARS-CoV-2 in kidney transplant recipients who do not develop neutralizing antibodies following vaccination.

2.3.1 Study hypothesis

We hypothesize that a single dose of AZD7442 allows reaching protective AZD7442 antibody levels (> 2.1 µl/ml) as well as neutralizing SARS-CoV-2 capacity in the serum for up to 12 months in kidney transplant recipients not developing neutralizing antibodies after full vaccination against SARS-CoV-2.

2.3.2 Primary objective

To assess pharmacokinetics of AZD7442 in kidney transplant recipients

2.3.3 Primary Endpoint

- AZD7442 serum concentration (µg/ml) at 2, 4, 8, 12, 24, 36, and 48 weeks

2.3.4 Secondary objective

To assess safety and efficacy of AZD7442 to induce protective immunity against SARS-CoV-2

2.3.5 Secondary endpoints

- Local and systemic adverse events will be assessed by post immunization diary cards at 2, 4, 8, 12, 24, 36 and 48 weeks.
- Neutralizing capacity of patient serum samples at 2, 4, 8,12,24, 36, and 48 weeks.
- Number of patients with AZD7442 serum levels < 2.1µl/ml at 2, 4, 8,12,24, 36, and 48 weeks
- SARS-CoV- spike protein antibodies at 2, 4, 8,12,24, 36, and 48 weeks.
- SARS-CoV-2 infection at 2, 4, 8,12,24, 36, and 48 weeks assessed by SARS-CoV-2 nucleocapsid antibodies and patient history (positive PCR test).
- Severe COVID-19; severe Covid-19 is characterised by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia (SPO2 <90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale Score of 5 or higher
- Hospitalization or death from COVID-19.
- Humoral and cellular immune response to additional SARS-CoV-2 vaccination (at 4 weeks after boost vaccination) in patients on AZD7442 treatment (additional vaccination is not a study intervention (observational); response rate will be compared to patients not receiving AZD7442 [results from the BOOST-TX study]). Cellular response will be assessed by ELISPOT (SARS-CoV-2 spike protein-specific).
- Alloimmune response assessed by Donor-specific HLA antibodies (humoral alloimmunity, n=200 at week 24 and 48) and donor-specific T-cells using donor-

specific ELISPOT assays in up to 40 patients with available donor cells (since 2016 PBMCs of local organ donors are routinely stored in liquid nitrogen at time of transplantation).

2.4 Study design

This is a single arm, prospective, open label observational study to assess safety and efficacy of AZD7442.

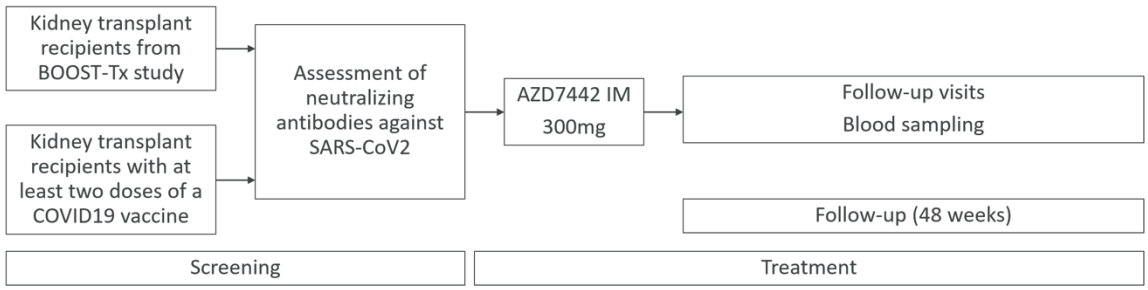

Figure 2: Study flow: RESCUE TX stud arm

2.4.1 Study population

Kidney transplant recipients followed at the Medical University of Vienna (n=1500); 80% of kidney transplant recipients have received full vaccination against SARS-Cov-2; Response rate after two doses of SARS-CoV-2 vaccine about 50%. We estimate that there are currently > 500 patients who fulfill the inclusion criteria followed at our outpatient department. We specifically estimate that 100 patients from the BOOST-TX trial arm will fulfill the inclusion criteria and additional 100 patients will be recruited at the outpatient department.

2.4.2 Inclusion criteria

- Participant has received a kidney transplantation.
- Participant has received at least two doses of a SARS-CoV-2 vaccine.
- > 18 years of age.
- No neutralizing SARS-CoV-2 antibodies at least 4 weeks after the last dose of any SARS-CoV-2 vaccine.

2.4.3 Exclusion criteria

- Prior documented infection with SARS-CoV-2.
- Triple anticoagulation therapy.
- Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug trial(s), or subject is receiving other investigational agent(s).
- Subject has known sensitivity or intolerance to any of the products to be administered for the purpose of this study.
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with the study procedures.
- Subject is pregnant or breast feeding.
- Prior receipt of any mAbs against COVID19 (licensed or investigational) ≤30 days before enrolment.
- Administration of immunoglobulins ≤30 days before enrolment.
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.

2.5 Methodology

2.5.1 Subject enrollment:

All subjects must personally sign and date the consent form before any screening procedures are performed. Patients are eligible for enrollment when they have satisfied all the inclusion/exclusion criteria. Following enrollment patients will be randomized to one of the treatment groups. All participants who enter the screening period for the study (after signing the informed consent) will receive a personal identification number. This number will be used to identify the subject throughout the trial and must be used on all study documentation related to the subject. The subject identification number must remain constant throughout the entire trial.

Both, patients from the BOOST-TX trial as well as *de novo* recruited patients can be enrolled in the RESCUE-TX study arm.

2.5.2 Patient screening

Patients followed at the transplant clinic of the Medical University of Vienna who received at least two doses of the mRNA-based SARS-CoV-2 vaccine will be invited to the study. In the screening phase kidney transplant recipients that are followed at the kidney transplant clinic of the Medical University of Vienna that fulfill the mentioned inclusion criteria will be identified. This includes patients from the BOOST-TX study arm as well as patients specifically recruited for the RESCUE-TX study arm.

Following informed consent, patients will be tested for neutralizing antibodies against SARS-CoV-2. Screening must be performed within 4 weeks prior to study drup administration (screening = visit 1).

2.5.3 Prohibited medication

The exclusion criteria describe triple anticoagulation as prohibited medication in this trial. There are no prohibited therapies during the Post-Treatment Follow-up phase.

2.5.4 Treatment

Patients will receive a single dose of AZD7442 (300mg) administered intra muscular at day 1 (visit 2) within 56 days after screening. Study drug administration will be performed at the outpatient clinic of the Division of Nephrology and Dialysis at the Medical University of Vienna (chronic hemodialysis unit and pre-transplant clinic).

2.6 Study medication, Dosage and Administration

The study drug AZD7442 contains two monoclonal antibodies: AZD8895 and AZD106. A single, fixed dose of AZD7442 300 mg will be administered intra-muscular (150 mg of AZD8895 and 150 mg of AZD1061 administered as 2 separate injections).

Investigational product	Dosage form and strength	Manufacturer
Evusheld (AZD7442)	300mg for intramuscular injection	AstraZeneca

2.6.1 Study-drug preparation, handling, storage and accountability

- AZD7442 will be shipped un-labelled: The doses will be certified and labelled for the study by the central pharmacy of the General Hospital of Vienna Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into German. The label will include the following information: name of sponsor, investigational product, study drug dosage form, route of administration,

  quantity of dosage units, storage conditions, the period of use e.g., expiry date
- The medication will be prepared by the central pharmacy of the General Hospital of Vienna. All trial substances will be handled and administered according to manufacturer's recommendations.
- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all investigational medicinal product (IMP) received, and any discrepancies are reported and resolved before use of the IMP.
- Only participants enrolled in the study may receive IMP and only authorized site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).Vials are

stored at 2-8°C (36-46°F. All study drugs should be kept in a secure place under appropriate storage conditions.

2.6.1.1 Dose Preparation and Administration for AZD7442 (AZD8895/AZD1061)

The dose of AZD7442 (AZD8895 and AZD1061) for administration must be prepared by the investigator's or site's designated IMP manager using aseptic technique. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2 °C to 8 °C (36 °F to 46 °F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials. Each AZD8895 and AZD1061 vial must be used only once to prepare a single dose. AZD7442 (AZD8895 and AZD1061) does not contain preservatives, and any unused portion must be discarded.

Use a separate disposable syringe with a 22 – 25 gauge and 1 – 1.5 in (25 – 38 mm) length needle for each AZD8895 and AZD1061 DP injection. Each DP should be administered as a separate single injection and administered sequentially. Intramuscular doses should be prepared by accurately withdrawing 1.5 mL volume of DP into an appropriately sized latex-free disposable polypropylene or polycarbonate syringe.

AZD8895 and AZD1061 should be administered according to standard practice procedures for IM injections, with one injection in each gluteal region. The IMP does not contain preservatives and any unused portion must be discarded.

2.6.2 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

2.7 Follow-up:

Follow up visits will be scheduled at week 2, 4, 8, 12,24 and 48 weeks after vaccination at the kidney transplant outpatient clinic to assess pharmacokinetics and the SARS-CoV-2 immune status as well as adverse reactions. Independent from study visits, patients are routinely followed at the transplant clinic of the Nephrology Department of the Medical University of Vienna at regular intervals including blood draws (creatinine, immunosuppression levels).

2.7.1 Study duration

The study duration is 365 days

2.7.2 End of study

The end of the trial is the last visit of the last patient.

2.8 Withdrawal of subject

Subjects may prematurely discontinue from the study at any time. Subjects must be withdrawn under the following circumstances:

- at their own request
- if the Investigator feels it would not be in the best interest of the subject to continue

- if the subject violates conditions laid out in the consent form / information sheet or disregards instructions by the study personal

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). In all cases, the reason why subjects are withdrawn must be recorded in detail in the CRF Should the study be discontinued prematurely, all study materials (completed, partially completed and empty CRFs) will be retained. The Investigator will follow up AEs outside of the clinical study. If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

2.8.1 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.
Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Sponsor immediately, and a discussion should occur between the Sponsor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Sponsor must ensure all decisions are appropriately documented.

2.8.2 Screening failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

2.9 Additional study related procedures

Table 3 shows summarizes Study visits and Assessments for the RESCUE-TX study arm.

2.9.1 Laboratory testing

- Serum concentration of AZD7442 (µg/ml) at visits 3, 4, 5, 6, 7, 8, 9 (9 ml)
- Neutralizing antibodies against SARS-CoV-2 at visits 1, 3, 4, 5, 6, 7, 8, 9 (9 ml)
- SARS-CoV-2 spike protein and nucleocapsid antibodies at visits 1, 3, 4, 5, 6, 7, 8, 9 (9 ml)
- Donor specific antibodies at visit 1 and 9
- T-cell response against SARS-CoV-2 in individuals receiving additional vaccination (not part of study protocol)
- T-cell response against the donor in individuals where donor cells are available (prospective biobanking study in kidney transplantation).

Serum concentration of AZD7442 (µg/ml) will be measured by PPD laboratories (North Carolina, USA). Neutralizing antibodies will be measured by the department of Virology using the surrogate virus neutralization test (sVNT) cPassTM (GenScript Biotech, Piscataway

Township, NJ, USA). SARS-CoV- spike protein and nuclocapside antibodies will be measured by the Department of Laboratory Medicine using clinically validated Roche Elecsys platform (Roche, Switzerland). T-cell analysis will be performed by the Transplant research laboratory at the Department of Surgery (Medical University of Vienna).

2.9.2 Clinical data

- Baseline clinical data will be recorded at visit 1 (current medication including maintenance immunosuppression, medical history including date of transplantation) using the CRF document.
- Adverse events will be assessed at visits 2, 3, 4, 5, 6, 7, 8, 9

2.10 Benefit and risk assessment

Immunocompromised patients such as transplant recipients are at high risk of developing severe COVID19 disease. Moreover, most patients do not develop a protective immunity after two doses of a COVID19 vaccine and currently there are no other means available to confer protection to this highly vulnerable patient population. Therefore, the study patients would benefit from receiving AZD7442 as pre-exposure prophylaxis.

In a recent Phase II study (RPOVENT) leading to emergency use authorization by the Food and Drug Administration(FDA) in the US, a higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events. All of the subjects with events had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern. A causal relationship

between EVUSHELD and these events has not been established. Therefor, prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, risks and benefits will be weighed against the risk for severe COVID-19 on an individual patient basis by the treating transplant physician and the patient. All participants will be advised to seek immediate medical attention if they experience any signs or symptoms suggestive of cardiovascular event.

2.11 Adverse event reporting

2.11.1 Definitions

2.11.1.1 Adverse Events

An adverse event is by definition “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (International Conference on Harmonisation [ICH] Guideline for Good Clinical Practice).

- Worsening of a pre-existing medical condition (e.g., cancer, diabetes, migraine headaches, gout) should be considered an adverse event if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.
- Interventions for pretreatment conditions (e.g., elective surgery) or medical procedures that were planned before study enrollment are not considered adverse events.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events. However, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

2.11.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (e.g., emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

2.11.2 Reporting procedures for all Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined above) observed by the investigator or reported by subjects are properly captured in the subjects' medical records.

In addition, the investigator is responsible for ensuring that, for those subjects randomized into the study, all adverse events captured on the subjects' medical records (as specified above) are reported on the case report form. This collection period will be from the time of administration of the study drug until the end of the study.

The following adverse event attributes must be assigned by the investigator:

- adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known)
- event description (with detail appropriate to the event)
- dates of onset and resolution
- severity
- assessment of relatedness to investigational product
- action taken

The relationship of the adverse event to the investigational product will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?" The investigator should respond to this question with either Yes or No.

Medically significant adverse events considered related to the investigational product by the investigator will be followed until resolved or considered stable.

Adverse events will be reported in the publication arising from this study.

2.11.3 Serious Adverse Event reporting procedures

Serious adverse events will be collected and recorded from the date the informed consent is signed through the end of the study. If a serious adverse event occurs before administration of the investigation product, the relationship of the adverse event to study screening is to be assessed. If a subject is permanently withdrawn from treatment because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the Case Report Forms.

A SAE that is a known and previously described side effect of the treatment will be reported to the Austrian Federal Office for Safety in Health Care as well as the responsible ethics committee once a year in the form of a Development Safety Update Report (DSUR). Events that are suspected unexpected serious adverse reactions (SUSARs) will be reported to the responsible ethics committee and the European Medicines Agency. Fatal SUSARs will be reported as soon as possible, but latest within 7 days and non-fatal SUSARs within 15 days.

2.11.4 Summary of known and potential risks of the study drug

Section 5.6 of the Investigator Brochure (IB) serves as the Reference Safety Information (RSI) for this trail. The reference document for definition of expectedness/listedness is the IB for the drug.

AZD7442 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither mAb has any human target. There are no potential risks based on mechanism of action.
Potential risks are associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs.
The important potential risks associated with the administration of immunoglobulin, include, but are not limited to, anaphylaxis and other serious hypersensitivity reactions including immune complex disease.

Other potential risks include, but are not limited to, injection site reactions, infusion-related reactions, and Antibody-dependent enhancement (ADE)disease.

ADE of disease is a theoretical risk. Two different syndromes exist: 1) ADE, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry. The monoclonal antibody in AZD7442 have been designed with a modification to prevent binding to cellular Fc receptors, so the risk of ADE occurring via this mechanism should range from very low to none. 2) Vaccinee-assocated enhanced respiratory disease (VAERD), which is a distinct clinical syndrome that occurred in young children in the 1960s when whole inactivated virus vaccines for measles and RSV were tested. Immunizing with limiting doses of RSV antigen, especially with conformationally incorrect antigens, can result in 2 major types of immunological phenomena: a) A relatively high ratio of antibody that binds, but does not neutralize, virus could potentially result in immunogenic cell death and complement activation (leading to inflammation and airway

obstruction); b) immunization with whole inactivated virus vaccines can result in allergic inflammation characterized by, eg, increased mucus production, airway hyperresponsiveness, and attenuated cytolytic T cell activity (T helper 2 cell immune response). This mechanism, induced by vaccines, should not be provoked by monoclonal antibodies.

2.11.5 Time period for collection of adverse events

AEs and SAEs will be collected from the time of the first dosing (visit 2) throughout the follow-up period (visit 9 = last visit).

2.11.6 Specific reporting of local and systemic AEs following injection

Local and systemic adverse reactions to the study drug will be specifically assessed at visit 2 (study drug administration) visit 3 (week 2) and visit 4 (week 4) using the solicitated AE as described in Table 4.

Table 4 – local and systemic AEs

Local solicited AEs	**Systemic solicited AEs**
Pain	Fever
Tenderness	Feverishness
Redness	Chills
Warmth	Joint pains
Itch	Muscle pains
Swelling	Fatigue

Induration	Headache
	Malaise
	Nausea
	Vomiting

Severity of local AEs at the injection site will be graded as outlined in Table 5.

Table 5 - Severity grading criteria for local adverse events

Adverse Event	**Grade**	**Intensity**
Pain at injection site	1	Pain that is easily tolerated
	2	Pain that interferes with daily activity
	3	Pain that prevents daily activity
	4	A&E visit or hospitalization
Tenderness	1	Mild discomfort to touch
	2	Discomfort with movement
	3	Significant discomfort at rest
	4	A&E visit or hospitalization
Erythema at injection site*	1	2.5 - 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis
Induration/Swelling at injection site	1	2.5 – 5 cm and does not interfere with activity

	2	5.1 - 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
	4	Necrosis

Systemic AEs will be graded as outlined in Table 6.

Table 6 - Severity grading criteria for systemic AEs.

GRADE 0	None
GRADE 1	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
GRADE 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
GRADE 4	Potentially Life-threatening: requires assessment in A&E or hospitalisation

2.11.7 Reporting of serious adverse events to Company

All SAEs have to be reported to Company, whether or not considered causally related to the investigational product. At the end of the Study a final unblinded summary line listing of all SAEs notified to the regulatory authority and/or Company during the Study, must be provided to the Company to enable reconciliation of safety information held by Company for its product(s). Send SAE reports (individual case reports and line listings) and

accompanying cover page to Company (TCS) via

Email:AEmailboxclinicaltrialTCS@astrazeneca.com

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to Company at the same time these events are notified to the Regulatory Authority.

2.11.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor and the Company. Pregnancy itself is not regarded as an adverse event. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

2.12 Statistical analysis

2.12.1 Sample size calculation

There has been no formal power calculation for the primary endpoint for the RESCUE-TX study: Pharmacokinetics of AZD7442 in immunosuppressed individuals (incl. kidney transplant recipients) and patients with reduced renal function are currently unknown. With inclusion of 200 subjects the study cohort will be representative for the approximately 1500 transplant patients managed at the Medical University of Vienna.

Inclusion of up to 200 kidney transplant recipients will further allow to offer study participation to a) all participants in the BOOST-TX intervention A arm as well as b) patients with low level antibodies at screening who were not eligible for boost vaccination and who have not developed neutralizing antibodies since.

2.12.2 Primary endpoint analysis

- AZD7442 serum concentrations will be recorded at all follow-up visits (3,4,5,6,7,8,9). Kinetics of AZD7442 serum concentration in kidney transplant recipients will be modeled.

An interim analysis for the primary endpoint will be performed after visit 4 and 6 (i.e.4 and 12 weeks after study drug administration)

2.12.3 Secondary endpoint analysis

- Rate of individuals with neutralizing antibodies against SARS-CoV-2 following treatment with AZD7442 will be calculated for all follow-up timepoints (cut off for neutralizing capacity is ≥30% signal inhibition in the cPass test).
- Rate of individuals with AZD7442 concentrations below the predefined threshold of < 2.1µl/ml.
- Quantitative analysis of SARS-CoV-2 spike protein concentrations
- Rate of systemic and local adverse reactions
- Rate of SARS-CoV-2 breakthrough infection
- Rate of hospitalization for COVID-19

For the secondary endpoints on tolerability (ie. local and systemic side effects) as well as primary efficacy (i.e. rate of individuals with neutralizing antibodies, antibody levels, infection rate, etc.) an interim analysis will be performed after visit 4 (i.e. 4 weeks after study drug administration)

3 Documentation and data management

3.1 Documentation and data management

A subject screening and identification Log will be completed for all enrolled subjects with the reasons for exclusion.

3.1.1 Case report form (CRF)

Paper-based CRFs will be used for this trial. All forms have to be completed and must be legible. Entry errors must be corrected according the ICH-GCP Guidelines.

For each subject enrolled a CRF will be completed and signed by the Investigator or a designated sub-Investigator. If a subject withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis. The entries will be checked by trained personnel (Monitor) and any errors or inconsistencies will be checked immediately. The monitor will collect original completed and signed CRFs at the end of the study. A copy of the completed and signed CRFs will remain on site, while the original data are handed out to the sponsor.

3.2 Safekeeping

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified (according to ICH-GCP “essential documents”).

The collected data will be inserted as an entry form into a password protected MySQL database, which is an open-source relational database management system. Only members of the research team will have access to the database. The obtained data in the database will de-personalize (pseudonymize). Depersonalization means that data with identifying information is collected, but the identifying information is then severed from the personal health information data in the research database and is stored separately.

3.3 Quality control and quality assurance

3.3.1 Monitoring

The designated monitor will contact and visit the Investigator on a regularly basis and will be allowed to have direct access to all source documents needed to verify the entries in the CRFs and other protocol-related documents provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals according to the monitoring plan throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them.

Monitoring will be performed by:

Assoc. Prof. Priv.-Doz. Dr. Gregor Bond, PhD; Division of Nephrology and Dialysis, Department of Internal Medicine III, Medical University of Vienna; Spitalgasse 23, 1090 Wien;

3.3.2 Inspections

Upon request, the Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the competent authority inspectors. The main purposes of an audit or inspection are to confirm that the rights and welfare of the

subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

3.4 Reporting and publication

The findings of this study will be published by the sponsor (Investigators) in a scientific journal and presented at scientific meetings. The manuscript will be circulated to all co-Investigators before submission. Confidentiality of subjects in reports/publications will be guaranteed.

4 Ethical and Legal aspects

4.1 Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical trial, the patient must give written consent to participation in the study. During the instruction the trial participants are to be made aware of the fact that they can withdraw their consent – without giving reasons – at any time without their further medical care being influenced in any way.

In addition to the comprehensive instructions given to the trial participants by the Investigator, the trial participants also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress.

The patients must agree to the possibility of study-related data being passed on to relevant authorities.

The patients must be informed in detail of their obligations in relation to the trial participants insurance in order not to jeopardize insurance cover.

4.2 Acknowledgement / approval of the study

The Investigator will submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the study.

The clinical trial shall be performed in full compliance with the legal regulations according to the Drug Law (AMG – Arzneimittelgesetz) of the Republic of Austria.

An application must also be submitted to the Austrian Competent Authorities (Bundesamt für Sicherheit im Gesundheitswesen (BASG) represented by the Agency for Health and Food Safety (AGES Medizinmarktaufsicht) and registered to the ClinicalTrials.gov database using the required forms.

4.3 Insurance

An insurance for each patient enrolled in this study will be taken out. Details on the existing patient's insurance are given in the patient information sheet. All subjects will be insured at the Zürich Versicherungs-AG, Schwarzenbergplatz 15, 1010 Wien, Tel.: +43 1 501255 1255, policy number 07229622-2.

4.4 Ethics and good clinical practice (GCP)

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 64th WMA General Assembly, Fortaleza, Brazil, 2013) and with the laws and regulations of the country in which the clinical research is conducted.

The Investigator of the clinical trial shall guarantee that only appropriately trained personnel will be involved in the study. All studies must follow the ICH GCP Guidelines and the regulatory requirements. Therefore, this study follows the EU Directive embedded in the Austrian drug act.

5 References

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