A Phase III, Prospective, Open-Label, Randomized Clinical Trial Evaluating the Augmenting of Anti-SARS-CoV2 Immunity in Kidney Transplant Recipients via a Heterologous Additional Dose with Janssen Ad26.CoV2.S vaccine

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Table of Contents

STUDY SUMMARY **7**

1. INTRODUCTION **9**

1.1 BACKGROUND 9
1.2 INVESTIGATIONAL AGENT 11
1.3 CLINICAL DATA TO DATE 11
1.4 DOSE RATIONALE 14
1.5 RISKS AND BENEFITS 15
1.5.1 Risks Related to Study Participation *15*
1.5.2 Risks Related to Janssen Ad26.CoV2.S Vaccine *15*
1.5.3 Risks Related to Adenoviral-vectored Vaccines *18*
1.5.4 General Risks Related to Vaccination *20*
1.5.5 Pregnancy and Birth Control *20*
1.5.6 Risks from Blood Draws *21*
1.5.7 Theoretical Risk of Enhanced Disease *21*
1.5.8 Unknown Risks *21*
1.5.9 Alteration in Immunosuppression Medication *22*
1.5.10 General Risks Related to the mRNA COVID-19 Vaccine 23

2STUDY OBJECTIVES **25**

3STUDY DESIGN **26**

3.1 GENERAL DESCRIPTION 28
3.1.1 Segment I *28*
3.1.2 Segment II *29*
3.1.3 Responders to mRNA Vaccination *29*
3.1.4 Exploratory Mechanistic Immunologic Studies *29*
3.1.5 Study Measurements *32*
3.2 NUMBER OF SUBJECTS 33
3.3 DURATION OF PARTICIPATION 33
3.4 PRIMARY STUDY ENDPOINTS 33
3.5 SECONDARY STUDY ASSESSMENTS/ENDPOINTS 34
3.6 PRIMARY SAFETY ENDPOINTS 35
3.7 IDENTIFICATION OF SOURCE DATA 35

4SUBJECT SELECTION ENROLLMENT AND WITHDRAWAL **36**

4.1 INCLUSION CRITERIA 36
4.2 EXCLUSION CRITERIA 37
4.3 SUBJECT RECRUITMENT, ENROLLMENT AND SCREENING 39
4.4 EARLY WITHDRAWAL OF SUBJECTS 39
4.4.1 When and How to Withdraw Subjects *39*
4.4.2 Data Collection and Follow-up for Withdrawn Subjects *40*
4.5 CRITERIA FOR TEMPORARILY DELAYING ADMINISTRATION OF STUDY VACCINATION 40

5STUDY DRUG **41**

5.1 DESCRIPTION 41

5.2 TREATMENT REGIMEN 42
5.2.1 Immunosuppression Adjustment *42*
5.2.2 Janssen Ad26.CoV2.S Vaccine Dosing *43*
5.3 METHOD FOR ASSIGNING SUBJECTS TO TREATMENT GROUPS 43
5.4 PREPARATION AND ADMINISTRATION OF STUDY DRUG 44
5.5 SUBJECT COMPLIANCE MONITORING 44
5.6 PRIOR AND CONCOMITANT THERAPY 45
5.7 PACKAGING 46
5.8 MASKING/BLINDING OF STUDY 46
5.9 RECEIVING, STORAGE, DISPENSING AND RETURN 46
5.9.1 Receipt of Drug Supplies *46*
5.9.2 Storage *46*
5.9.3 Dispensing of Study Drug *47*
5.9.4 Return or Destruction of Study Drug *47*

6STUDY PROCEDURES 47

6.1 SEGMENT I 47
6.1.1 Day - 21 (-30 /+7 Days) *47*
6.1.2 Day -14 (+/-3 Days) Non-Responder Group Immunosuppression Change ONLY *48*
6.1.3 Baseline Visit (+1/- 4 Day) *48*
6.1.4 Days 0-7 post-vaccination *49*
6.1.5 Days 14 (+/- 7 Day) and 28 (+/- 7 Days) *50*
6.1.6 Day 90 (+/-15 Days) and 180 (+/- 30 Days) *50*
6.1.7 Year 1 and 2 (+/- 60 Days) *50*
6.1.8 Mechanistic Studies *51*
6.2 SEGMENT II 51
6.3 INITIAL RESPONDERS 51
6.4 UNSCHEDULED VISIT 51
6.5 ASSESSMENT FOR COVID-19 INFECTIONS 52
6.5.1 Pre-specified Criteria for Suspected COVID-19 ..... *52*
6.5.2 Procedures in the Event of (Suspected) COVID-19 ..... *53*
6.6 SCHEDULES OF EVENTS 53
6.7 SAMPLE SIZE DETERMINATION 66
6.8 STATISTICAL METHODS 68
6.9 SUBJECT POPULATION(S) FOR ANALYSIS 70

7SAFETY AND ADVERSE EVENTS 71

7.1 DEFINITIONS 71
7.2 RECORDING OF ADVERSE EVENTS 76
7.2.1 COVID-19 Related Adverse Events *76*
7.2.2 Adverse Events of Special Interest *76*
7.2.3 Pregnancy *80*
7.3 Reporting of Serious Adverse Events and Unanticipated Problems 80
7.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB *83*
7.3.2 Sponsor-Investigator reporting: Notifying the FDA *85*
7.4 UNMASKING/UNBLINDING PROCEDURES 85
NOT APPLICABLE TO THIS STUDY AS OPEN-LABEL, UNBLINDED PROSPECTIVE DESIGN. 85
7.5 STOPPING RULES 85
7.6 MEDICAL MONITORING 86
7.6.1 Internal Data and Safety Monitoring Board *86*

8DATA HANDLING AND RECORD KEEPING 87

8.1 CONFIDENTIALITY 87
8.2 SOURCE DOCUMENTS 87
8.3 CASE REPORT FORMS 87
8.4 DATA MANAGEMENT 88
8.5 DATA PROCESSING 88

9STUDY MONITORING, AUDITING, AND INSPECTING 89

9.1 STUDY MONITORING PLAN 89
9.2 AUDITING AND INSPECTING 89

10ETHICAL CONSIDERATIONS 90

11STUDY FINANCES 90

11.1 FUNDING SOURCE 90
11.2 CONFLICT OF INTEREST 90

12PUBLICATION PLAN 90

13 ..... REFERENCES 91

14 ..... ATTACHMENTS 93

14.1 TTS AESI FORM 93
14.2 GUILLAIN-BARRÉ SYNDROME SYMPTOMS 94
14.3 SYMPTOMS OF INFECTION WITH CORANAVIRUS-19 (SIC) 95
14.4 RISK FACTOR ASSESSMENT 99
14.5 KIDNEY TRANSPLANT FOLLOW UP QUESTIONNAIRE 100
14.6 COVID-19 SURVEILLANCE AND EVALUATION QUESTIONNAIRE 102
14.7 Myocarditis and Pericarditis Symptom Questionnaire 103

List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AESI	Adverse Event of Special Interest
AZA	Azathioprine
CNI	Calcineurin Inhibitor
CTCAE	Common Terminology Criteria for Adverse Events
CVST	Cerebral Venous Sinus Thrombosis
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin Induced Thrombocytopenia
IB	Investigator's Brochure
Ig	Immunoglobulin
IM	Intramuscular Injection
IND	Investigational New Drug Application
IRB	Institutional Review Board
MAAE	Medically-Attended Adverse Event
MERS-CoV	Middle Eastern Respiratory Syndrome Coronavirus
MMF	Mycophenolate Mofetil
PHI	Protected Health Information
PI	Principal Investigator
PQC	Product Quality Complaint
SAE	Serious Adverse Event/Serious Adverse Experience
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure
TTS	Thrombosis with Thrombocytopenia Syndrome

Study Summary

Title	A Phase III, Randomized, Open Label, Clinical Trial Evaluating the Augmentation of Anti-SARS-CoV-2 Immunity in Kidney Transplant Recipients via a Heterologous Additional Dose with Janssen Ad26.CoV2.S Vaccine
Running Title	Additional Dose with Janssen Ad26.CoV2.S Vaccine in Kidney Transplant Recipients
Protocol Number	21-008036
Phase	III
Methodology	Prospective, randomized, open label clinical trial
Overall Study Duration	Three years.
Subject Participation Duration	Each subject will be followed for two years. Vaccinated subjects will be followed for two years after their last dose of the Janssen Ad26.CoV2.S vaccine.
Single or Multi-Site	Multiple (3 Mayo Clinic Transplant sites)
Objectives	**Primary Objectives** 1. To assess whether an anti-SARS-CoV-2 spike protein antibody level of ≥250 U/mL can be achieved 28 days after a dose of the Janssen Ad26.CoV2.S vaccine in kidney transplant recipients who did not form acceptable levels of anti-SARS-CoV-2 spike protein antibody (<250 U/ml but >0 U/mL) after receiving two or more doses of a mRNA vaccine: Pfizer-BioNTech (BNT162b2 vaccine) or Modena (mRNA-1273). This includes any combination of the Pfizer-BioNTech (BNT162b2 vaccine) or the Moderna (mRNA-1273) results in two or more doses of mRNA vaccine. **2.** To compare whether a dose of the Janssen Ad26.CoV2.S vaccine can achieve an anti-SARS-CoV-2 spike protein level ≥250 U/mL in kidney transplant recipients with no detectable anti-SARS-CoV-2 spike protein antibody after two or more mRNA vaccines. Kidney transplant recipients will be randomized to either maintenance of current immunosuppression or adjustment in immunosuppression around the time of receiving the Janssen Ad26.CoV2.S vaccine. The number of subjects with anti-SARS-CoV-2 spike protein level ≥250 U/mL between the two randomized groups will be compared.

	Secondary Objectives 1. To determine the response* of the Janssen Ad26.CoV2.S vaccine in the subset of subjects who did not respond to an additional dose of the Janssen Ad26.CoV2.S vaccine in Segment I while on their maintenance immunosuppression. In this instance immunosuppression is adjusted (Segment II). 2. To determine the incidence of COVID-19 infection up to 2 years after enrollment or additional dose in all enrolled kidney transplant recipients (received Janssen Ad26.CoV2.S vaccine or not). 3. To determine the safety of an additional dose with the Janssen Ad26.CoV2.S vaccine after two or more doses of mRNA vaccine including vaccination with or without immunosuppression adjustment. *Response is defined as achieving an anti-SARS-CoV-2 spike protein antibody level $\geq$250 U/ml 28 days after an additional dose with the Janssen Ad26.CoV2.S vaccine.
	Exploratory Objective 1. To perform exploratory in vitro assays to better understand the mechanisms of response to COVID-19 vaccination.
Number of Subjects	Up to 1200 kidney transplant recipients at least 90 days after transplantation. 400 patients with low or no anti-SARS-CoV-2 spike protein antibody levels will receive one or two additional doses of the Janssen Ad26.CoV2.S vaccine per protocol. Approximately 800 kidney transplant recipients who had a good response to mRNA vaccines will be followed for 2 years for COVID infection and other outcomes.
Diagnosis and Main Inclusion	Kidney transplant recipient who have previously received two or more COVID-19 vaccinations (either the Pfizer or Moderna vaccines).
Study Product, Dose, Route, Regimen	Janssen Ad26.CoV2.S, vaccine. The Janssen Ad26.COV2.s vaccine will be supplied at a concentration of 1 x 10^{11} vp/mL in single-use vials, with an extractable volume of 0.5 mL, and dose at 5 x 10^{10} vp. All participants will receive a single 0.5 mL dosage, typically in the deltoid. Segment I—one dose Segment II—two doses (see protocol)
Duration of Administration	Each dose will be a single dose of Janssen Ad26.CoV2.S vaccine
Reference therapy	No

Statistical Methodology	A chi-square test will be used to assess whether there is a statistically significant difference in the response rate for subjects receiving an additional dose with the Janssen Ad26.CoV2.S vaccine either with immunosuppression reduction (N = 150) or without reduction (N = 150).

1. Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

As of October 1, 2021, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more that 219 million people globally[1], resulting in more than 4.55 million deaths. Unprecedented scientific effort has led to advances in understanding the biology of the virus, pathogenesis of disease, modes of transmission, and treatment approaches. Despite this, the morbidity and mortality from infection remains unacceptably high, and a greater emphasis on disease prevention afforded by a variety of vaccines is proving effective in reducing incidence of disease.

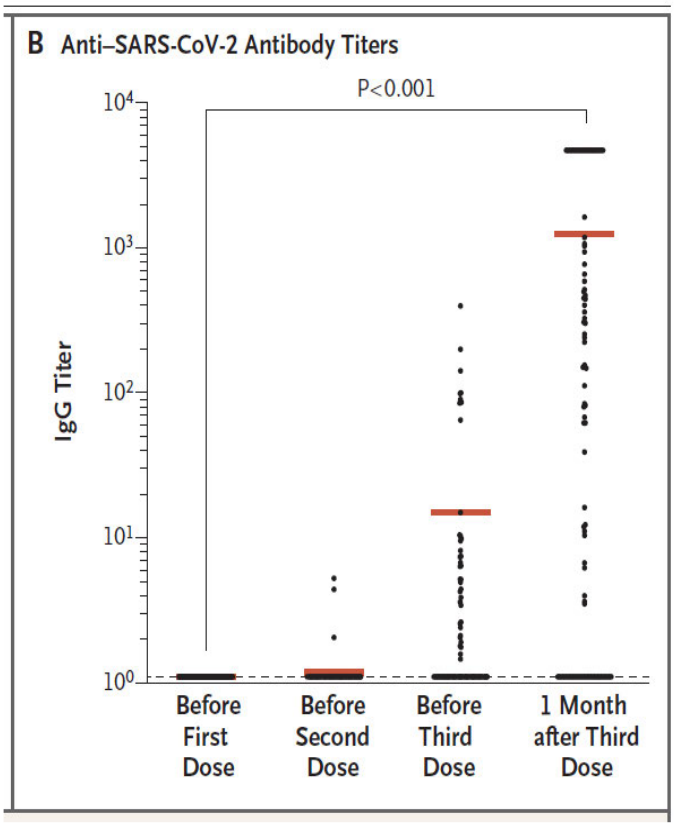
Within the United States, the FDA has granted full approval for the Pfizer and Moderna vaccines and emergency use authorization (EUA) for the Janssen vaccine, Janssen Ad26.CoV2.S. In phase III trials, the two-dose Moderna mRNA vaccine showed 94.1% efficacy at preventing COVID-19 illness, including severe disease[2]. The Pfizer mRNA two-dose vaccine conferred 95% protection against COVID-19 in persons 16 years of age or older[3]. The Janssen Ad26.CoV2.S vaccine uses a single dose, adenoviral delivery platform that has been used in other vaccine campaigns. Recently-published data from the initial trial (the ENSEMBLE trial) demonstrated that Janssen Ad26.CoV2.S vaccination was 85 percent effective against severe/critical disease[4]. Additionally, the trial met its co-primary endpoints of protecting against moderate to severe COVID-19 at 14 and 28 days after vaccination, achieving 67 percent efficacy at 14 days after vaccination; and 66 percent efficacy at 28 days after vaccination, with prevention against COVID-19-related hospitalization and death across all participants (N=44,325). Protection was generally consistent across race, age groups, including adults over 60 years of age (N=14,672), and those with and without comorbidities. There was also robust immunogenicity across both humoral on cell mediated effector arms[4].

Optimal vaccine induced immunity requires functional immune effector arms. In the general population, almost all recipients of the mRNA vaccine developed anti-SARS-CoV-2 spike protein levels of $\geq$250 U/ml[5]. In contrast, immunocompromised populations have reduced quantitative responses to COVID vaccines compared to non-immunocompromised populations. For example, in 658 transplant recipients who received 2 doses of SARS-CoV-2 mRNA vaccine, 301 (46%) had no antibody response after dose 1 or dose 2 [6]. Quantitative levels of anti-SARS-CoV-2 spike protein

antibodies also appeared lower than in non-immunocompromised hosts. These data are aligned with available data across a broad range of vaccines in solid organ transplant recipients suggesting lower humoral response rates (approximately 50%–70%) compared to non-transplant populations [7].

At least three approaches are being explored to augment the vaccine responsiveness of immunocompromised populations to enhance their responses to vaccination: (i) revaccination with the same vaccine (i.e., a third dose on an mRNA vaccine (ClinicalTrials.gov Identifier: NCT04885907), (ii) reduced immunosuppression followed by revaccination (ClinicalTrials.gov Identifier: NCT04805125), or (iii) revaccination with a different vaccine.

In solid organ transplant recipients, there is one small, non-randomized publication of revaccination showing that patients with low, detectable levels developed high levels after a booster[8]. The authors state that 44% of patients who were anti-S protein seronegative after the conventional two-dose regimen became seropositive after a third "booster dose" (see adjacent plot). However, a closer look at the data shows that the levels of anti-S antibody after revaccination were much lower in the previously-negative group compared to the previously low-positive group (signal to cutoff ratio 690±293 vs 2676±350). While direct comparisons of these results using U/ml are not possible, we can conservatively assume that the rate of patients achieving the endpoint for our studies (≥250 U/ml) would be approximately 20% or less.



The concept of revaccination with a different vaccine (aka heterologous prime boost vaccination) is not a new concept. A landmark study in Macaques demonstrated that a heterologous prime boost approach resulted in superior immunogenicity and enhanced protection from infectious challenge compared to a single vaccine alone [9]-[10]. That study evaluated responses to Simian immunodeficiency virus (SIV) and has been recapitulated in other vaccine models, such as Hepatitis C [11]. Small safety focused studies of a heterologous prime boost strategy in the setting of SARS-CoV2 vaccination have been reported and demonstrate both feasibility and safety of the approach[12] [13]. One study suggested that heterologous prime-boost regimen with an adenovirus vector vaccine also improved Th1-based T cell responses [12], consistent with prior reports that adenoviral vector vaccines drive potent CD8 and CD4 T cell immunity[14].

Based on these data, we have developed the current protocol.

1.2 Investigational Agent

Janssen Ad26.CoV2.S vaccine is comprised of the following ingredients: recombinant, replication-incompetent adenovirus type 26 expressing the SARS-CoV-2 spike protein, Sodium chloride, Citric acid monohydrate, Polysorbate 80, 2-hydroxypropyl-β-cyclodextrin (HBCD), Ethanol (absolute), Sodium hydroxide and Water for injection (WFI).

The Janssen Ad26.COV2.s vaccine will be supplied at a concentration of 1 x 10^{11} vp/mL in single-use vials, with an extractable volume of 0.5 mL, and dose at 5 x 10^{10} vp. It is a single dose vaccine of 0.5mL administered via intramuscular injection, typically in the deltoid muscle.

1.3 Clinical Data to Date

Kidney Transplant Patients at Mayo Clinic: The Study Cohort

The 3 Mayo Clinic transplant sites (located in Rochester, MN, Phoenix, AZ and Jacksonville, FL) collectively perform more than 900 kidney transplants per year and follow more than 5000. Many clinical trials are performed simultaneously across all 3 sites. Over the past 7 years, total enrollment in clinical trials across all sites has been more than 1500 patients. Two of these studies involved more than 500 patients in each trial, demonstrating Mayo Clinic's ability to implement large clinical trials.

Vaccinated Patients

The number of solid organ transplant recipients seen at Mayo Clinic with EPIC documented vaccination (multiple dates of Moderna/Pfizer; or 1 Janssen) as of July 2021 is shown in the table below.

	Heart	Kidney	Liver	Lung	Pancreas	Total
Mayo site						
Jacksonville	108	583	613	159	11	1474
Phoenix	109	461	319		7	896
Rochester	170	2014	903	56	68	3211
Total	387	3058	1835	215	86	5581

A similar percentage of transplant recipients were vaccinated with the Pfizer (49%) and Moderna (47%) vaccines. Only 4% have received the Janssen Ad26.CoV2.S vaccine.

VACCINE_DESCRIPTION	# Pts	%
SARS-COV-2 (COVID-19) - JANSSEN (J&J)	242	4%
SARS-COV-2 (COVID-19) - MODERNA	2596	47%
SARS-COV-2 (COVID-19) - PFIZER	2749	49%

Anti-SARS-CoV-2 Spike Protein Antibody Testing and Rationale for the Primary Endpoint

Mayo Clinic has reviewed and tested multiple platforms for anti-SARS-CoV-2 spike protein antibody determination. The one selected for use is the Roche Elecsys® Anti-SARS-CoV-2 S, assay which is a one-step double antigen sandwich assay, which has a linear range of antibody determination from 0.4 to 250 U/ml. It is currently unknown what level of antibody response is associated with maximal protection from SARS-CoV2 infection or COVID disease. Our rationale for adopting a level of ≥250 U/ml is presented here.

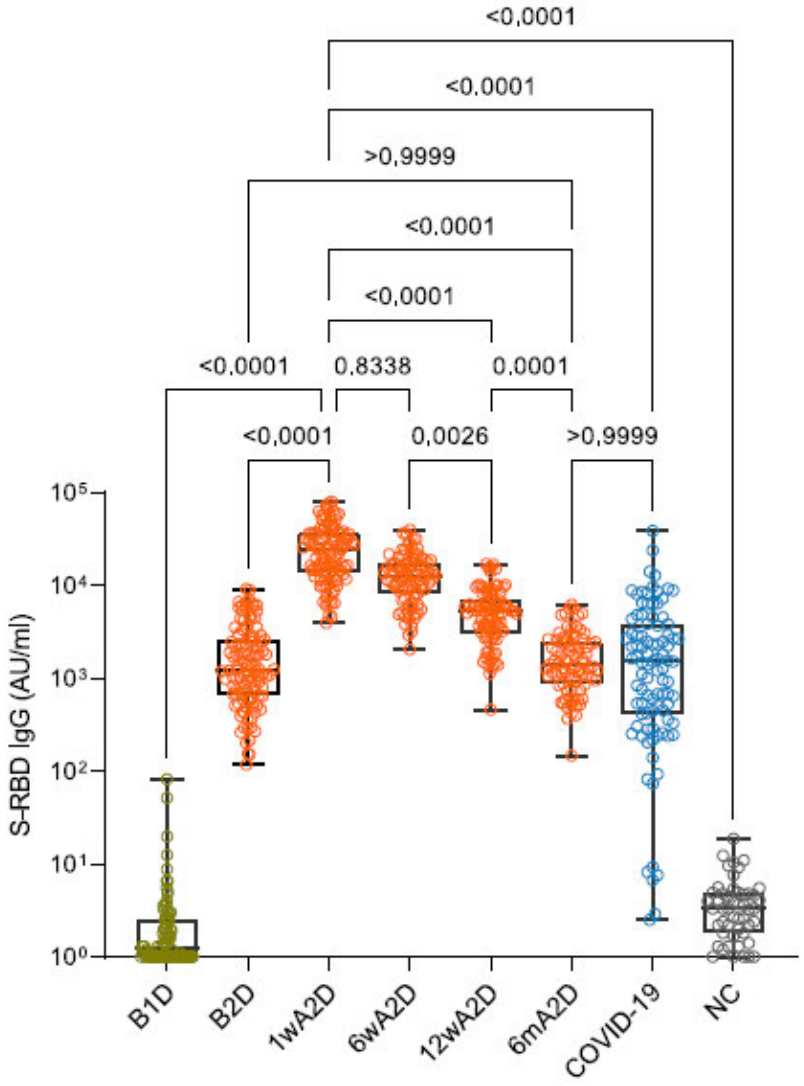


Fig. 1. Antibody responses in individuals vaccinated with Pfizer-BioNTech Comirnaty vaccine. S-RBD IgG levels before vaccination (B1D, n=88), after the single (B2D, n=111) and two-dose immunizations (1 week (1wA2D, n=106); 6 weeks (6wA2D, n=89), 12 weeks (12wA2D, n=90), and 6 months (6mA2D; n=84) in vaccinated individuals compared with post-infection levels in patients recovered from COVID-19 (COVID-19, n=97) and pre-COVID-19 negative controls (NC, n=50). The box plot comparisons were performed with the Kruskall-Wallis test and Dunn's multiple testing correction; p-values >0·0001 are reported as exact numbers.

Rationale for Anti-SARS-CoV-2 Spike Protein Antibody Levels as Endpoints

Early after receiving an mRNA COVID vaccination, most of the general population achieves an anti-SARS-CoV-2 spike protein antibody ≥250 U/ml (Figure on the right from Naaber et al. [5]). Anti-SARS-CoV-2 spike protein antibody levels do decrease with time, but almost all patients in this study from Europe continued to have levels ≥250 U/ml. Given that vaccination in the general population results in protection from severe disease in the vast majority of patients, there is a high correlation between high anti-SARS-CoV-2 spike protein antibody levels and protection from severe disease.

In contrast, several studies mentioned above have shown that **a large percentage of transplant patients form no anti-**SARS-CoV-2 **spike protein antibody or have levels <250U/ml even early after vaccination.** While a direct correlation between any specific anti- SARS-CoV-2 spike protein antibody has not been studied extensively, transplant patients do appear to have higher rates of COVID infections and possibly higher mortality rates.

No specific anti-spike protein antibody level is supported by the literature, but a level of <250 U/ml is clearly below the levels achieved both early and at 6 months after vaccination in the general population. Thus, we have chosen 250 U/ml (the saturation level of the assay below which does not require dilutions) as the target level of anti- SARS-CoV-2 spike protein antibody because we consider that a "normal" response to vaccine. There is no data for intermediate levels of antibody (likely the higher the better the protection). So, in the absence of any intermediate level data, we are aiming to achieve a normal response in transplant recipients receiving the Janssen Ad26.COV2.S vaccine in our trial.

Mayo Clinic Experience with Anti-SARS-CoV-2 **Spike Protein Antibody Testing in Transplant Recipients**

As of August 2021, more than 400 anti-SARS-CoV2 spike protein antibody tests had been performed in the Mayo Clinic solid organ transplant recipient population. Of these, 245 were in patients with documented vaccination post-transplantation. The time from vaccination to anti-SARS-CoV-2 spike protein test averaged 72 days (Range 1-181d) The majority of recipients had no response (51%) or had a low-level response (<250 U/ml, 33%). Only 16% had a value ≥250 U/mL of anti-SARS-CoV-2 spike protein antibody.

Post-Vaccination Spike protein result			
No_Responder	<250 U/ml	>250 U/ml	Total
125	81	39	245
51%	33%	16%	100%

In stark contrast to the response rate to the COVID-19 vaccine series post-transplant, if a recipient received vaccination prior to transplant, then 61% (1423) of patients had a response ≥250 U/ml. Nine patients had a low response (<250 U/mL) with 3 between 50-250 U//ml and 6 <50 U/ml). These data are similar to the overall Mayo Clinic patient cohort tested to date. Among >3800 anti-SARS-CoV-2 spike protein antibodies test results 56% of patients have a value ≥250 U/ml by 28 days post-vaccination.

COVID Infections and Deaths

Recent studies have suggested that solid organ transplant recipients have 4 times the rate of death after COVID infection compared to the general population (reviewed by Osmanodja et al[15]) suggesting that transplant recipients have mortality rate with COVID infection 4 times that of otherwise healthy people. At Mayo, the overall known mortality rate has been 3.8% compared to a

mortality rate of 0.8% in the general population—almost exactly the 4 time observed in other studies.

As of August 1, 2021, using the Mayo clinic COVID data registry, we identified 25 patients with breakthrough infection despite re-vaccination. Nine patients required oxygen therapy, 1 required mechanical ventilation support and 1 ECMO. None of the fully vaccinated individuals have died. [16]

1.4 Dose Rationale

The dose of Janssen Ad26.COV2.S vaccine used in this study will be the dose with EUA by the FDA[17]. Data on that dose are summarized here.

The dose level of Janssen Ad26.COV2.S vaccine to be assessed in the present study (5×10^{10} vp) is based on other Ad26-vectored vaccines administered to adults in clinical studies includingAd26.ZEBOV (Ebola virus program); Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV (HIV program); Ad26.CS.01 (malaria program); Ad26.RSV.FA2 and Ad26.RSV.preF (RSV program); and Ad26.ZIKV.001 (Zika virus program). Studies with Ad26.RSV.preF also included participants aged ≥60 years. The dose level of 5×10^{10} vp is the most extensively tested dose to date and has shown to be well tolerated and immunogenic in these vaccine programs.

Initial immunogenicity and safety data (28 days post dose 1 from Cohort 1a) from study VAC31518COV1001 has demonstrated that a single dose with the 5×10^{10} vp and 1×10^{11} vp Janssen Ad26.COV2.S vaccine dose levels is immunogenic (according to the study's prespecified criteria) and safe in adults ≥18 - ≤55 year of age. The sponsor has therefore decided to proceed with the Janssen Ad26.COV2.S vaccine at a dose level of 5×10^{10} vp in the Phase 3 studies.

Non-human primates immunized with a single-dose of Janssen Ad26.COV2.S vaccine (Study 20-14, dose level titration study) showed robust protection after intranasal and intratracheal challenge with SARS CoV-2. Janssen Ad26.COV2.S vaccine at 5×10^{10} vp provided complete protection in the lung in 5 of 5 animals, and in 5 of 6 animals in the upper respiratory tract. All control animals showed substantial viral load in both the lower and upper respiratory tract.

Use of the Janssen Ad26.COV2.S vaccine has not been studied extensively especially after mRNA vaccines. Recently some data was published in the interim results from the NIAID MixNMatch study on a pre-print server [18]. The findings noted homologous and heterologous boosters were overall well-tolerated and immunogenic. Similarly, currently, there are limited published data on optimal timing between 2 doses of the Janssen Ad26.CoV2 vaccine. Data published in Janssen's VRBPAC briefing document note that the number of participants in clinical trials that have received a second dose between 2 to greater than 6 months is 9,379 for those 18 and older and 2,383 for those 60 and older [19]. From these clinical trials, no new safety concern have been identified after a second dose. The reactogenicity after dose two was noted to be similar or milder than the first dose. In the current protocol, all patients will be at least 3 months from their last mRNA vaccine and at least 29 days from their last Janssen Ad26.CoV2.S vaccine.

1.5 Risks and Benefits

More detailed information about the known and expected benefits and risks of the Janssen Ad26.CoV2.S vaccine may be found in the IB and its addenda (if applicable) [25].

1.5.1 Risks Related to Study Participation

The following potential risks of the Janssen Ad26.CoV2.S vaccine will be monitored during the study and are specified in the protocol.

1.5.2 Risks Related to Janssen Ad26.CoV2.S Vaccine

Recent data generated from the ongoing clinical studies VAC31518COV1001, VAC31518COV1002, VAC31518COV2001 and VAC31518COV3001, demonstrated that a single dose of the Janssen Ad26.CoV2.S vaccine has an acceptable safety and reactogenicity profile and is sufficient to elicit SARS-CoV-2 neutralizing antibodies in adults ≥18 years of age, including adults ≥60 years of age when compared to no vaccine.

For emerging clinical data and the most comprehensive nonclinical information regarding the Janssen Ad26.CoV2.S vaccine, refer to the latest version of the IB and its addenda (if applicable) [20-25].

Sites will advise participants that side effects include fever as well as injection site pain, headache, fatigue, myalgia, and nausea per the current ICF; however, the occurrence of fever appears to be more common in younger adults and can be severe. This is based on information from study VAC31518COV1001.

Anaphylaxis is considered an important identified risk for the Janssen Ad26.CoV2.S vaccine. Individuals should be observed by a healthcare provider after vaccination per protocol requirements. Refer to the latest version of the IB and its addenda (if applicable) for further details [20-25].

1.5.2.1 Thrombosis with Thrombocytopenia Syndrome [TTS]

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by bleeding, has been observed very rarely following vaccination with the Janssen Ad26.COV2.S vaccine. Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis, and arterial thrombosis, in combination with thrombocytopenia. Cases of TTS occurred mostly within the first 3 weeks following vaccination, in males and females 18 years of age and older and were reported more frequently in females under 50 years of age. Fatal outcomes have been reported. The exact physiology of TTS is unclear. Thrombosis with thrombocytopenia, following administration of Ad26.COV2.S has a clinical course that resembles autoimmune heparin-induced thrombocytopenia (HIT) (Arepally

2021). Individuals who have experienced TTS or HIT are not eligible for participation in clinical studies.

Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

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TTS is considered an important identified risk for the Janssen Ad26.COV2.S vaccine. Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, and skin bruising and/or petechiae beyond the site of vaccination. The medical management of thrombosis with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (e.g., from the American Society of Hematology [26], British Society of Haematology – Expert Haematology Panel [27], and the CDC [28]. The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended. Management of the participant should not be delayed. Refer to the latest version of the IB and its addenda (if applicable) for further details. Due to the possibility of the occurrence of TTS after vaccination with the Janssen Ad26.COV2.S vaccine, additional reporting and data collection procedures have been included in the study for thrombotic events, thrombocytopenia, and TTS (see Section 7.2.3), which may facilitate diagnosis and clinical management of the event.

Similarly, TTS is considered to be an adverse event of special interest (AESI). Due to their immunosuppression and underlying diseases, kidney transplant recipients have fluctuations in their platelet counts below the typical reference range among the general population (>150,000/µl). A platelet count >75,000/µl is required for inclusion in this trial. The following will be considered as suspected AESIs and will be reported to the sponsor-investigator, Janssen, IRB and DSMB within 1 business day of awareness:

- Platelet count below 150,000/µl after receiving the Janssen Ad26.CoV2.S Vaccine without any identifiable alternative cause as determined by the study physicians,
- Platelet count below 150,000/µl and a decrease ≥25% from baseline after receiving the Janssen Ad26.CoV2.S Vaccine, or
- Any thrombotic event without any identifiable alternative cause as determined by the study physicians will be considered as suspected AESIs and will be reported to the sponsor-investigator, Janssen, IRB and DSMB within 1 business day of awareness.

See Section 7.2.3 for the management of patients with suspected TTS.

1.5.2.2 Venous Thromboembolism

An numerical imbalance of venous thrombotic events, particularly deep vein thrombosis and pulmonary embolism, was observed in the double-blind phase of VAC31518COV3001. Natural infection with SARS-CoV-2 has shown to be associated with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and VTE or arterial thrombosis. It is unknown whether these proposed mechanisms linking COVID-19 and thromboembolic events could also be applicable for vaccines against COVID-19 [29].

Healthcare professionals should be alert to signs and symptoms of thromboembolism and are advised to take the occurrence of VTE into consideration for individuals at increased risk for VTE.

1.5.2.3 Immune Thrombocytopenia

No cases of immune thrombocytopenia have been reported in the context of clinical studies. Very low platelet levels (<20,000 per μL) have been reported very rarely in the post-marketing setting typically within the first four weeks after receiving the Janssen Ad26.COV2.S vaccine. Some of these cases occurred in individuals with a history of immune thrombocytopenia (ITP).

Healthcare professionals should assess an individual's relevant medical history prior to administering the Janssen Ad26.COV2.S vaccine. If an individual has a history of ITP, discuss the risks and benefits of developing low platelet levels before administering the vaccine.

Healthcare professionals should be alert to signs and symptoms of ITP, such as spontaneous bleeding, bruising or petechiae. It is recommended to monitor platelet levels in individuals with a history of ITP following vaccination with the Janssen Ad26.COV2.S vaccine. If ITP diagnosis is confirmed, promptly initiate appropriate medical intervention.

Vaccine-associated Enhanced Disease, Including Vaccine-associated Enhanced Respiratory Disease

VAED, refers to an AE characterized by an exacerbated course of a vaccine-preventable disease following vaccination. The phenomenon has been observed primarily in vaccines targeting respiratory viruses, including RSV and SARS-CoV1, leading to it being commonly referred to as VAERD.

VAED/VAERD has been linked to a non-protective antibody response of low affinity for the target vaccine antigen. Subsequent natural infection leads to immune complex formation and complement activation with a Th2 biased CD4 T-cell response. In the case of VAERD, this results in pulmonary injury due to eosinophilic pulmonary infiltrations (Munoz 2021).

No cases of VAED/VAERD have been reported following vaccination with Ad26.COV2.S both in the clinical trial and post-marketing setting.

1.5.2.4 Capillary Leak Syndrome

Capillary leak syndrome (CLS) is a rare, potentially life-threatening clinical disease that causes edema, hypoproteinemia, episodic hypotension, dyspnea, hyponatremia, and weight gain that can be life threatening. Capillary leak syndrome may be idiopathic or secondary to an underlying cause. Cases of CLS have been observed secondary to COVID-19 disease caused by infection with SARS-CoV-2 [30-33] , and after both adenoviral vector-based and mRNA-based vaccine administration [34]. Capillary leak syndrome (CLS) was not observed in the 21,895 participants exposed in Study COV3001. A total of 10 cases were reported in the postmarketing setting in an estimated exposure of more than 36 million doses.
The Janssen Ad26.COV2.S vaccine is contraindicated in subjects with a prior medical history of CLS.

1.5.2.5 Guillain-Barré Syndrome (GBS)

Guillain-Barré syndrome (GBS) is considered an important identified risk for the Janssen Ad26.CoV2.S vaccine. Investigators should be alert to GBS signs and symptoms to facilitate diagnosis, to initiate adequate supportive care and treatment, and to rule out other causes. Refer to the latest version of the IB and its addenda (if applicable) for further details.

Facial Paralysis
A pooled analysis of the double-blind phases of 5 company-sponsored trials (VAC31518COV1001, VAC31518COV1002, VAC31518COV2001, VAC31518COV3001, and VAC31518COV3009) conducted by the Company at the time of the preparation of this IB update showed a numerical imbalance for facial paralysis between Ad26.COV2.S (n=4) and placebo (n=1). Based on this observation and the review of all available data; the Company concluded that there is a reasonable possibility that facial paralysis may be associated with Ad26.COV2.S.

1.5.3 Risks Related to Adenoviral-vectored Vaccines

The clinical AdVac® safety database (report version 5.0, dated 10 April 2020, cut-off date 20 December 2019) contains pooled safety data from 26 Janssen-sponsored clinical studies with Ad26 vaccine candidates: Ad26.ZEBOV (Ebola; 10 studies), Ad26.ENVA.01, Ad26.Mos.HIV and Ad26.Mos4.HIV (HIV; 8 studies), Ad26.CS.01 (malaria; 1 study), Ad26.RSV.FA2 and Ad26.RSV.preF (RSV; 6 studies), and Ad26.Filo (filovirus; 1 study). In these studies, 4,224 adult participants and 650 children received at least 1 vaccination with an Ad26-based vaccine. The AdVac® safety database report includes data only from studies for which the database has been locked for the final analysis.

Overall the Ad26-based vaccines were well tolerated, without significant safety issues identified.

The majority of solicited local and systemic AEs were of mild or moderate severity and usually started within 1 to 2 days after vaccination. Most of the events resolved within 1 to 3 days.

In adults, the most frequently reported solicited local AE was injection site pain (56.9% of Ad26 participants, compared with 22.5% of placebo participants). All other solicited local AEs were experienced by less than 25% of adult participants. The most frequently experienced solicited local AE in children was injection site pain, reported in 13.9% of children aged 1-3 years, 29.8% of children aged 4 to 11 years, and 24.8% of children aged 12 to 17 years after vaccination with an Ad26-based vaccine. For placebo, these percentages were 29.2% in children aged 4 to 11 years and 14.3% in children aged 12 to 17 years. No children aged 1 to 3 years have received placebo.

Severe injection site pain was experienced by 1.0% of adult Ad26 participants and 0.8% of children aged 4 to 11 years. No children in the other 2 age groups and no placebo participants experienced severe injection site pain.

There was a trend toward an increase in the frequency of some local AEs with an increase in Ad26 dose, i.e., injection site pain (18.7% of participants at the 0.8×10^{10} vp dose level, 38.7% of participants at the 2×10^{10} vp dose level, 52.0% of participants at the 5×10^{10} vp dose level, and 77.1% of participants at the 1×10^{11} vp dose level), and to a lesser extent injection site swelling (6.7%, 2.7%, 9.3%, and 17.6%, respectively). Injection site warmth was not collected at the 0.8×10^{10} vp and the 2×10^{10} vp dose level. The frequency of injection site warmth at the 5×10^{10} vp and the 1×10^{11} vp dose level was 19.5%, and 26.7%, respectively. This trend needs to be interpreted with caution since the participants in the lower dose groups (0.8×10^{10} vp and 2×10^{10} vp dose level) were all from a single study (VAC52150EBL3002), and the majority of the participants in the highest dose group (1×10^{11} vp dose level) were also from a single study (VAC18193RSV2003).

The most frequently reported solicited systemic AEs (i.e., reported in more than 30% of participants) for adult Ad26 participants were malaise (53.8%), fatigue (48.3%), headache (45.7%), and myalgia (38.3%), all of which were more frequent for Ad26 participants compared with placebo (36.4%, 30.7%, 30.0%, and 17.7% of placebo participants, respectively). Most of these events were considered related to the study vaccine. Pyrexia (9.9%) and vaccine-related pyrexia (9.0%) were also reported more frequently after administration of an Ad26-based vaccine compared with placebo (3.5% and 2.9%, respectively).

Solicited systemic AEs reported in ≥10% of children aged 1 to 3 years were decreased appetite (13.9%), decreased activity (13.2%), pyrexia (11.1%), and irritability (10.4%). The most frequently reported solicited systemic AEs in children aged 4 to 11 years (reported in ≥15% of Ad26 participants) were headache (23.6%; no data are available for the placebo group in this age group), and decreased activity (18.5%) and irritability (17.6%), which were both reported in 4.2% (N=1) of placebo participants. The most frequently reported solicited systemic AEs in children aged 12 to 17 years (reported in ≥15% of Ad26 participants) were headache (34.6%) and fatigue (24.0%), compared to 33.3% and 19.0% of placebo participants, respectively. Most of the frequently experienced solicited systemic AEs in children were considered related to the study vaccine.

The majority of solicited systemic AEs were of mild or moderate severity. For adults, 6.5% of Ad26 participants and 2.0% of placebo participants reported severe solicited systemic AEs, mostly malaise and fatigue. Other severe solicited systemic AEs were reported in less than 3% of adult Ad26 participants.

There was a trend toward an increase in the frequency of solicited systemic AEs with an increase in Ad26 dose (35.3% at the 0.8×10^{10} vp dose level, 49.3% at the 2×10^{10} vp dose level, 64.5% at the 5×10^{10} vp dose level, and 70.4% at the 1×10^{11} vp dose level). The frequency of severe solicited systemic AEs also tended to increase with higher Ad26 dose, i.e., 1.3% of participants at the 0.8×10^{10} vp and the 2×10^{10} vp dose level, 5.3% of participants at the 5×10^{10} vp dose level, and 14.4% of participants at the 1×10^{11} vp dose level. This trend needs to be interpreted with caution since the participants in the lower dose groups (0.8×10^{10} vp and 2×10^{10} vp dose level) were all from a single study (VAC52150EBL3002), and the majority of the participants in the highest dose group (1×10^{11} vp dose level) were also from a single study (VAC18193RSV2003).

The most frequently reported unsolicited AE in adult Ad26 participants was upper respiratory tract infection (5.3% vs. 7.0% in adult placebo participants). The most frequently reported unsolicited AEs considered related to the vaccine were neutropenia (1.0% of adult Ad26 participants vs. 0.5% of adult placebo participants) and dizziness (0.7% vs. 0.2%, respectively).

1.5.4 General Risks Related to Vaccination

In general, intramuscular (IM) injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration, swelling, arm discomfort, or bruising of the skin. Participants may exhibit general signs and symptoms associated with IM injection of a vaccine and/or placebo, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. These side effects will be monitored but generally are short-term. Instructions regarding use of antipyretic medication can be found in Section 5.6.

Syncope can occur in association with administration of injectable vaccines. Syncope can be accompanied by falls. Procedures should be in place to avoid falling injury. If syncope develops, participants should be observed until the symptoms resolve. Fear of injection might lead to fainting and fast breathing.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, urticaria, or even anaphylaxis (see above risks related to the Janssen Ad26.CoV2.S vaccine). Severe reactions are rare. Participants with a known or suspected allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine), will be excluded from the study.

After each vaccination, participants will remain at the study site for close observation by study staff to monitor for the development of any acute reactions. Necessary emergency equipment and medications will be available in the study site to treat severe allergic reactions.

1.5.5 Pregnancy and Birth Control

The effect of the study vaccine on a fetus or on nursing baby is unknown.
Given the limited number of incident pregnancies in the clinical studies with Ad26-based vaccines in the AdVac® safety database report (HIV vaccine: 20 pregnancies in participants and 10 in partners of participants; Ebola vaccine: 32 pregnancies in participants and 13 in partners of participants), it is not possible at present to draw firm conclusions on the safety of the vaccines when administered around the time of conception or prior to the initiation of the pregnancies. There is currently no concerning pattern of AEs in the pregnancies initiated around the time of vaccination or after exposure to the Ad26-based vaccines in the Janssen vaccines clinical development programs.

Participants of childbearing potential will be required to agree to practicing an acceptable effective method of contraception and agree to remain on such a method of contraception from providing consent until 3 months after receiving the last dose of the study vaccine (see Section 4.2). Use of condoms is not considered as an acceptable contraceptive barrier method due to the failure rate of female and male condoms[16]. Participants who are pregnant will be excluded from entering Segment I of the study. Participants who become pregnant during the study and received the Janssen Ad26.CoV2.S vaccine will not receive further vaccination. Participants will remain in the study and will continue to undergo all procedures for surveillance and follow-up of COVID-19 and all safety follow-up as outlined in the protocol for all participants.

Participants who are breastfeeding are allowed to participate.

1.5.6 Risks from Blood Draws

Blood draws may cause pain, tenderness, bruising, bleeding, dizziness, vasovagal response, syncope, and rarely, infection at the site where the blood is taken.

1.5.7 Theoretical Risk of Enhanced Disease

Vaccine-associated enhanced disease has been described for SARS-CoV and MERS-CoV in some animal models ([35-38]), and is associated with non-neutralizing antibodies and a Th2-skewed immune response. In contrast, the Ad26-based vaccines have been shown to induce a clear Th1-skewed immune response and generate potent neutralizing antibody responses in both humans and animal models (see Section 1.1). Participants in the present study will be informed of the theoretical risk of disease enhancement in the informed consent form (ICF). Initially, this study will include healthy adults ages ≥18. As a risk mitigation strategy, all enrolled participants will be intensively monitored during the conduct of the study to rapidly diagnose COVID-19 and refer for treatment, if applicable. All participants will be monitored for safety (including enhanced disease) for 2 years after the last vaccination, i.e., until the last study visit.

1.5.8 Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, Janssen Research and Development will notify the sponsor-investigator and participants will be informed.

1.5.9 Alteration in Immunosuppression Medication

One of the most likely reasons why kidney transplant patients fail to generate high levels of anti-SARS-CoV-2 spike protein antibodies after vaccination is the fact is that they are maintained on immunosuppressive medicines to prevent kidney transplant rejection. Standard-of-care immunosuppression at our 3 sites (and most institutions) is dual or triple maintenance therapy (a calcineurin inhibitor, usually tacrolimus, and some form of mycophenolate mofetil and sometimes prednisone). While general protocols are in place, the specific details of immunosuppression are determined clinically.

For this study, some patients will have their maintenance immunosuppression transiently adjusted (reduced) to potentially enhance their response to the Janssen Ad26.CoV2.S vaccine (see Section 5.2.1 for details). All patients will continue to be maintained on dual therapy at least (see protocol, section) and monitored closely with serum creatinine levels. It is important to recognize that in clinical practice, immunosuppressive doses are commonly reduced for many conditions—especially for short periods of time—with close monitoring for rejection. Long-term maintenance immunosuppressive therapy is commonly tapered and tailored to the individual recipient based on toxicity (for example, for chronic diarrhea, mycophenolate mofetil is reduced or even discontinued) or due to concomitant clinical problems (for example, for polyoma virus infections or cancer, immunosuppression is reduced or even stopped completely). Clinical rejection is less than 10% in our experience in these settings and the time of reduced immunosuppression is usually much longer than the 6 weeks dictated by the current study. Study subjects undergoing immunosuppressive drug alterations in this study have already shown that they do not make antibodies against anti-SARS-CoV-2 spike protein at the same levels of other patients that will be screened. Thus, one could hypothesize that the low-responders and non-responders to mRNA vaccines are already significantly immunosuppressed and thus might be at low risk for allograft rejection during transient immunosuppressive alterations.

Importantly, for this trial, alterations in immunosuppression will involve changes in the dosage and sometimes type of drug administered (prednisone added when mycophenolate discontinued, for example). Drug levels for tacrolimus, cyclosporine and mycophenolate mofetil are monitored as standard of care in subjects receiving these drugs (usually monthly) and will continue to be monitored. Drug levels also will be measured at the time 0 visit in all patients in both Segment 1 and 2. However, alterations in immunosuppression will not be directed by these drug levels. They are obtained to help support patient management as needed.

We recognize that there may be an increased risk of allograft rejection or even graft loss due to the transient 6-week alteration in immunosuppression in the current study. The actual risk is unknown, but we do have clinical experience with transient immunosuppression reduction in other settings and the outcomes have been good. The DSMB will monitor for allograft rejection episodes and graft losses in this study for all groups and will examine any instance. If a rejection rate of 10% occurs at any time in the study, the study will be paused, and the protocol re-examined.

1.5.10 General Risks related to the Covid-19 Vaccines

The current protocol involves the use of the Janssen Ad26.CoV2.S vaccine of which it is a Adenoviral-vectored Vaccine. New safety data has been released with the use of the mRNA vaccine (Moderna, Pfizer, etc.). Although cases of myocarditis and pericarditis have been reported in temporal association following vaccination with Ad26.COV2.S, it is worth noting that disproportionality of reporting has been observed mainly following the usage of mRNA-based S-protein Covid-19 vaccines compared to Ad26.COV2.S and other adenovector-based vaccines. In contrast to mRNA based vaccines, myocarditis and/or pericarditis following administration is not considered an identified risk for Ad26.COV2.S and currently no warning text has been included in the fact sheets for both HCPs and vaccine recipients. The new potential risk with the Covid-19 vaccines have been incorporated within the protocol.

Myocarditis and pericarditis have been reported in greatest numbers in males under the age of 40 years following a second dose of mRNA vaccines, but cases have been reported in older males and in females as well, and also following other doses. The observed risk is highest in males 12 to 17 years of age. While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolve in most individuals with conservative management. Information is not yet available about potential long-term sequelae. The risk in children younger than 12 years old is currently being assessed, and both the size of the database and length of follow-up in this population are relatively smaller than that of those older than 12 years old. Therefore, the characterization of the risk in children younger than 12 years old is not as well-known as in adolescents and adults.

Our study population involves relatively few males less than 40 years of age and we are not enrolling subjects <18 years of age.

Based on published literature, we expect that no patient in our study will develop myocarditis or pericarditis after vaccination—at the most 1 or 2. Most patients who developed this complication were males <40 years of age with an incidence of approximately 70-100 per million doses in this group. Detailed data in people over 50 years of age is almost never reported. One report of 1226 cases of myocarditis after >320 million doses of the mRNA vaccine in the US had only 70 cases in people >50 years of age.
(https://www.dicardiology.com/article/overview-myocarditis-cases-caused-covid-19-vaccine).

Healthcare professionals should be alert to signs and symptoms of clinical Myocarditis and Pericarditis, such as acute chest pain, and pain that spreads to the left shoulder and neck which may get worse when coughing, lying down or taking a deep breath or get better when sitting up or leaning forward. Other signs and symptoms may include cough, fatigue or general feeling of weakness or being sick, swelling of legs, ankles and feet, flu like symptoms, low-grade fever, arrhythmias or heart palpitations, light- headedness, shortness of breath or swelling of the abdomen. If clinical myocarditis or pericarditis is suspected within 4 to 6 weeks of vaccination, promptly initiate appropriate medical intervention and if diagnosis is confirmed a referral to a Mayo Clinic cardiologist will be performed. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings. Participants with events of

myocarditis and or pericarditis will be discontinued from further vaccination. Participants will remain in the study and continue to undergo all procedures for surveillance and follow-up of COVID-19 and all safety follow-up as outlined in the protocol for all participants.

Benefits of Study Participation

Participants may benefit from clinical testing and physical examination.

The efficacy, immunogenicity and safety data generated to date suggest a favorable benefit-risk profile for the Janssen Ad26.CoV2.S vaccine in the proposed indication when compared to no vaccine, i.e., active immunization to prevent COVID-19 caused by the SARS-CoV-2 virus in adults ≥18 years of age. The overall benefit and risk balance for individual participants is ongoing.

Benefit-Risk Assessment of Study Participation

Based on the available data and proposed safety measures, the overall benefit-risk assessment for this clinical study is considered acceptable for the following reasons:

- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 4.1 and 4.2) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:
  - In general, safety evaluations will be performed at scheduled visits during the study, as indicated the Schedule of Events.
  - All vaccine recipients will remain under observation at the study site for at least 30 minutes after each vaccination to monitor for the development of acute reactions.
  - The sponsor-investigator or the designee will document AEs and SAEs and medically-attended adverse events (MAAEs) for all participants as indicated in Section 7.
  - TTS is considered to be an adverse event of special interest (AESI) (Section 7.2.2.1). Suspected AESIs (thrombotic events and thrombocytopenia) must be reported as per Section 7.2.2 and Section 7.3 within 1 business day of awareness. Suspected AESIs will be followed up as described in the Schedule of Events in Section 6.6.
  - Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the sponsor-investigator until resolution or until clinically stable.
  - A Data Safety Monitoring Board will be established to monitor safety data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. This committee will review interim unblinded data. The DSMB responsibilities, authorities, and procedures will be documented in its charter. Additional ad hoc review may be performed further to the occurrence of any SAE leading to a study pausing.

Benefit-Risk Assessment for Segment II: A Second Janssen Ad26.CoV2.S vaccine with Immunosuppression Adjustment

Segment II involves a second Janssen Ad26.CoV2.S vaccine with immunosuppression adjustment. The subset of patients in Segment I who did not have immunosuppression adjustment will be offered a second Janssen Ad26.CoV2.S vaccine with adjustment of their immunosuppression. The risks of receiving a second Janssen Ad26.CoV2.S vaccine in immunocompromised populations are unknown. Clinical trials presented from the VRBPAC briefing document showed no new safety concerns identified after a second dose and that reactogenicity of a second dose was similar or milder than after the first dose [19]. SAEs and AEs will be monitored as in Segment I. The risk of immunosuppression adjustment will likely be the same as in Segment I and these will be monitored similarly.

2 Study Objectives

Primary Objectives

1. To assess whether an anti-SARS-CoV-2 spike protein antibody level of ≥250 U/mL can be achieved 28 days after a dose of the Janssen Ad26.CoV2.S vaccine in kidney transplant recipients who did not form acceptable levels of anti-SARS-CoV-2 spike protein antibody (<250 U/ml but >0 U/mL) after receiving two or more doses of a mRNA vaccine: Pfizer-BioNTech (BNT162b2 vaccine) or Modena (mRNA-1273). This includes any combination of the Pfizer-BioNTech (BNT162b2 vaccine) or the Moderna (mRNA-1273) results in two or more doses of mRNA vaccine.

2. To compare whether a dose of the Janssen Ad26.CoV2.S vaccine can achieve an anti-SARS-CoV-2 spike protein level ≥250 U/mL in kidney transplant recipients with no detectable anti-SARS-CoV-2 spike protein antibody after two or more mRNA vaccines. Kidney transplant recipients will be randomized to either maintenance of current immunosuppression or adjustment in immunosuppression around the time of receiving the Janssen Ad26.CoV2.S vaccine. The number of subjects with anti-SARS-CoV-2 spike protein level ≥250 U/mL between the two randomized groups will be compared.

Secondary Objectives

1. To determine the response* of the Janssen Ad26.CoV2.S vaccine in the a subset of patients who did not respond to an additional dose of the Janssen Ad26.CoV2.S vaccine in Segment I while on their maintenance immunosuppression. In this instance immunosuppression is adjusted (Segment II).
2. To determine the incidence of COVID-19 infection up to 2 years after enrollment or additional dose in all enrolled kidney transplant recipients (received Janssen Ad26.CoV2.S vaccine or not).
3. To determine the safety of an additional dose with the Janssen Ad26.CoV2.S vaccine after two or more doses of mRNA vaccine including vaccination with or without immunosuppression adjustment.

*Response is defined as achieving an anti-SARS-CoV-2 spike protein antibody level ≥250 U/ml 28 days after receiving the Janssen Ad26.CoV2.S vaccine.

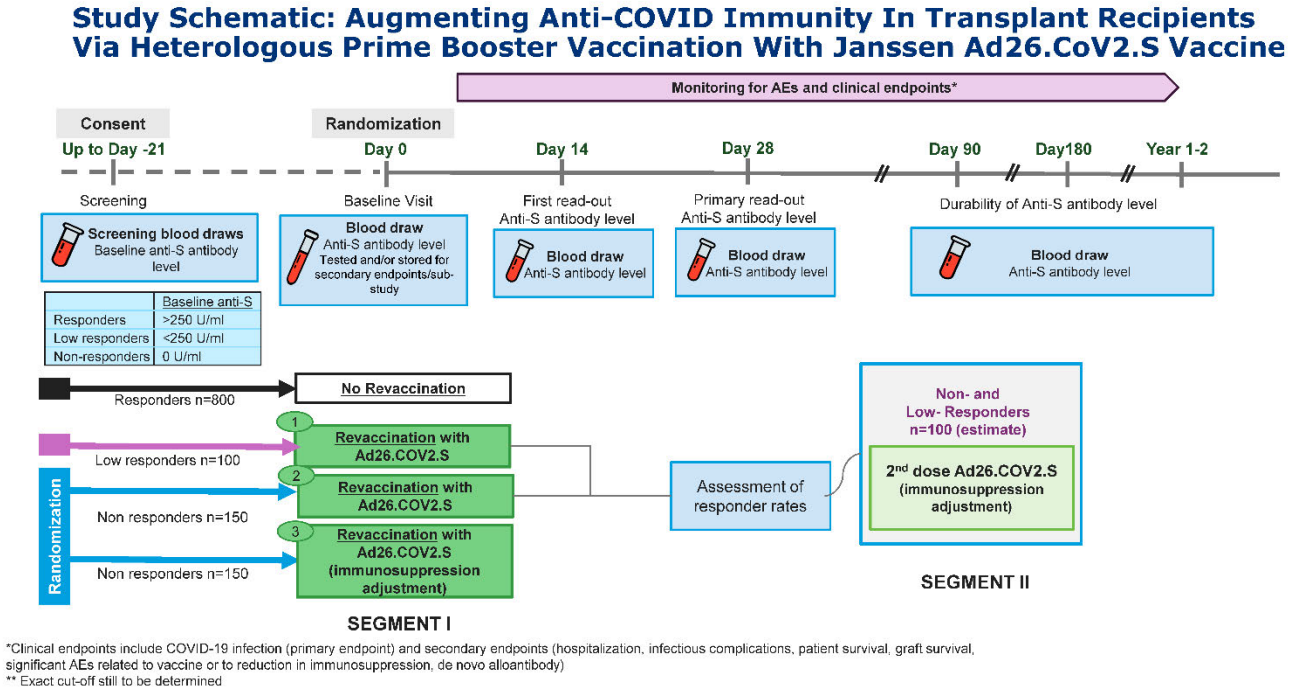
Exploratory Objective

1. To perform exploratory in vitro assays to better understand mechanisms of response to COVID-19 vaccination.

3 Study Design

This study is a phase III, prospective, open label clinical trial with one randomized arm. Its goal is to meet the unmet clinical need to provide vaccine induced immunity for our immunocompromised kidney transplant patients after receiving two or more doses of the Pfizer or Moderna COVID-19 vaccine (see Figure below for overview). Subjects will be pre-screened and interested qualified

subjects will be offered participation in this trial and, if applicable, consented. Once consented, serum levels of anti-SARS-CoV-2 spike protein antibody will be obtained. Patients with levels ≥250 U/ml will be followed for two years without receiving the Janssen Ad26.CoV2.S vaccine for clinical outcomes (COVID infection, graft and patient survival).



Segment I

Patients with levels >0 but <250U/ml of anti-SARS-CoV-2 spike protein antibody levels will receive one dose of the Janssen Ad26.CoV2.S vaccine. Their anti-SARS-CoV-2 spike protein antibody levels will be measured at multiple time points after receiving the Janssen Ad26.CoV2.S vaccine. Patients with undetectable anti-SARS-CoV-2 spike protein antibody levels (i.e. with levels = 0) will be randomized 1:1 (stratified by the number of mRNA doses received 2 vs 3) to receive the Janssen Ad26.CoV2.S vaccine and either: 1) continue on their current immunosuppression regimen or 2) have a transient immunosuppression medication adjustment prior receiving the Janssen Ad26.CoV2.S vaccine (described in Section 5.2.1).

Segment II

Patients in Segment I who received Janssen Ad26.CoV2.S vaccine while maintained on their usual immunosuppression medication dosage and did not reach the anti-SARS-CoV-2 spike protein antibody endpoint (≥250 U/ml) at 28 days will be offered an additional Janssen Ad26.CoV2.S vaccination. In this segment, immunosuppression will be adjusted (as described in Section 5.2.1)

and anti-SARS-CoV-2 spike protein antibody levels will be assessed at 28 days after the second vaccination with the Janssen Ad26.CoV2.S vaccine as the primary endpoint.

All study subjects will be followed for two years after their last vaccination and have their medical information recorded, including COVID 19 infections.

3.1 General Description

This is an open-labeled study to test the response of a heterologous additional dose with the Janssen Ad26.CoV2.S vaccine in patients who had a poor anti-SARS-CoV-2 spike protein response to mRNA vaccinations. The study includes a randomized trial of the adjustment of immunosuppression on the response to receiving the Janssen Ad26.CoV2.S vaccine.

3.1.1 Segment I

From the screened population, 100 kidney transplant recipients with an anti-SARS-CoV-2 spike protein antibody levels >0 but <250U/ml (termed low responders) will receive an additional dose of the Janssen Ad26.CoV2.S vaccine. 300 kidney transplant recipients with undetectable anti-SARS-CoV-2 spike protein antibody levels (termed non responders) will receive an additional dose of the Janssen Ad26.CoV2.S vaccine after randomization 1:1 to either a continuation of their current immunosuppression regimen, or after immunosuppression adjustment as defined in Section 5.2.1.

The primary endpoint for Segment I is a SARS-CoV-2 spike protein antibody level ≥250 U/ml 28 days after vaccination. Anti- SARS-CoV-2 spike protein antibody levels along with anti-SARS-CoV-2 nucleocapsid antibody levels will be evaluated on days 14, 28, 90 and 180 days. If levels are detectable at Day 180, an additional sample collection will be obtained between one to two yeas after receiving the Janssen Ad26.CoV2.S vaccine.

1) Non-responders (n=300): These are patients who had no antibody response to their initial COVID mRNA vaccination (SARS-CoV-2 spike protein antibody = 0 U /mL). For this randomized portion involving non-responders, we will stratify patients so that we will have equal numbers of patients in each arm who have received 2 doses of mRNA vaccine and equal numbers that have received 3 doses of mRNA vaccine.
    a. Randomization:
        i. 150 subjects to receive Janssen Ad26.CoV2.S vaccine.
        ii. 150 subjects to receive Janssen Ad26.CoV2.S vaccine AFTER immunosuppression adjustment as defined in “Immunosuppression Adjustment” section 5.2.1.

2) Low responders (n=100): Patients who had a demonstrable response to COVID mRNA vaccination but were below cutoff (SARS-CoV-2 spike protein antibody 0 to <250 U/mL) will receive the Janssen Ad26.CoV2.S vaccine.

3.1.2 **Segment II**

In Segment I, 250 subjects will receive the Janssen Ad26.CoV2.S vaccine without immunosuppression adjustment (i.e. they will be maintained on their current immunosuppression). We expect that adjusting immunosuppression increases the response to the Janssen Ad26.CoV2.S vaccine compared to no adjustment. Thus, it is possible that patients from Segment I who were maintained on current immunosuppression, but did respond to receiving the Janssen Ad26.CoV2.S vaccine (i.e. they failed to reach the SARS-CoV-2 spike protein antibody cutoff (≥250 U/mL) at 28 days might respond if they underwent immunosuppression adjustment and receive a 2nd vaccination of using the Janssen Ad26.CoV2.S vaccine. A 2nd dose of the Janssen Ad26.CoV2.S vaccine will be offered to these patients. The approach will be similar to Segment I, in that the dose of the Janssen Ad26.CoV2.S vaccine will occur at 2 weeks after immunosuppression adjustment.

The number of patients in this segment could be anywhere between 0 and 250. There is no data to provide an estimate of enrollment, as it can be affected many factors. In prior studies of the mRNA vaccine, most of the low responders developed high levels of antibody after revaccination. If 50% of the non-responders are included here (n=75) and 25 low responders, then the number of subjects receiving the Janssen Ad26.COV2.S vaccine in Segment II would be 100.

Clinical follow-up will be for two years after receiving the Janssen Ad26.CoV2.S vaccine and analysis will focus on transplant specific outcomes (graft and patient survival, rejection episodes, etc.), general health outcomes (incidence of new diagnoses) and COVID specific outcomes (incidence of *de novo* SARS-CoV2 infection and clinical course/outcome).

3.1.3 **Responders to mRNA Vaccination**

Those participants who were determined to have an initial response to either the Pfizer or Moderna vaccine series (defined as having a screening SARS-CoV-2 spike protein antibody result ≥250 U/mL) will not be offered the Janssen Ad26.CoV2.S vaccine. Participants will continue to be followed for approximately 2 years so their information can be used as a comparison for Segments I and II. These participants will be followed for 2 years for clinical outcomes (COVID infections, graft and patient survival). During this time their medical information will be collected, both through medical chart review and by the study team, and Mechanistic Studies will be performed (in a subset of subjects).

3.1.4 **Exploratory Mechanistic Immunologic Studies**

The immunologic mechanisms associated with a poor anti-spike protein antibody response after vaccination have not been studied in detail. We plan to explore the causes through a battery of immunologic assays. These detailed studies of T and B cells will be performed in a subset of patients to determine if specific alterations in immunity correlate with poor responsiveness to vaccination.

The following patients will have blood drawn for immunologic assays:

1) Initial responders (n=50):

   a. Patients who during screening have anti-SARS-CoV-2 spike protein antibody levels ≥250; one time point.
2) Low responders (n=50):
   a. Patients who are low responders (anti-SARS-CoV-2 spike protein antibody >0, but less than 250 U/ml) at screening.
3) Non-responders (n=50) with no change in immunosuppression:
   a. Patients who have no detectable anti-SARS-CoV-2 spike protein antibody that are randomized to remain on their current immunosuppression.
4) Non-responders (n=50) with a reduction in immunosuppression:
   a. Patients who have no detectable anti-SARS-CoV-2 spike protein antibody that are randomized the immunosuppression adjustment arm.
   b. Unlike the other patient groups, these subjects will have blood drawn for immunologic assessments at two time points; one prior to adjustment in their immunosuppression and a second performed 2 weeks after their immunosuppression is adjusted, but prior to receiving the Janssen Ad26.CoV2.S vaccine. This is intended to document any changes in immunologic profile secondary to immunosuppression adjustment.

Note, the immunologic assays will not be used for patient management or for decision-making in the trial. Thus, assays will be performed over the entire enrollment period until the target number of assays are performed. Patients receiving the Janssen Ad26.CoV2.S vaccine in Segment I will have anti-SARS-CoV-2 memory B cells and anti-SARS-CoV-2 T cell assays performed before and after vaccination. In addition to the tests described above, additional blood samples will be collected and stored for future testing. The details of the future tests will be outlined in a subsequent protocol amendment. The stored blood samples will not be analyzed until the protocol amendment is approved by the IRB.

Exploratory Mechanistic Study Lab Assessments.

The table below details the timing of each mechanistic study assay for each patient group but may not be limited to those studies included on the list. Samples will be collected as close to the timepoint as possible, but some variation is expected and will not be considered a deviation. All these studies will be performed on peripheral blood. These assays will be performed in multiple laboratories located at Mayo Clinic Rochester or in Rochester, Minnesota.

Only a subset of subjects in each group will be included in the mechanistic studies. Subjects will be selected based on their availability to have blood drawn. In the initial responder group 50/800 subjects will have blood drawn on the day of a routine clinic visit. The remaining subject groups will have blood drawn prior to and post-vaccination on 50 unique subjects from each group (see table below).

Mechanistic study	Initial responders (n=50) ANY visit	Low responders (n=50) Day 0	Day 28	Day 1-2 yrs	Non-responders (No Immuno change; n=50) Day 0	Day 28	Day 1-2 yrs	Non-responders (Immuno change; n=50) Day -14	Day 0	Day 28	Day 1-2 yrs
Total Immunoglobulin levels	X	X			X			X	X		
T-cell immunophenotyping	X	X			X			X	X		
B-cell immunophenotyping	X	X			X			X	X		
Covid T-cell ELISPOT	X	X	X		X	X			X	X	
Covid Memory B-cell	X	X	X		X	X			X	X	
Neutralizing antibody	X	X	X		X	X			X	X	
T-cell repertoire (spectratyping)	X	X			X			X	X		

Note: Subjects enrolled in Segment I who end up in Segment II will not have the 1-2 year mechanistic study specimens collected. Once subjects are enrolled in Segment II, they will not have mechanistic studies.

1. Total Immunoglobulin Levels:
    a. Total serum immunoglobulin levels – IgG, IgA and IgM will be tested.
    b. Samples will be collected prior to vaccination (Day 0) in all groups receiving vaccination and in the group receiving reduced immunosuppression prior to immunosuppression reduction (Day -14).
    c. These assays will be performed in the Protein Immunology Laboratory at Mayo Clinic Rochester (clinical lab).
2. T-cell and B-cell Immunophenotyping:
    a. Flow cytometric analysis using pertinent cell markers: CD3, CD8, CD4, CD20, CD38, CD27, IgD, Ki67. This will determine total T cells, T helper cells and CD8 T cells and naïve B cells, memory B cells, plasmablasts and plasma cells.
    b. Samples will be collected prior to vaccination (Day 0) in all groups receiving vaccination and in the group receiving reduced immunosuppression prior to immunosuppression reduction (Day -14).
    c. These assays will be performed in the Cellular and Molecular Immunology Laboratory in the Mayo Clinic Rochester Campus (Directed by Dr. Attila Kumanovics).
3. SARS-CoV-2 T-cell ELISPOT:
    a. This assay tests for T-cell activation when exposed to COVID spike protein.
    b. Samples will be collected prior to vaccination (Day 0) in all groups receiving vaccination and at Day 28 (post-vaccination).
    c. These assays will be performed in the Cellular and Molecular Immunology Laboratory in the Mayo Clinic Rochester Campus (Directed by Dr. Attila Kumanovics).
4. SARS-CoV-2 Memory B-cell:
    a. Flow-cytometric assay that measures the percentage of memory B cells that bind SARS-CoV-2 -spike protein (flourochrome labeled).
    b. Samples will be collected prior to vaccination (Day 0) in all groups receiving vaccination and at Day 28 (post-vaccination).
    c. These assays will be performed in Dr. Mark Stegall's research laboratory located on the Mayo Clinic Rochester campus.
5. Neutralizing antibodies:
    a. This assay quantifies the SARS-CoV-2 virus neutralizing antibodies.

   b. Samples will be collected prior to vaccination (Day 0) in all groups receiving vaccination and at Day 28 (post-vaccination).
   c. These assays will be performed at Imanis Life Sciences (Rochester, MN).
6. T cell repertoire:
   a. This is a PCR assay that determines the number and type of T cell receptors present in a population of cells.
   b. Samples will be collected from Day 0 to 1-2 years in the Low Responder and Non-Responder groups. Samples will be collected in the Initial Responder group at any visit. In addition, the immunosuppression reduction group will have a specimen processed at the time of immunosuppression reduction (Day -14).
   c. These assays will be performed in the Cellular and Molecular Immunology Laboratory in the Mayo Clinic Rochester Campus (Directed by Dr. Attila Kumanovics).

The study team has been in contact with all included laboratories. All labs have agreed to participate in the study **AND** have the capacity to complete the study as designed. Whenever possible, residual specimens will be stored in Dr. Stegall's research laboratory for future use. The Stegall laboratory is equipped with multiple large cryogenic tanks, 5 – 20 ft^3 supercold (-80^o) freezers and sample tracking methods suitable for long-term sample storage.

3.1.5 Study Measurements

The following are the study measurements to be obtained in this clinical trial:

- Roche anti-SARS-CoV-2 spike antibody testing will be performed prior to receiving the Janssen Ad26.CoV2.S vaccine
  - These tests will be performed at Mayo Clinic Rochester using specimen kits mailed in or on specimens collected at the study site.
  - The data from the 28 day measurement will be used as primary endpoint. The other measurements will be used to assess the response to the Janssen Ad26.CoV2.S vaccine early (post - 14 days) and late (post - 90 to 180 days). If levels are detectable at Day 180, an additional sample collection will be obtained from one to two years.
- Anti-SARS-CoV-2 nucleocapsid total antibody testing will be performed at the same time as the anti-SARS-CoV-2 spike protein testing.
  - This assay is intended for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2 virus, indicating recent or prior infection.
  - These assays will be performed in the Central Clinical Laboratory in the Mayo Clinic Rochester campus.
- Clinical data:
  - Mayo Clinic Transplant utilizes the "Phoenix" module for EPIC to capture Transplant Specific information.
  - This will be used to collect all relevant clinical information including patient demographics, patient and graft status, adverse events, follow-up, etc.
- Study data:

  - Study specific data (labs, study diary, adverse events, etc.) will be entered into a RAVE database that can be easily interfaced with the EPIC (Phoenix [Transplant] and Healthy Planet [COVID]) databases.
- Mechanistic studies (Section 3.1.4)

3.2 Number of Subjects

400 study subjects will receive vaccination with the Janssen Ad26.CoV2.S vaccine in Segment I, We will enroll and screen up to 1200 patients to achieve this number of vaccinated subjects expecting that up to 800 patients will have anti-SARS-CoV-2 spike antibody levels at the time of screening. Approximately 800 patients that will not receive the Janssen Ad26.CoV2.S vaccine will be followed for outcomes such as COVID infections up to 2 years. Up to 250 subjects in Segment I might participate in Segment II.

3.3 Duration of Participation

Subjects who only participate in Segment I will be followed for 2 years after receiving the Janssen Ad26.CoV2.S vaccine. Those who participate in Segment II will have their participation extended, with 2 years of clinical follow up after receiving the second Janssen Ad26.CoV2.S vaccine date. Screened patients not receiving the Janssen Ad26.CoV2.S vaccine will be followed for 2 years.

3.4 Primary Study Endpoints

The primary endpoint of all studies is the detection of antiSARS-CoV-2 spike antibody levels $\geq$250 U/ml in serum 28 days after receiving the Janssen Ad26.CoV2.

We have dual primary objectives in this study with the response defined as the following: achieving an anti-SARS-CoV-2 spike protein antibody level $\geq$250 U/ml 28 days after an additional dose with the Janssen Ad26.CoV2.S vaccine.

1. To assess whether an anti-SARS-CoV-2 spike protein antibody level of $\geq$250 U/mL can be achieved 28 days after a dose of the Janssen Ad26.CoV2.S vaccine in kidney transplant recipients who did not form acceptable levels of anti-SARS-CoV-2 spike protein antibody (<250 U/ml but >0 U/mL) after receiving two or more doses of a mRNA vaccine: Pfizer-BioNTech (BNT162b2 vaccine) or Modena (mRNA-1273). This includes any combination of the Pfizer-BioNTech (BNT162b2 vaccine) or the Moderna (mRNA-1273) results in two or more doses of mRNA vaccine. This is not randomized and not controlled.

2. To compare whether a dose of the Janssen Ad26.CoV2.S vaccine can achieve an anti-SARS-CoV-2 spike protein level $\geq$250 U/mL in kidney transplant recipients with no detectable anti-SARS-CoV-2 spike protein antibody after two or more mRNA vaccines. Kidney transplant recipients will be randomized to either maintenance of current immunosuppression or

adjustment in immunosuppression around the time of receiving the Janssen Ad26.CoV2.S vaccine. The number of subjects with anti-SARS-CoV-2 spike protein level ≥250 U/mL between the two randomized groups will be compared.

Thus, the ***primary comparison*** for this study is the rate of achieving this endpoint after receiving the Janssen Ad26.CoV2.S vaccine in patients who: 1) had undetectable anti-SARS-CoV-2 spike protein antibody levels after 2 or more doses of mRNA vaccine; and then were 2) randomized to either no alteration in immunosuppression vs alteration in immunosuppression around the time of receiving the Janssen Ad26.CoV2.S vaccine. The power calculations will focus on the difference in the proportion of patients who meet this endpoint between those with no alteration and those with an alteration in immunosuppression.

3.5 Secondary Study Assessments/Endpoints

- Any response in non-responders: Number and percentage of patients with undetectable anti-SARS-CoV-2 spike protein antibody level after 2 or more doses of mRNA vaccine who receive the Janssen Ad26.CoV2.S vaccine who develop anti-SARS-CoV-2 spike protein antibody levels >0 or <250 at 28 days.
- Good response in low-responders: Number and percentage of patients with anti-SARS-CoV-2 spike protein antibody levels >0 but <250U/ml after 2 or more doses of mRNA vaccine who receive the Janssen Ad26.CoV2.S vaccine who develop anti-SARS-CoV-2 spike protein antibody levels ≥250 at 28 days.
- Segment II. Rate of achieving an anti-SARS-CoV-2 spike protein antibody level ≥250 U/ml 28 days after receiving the Janssen Ad26.CoV2.S vaccine in patients who failed to achieve the response in Segment I who received a second dose of the Janssen Ad26.CoV2.S vaccine after adjustment of immunosuppression.
- Durability of anti-SARS-CoV-2 spike protein antibody levels in patients who developed any level of antibody response after receiving the Janssen Ad26.CoV2.S vaccine at 180 days and/or between 1 and 2 years after receiving the Janssen Ad26.CoV2.S vaccine.
- Incidence of COVID-19 infection at 2 years.

Exploratory Endpoints (Mechanistic studies):

Baseline Differences

It is expected that at baseline (prior to receiving the Janssen Ad26.CoV2.S vaccine), when compared to responders, low responders and non-responders will demonstrate no SARS-CoV-2 specific T and B cells and lower mean number of T cell receptors. Non-responsiveness will correlate with lower mean numbers of T and B cells including specific subtypes such as T-helper cells and memory B cells.

Response to Alterations in Immunosuppression

Alterations in immunosuppression will lead to increased number of T and B cells from baseline. Paired t test with each patient serving as their own controls.

Additional Dose with the Janssen Ad26.CoV2.S Vaccine

Compared to those who do not respond, patients who respond to receiving the Janssen Ad26.CoV2.S vaccine will demonstrate new or increased levels of SARS-CoV-2-specific T and B cells. They also will have higher baseline levels of T cells, B cells, serum immunoglobulin levels and T cell repertoire.

3.6 Primary Safety Endpoints

Primary Endpoint

SAEs related to the Janssen Ad26.CoV2.S vaccine.

Secondary Endpoints

1. SAEs related to reduction in immunosuppression.
2. Any hospitalization within 2 years of randomization.
3. Microbiologically defined infectious complications.
4. Patient survival at 2 years post randomization.
5. Graft survival at 2 years post randomization.
6. Adverse events related to the Janssen Ad26.CoV2.S vaccine.
7. Adverse events related to reduction in immunosuppression (rejection, graft loss, new onset donor-specific alloantibody formation).
8. Incidence of de novo alloantibody found as SOC.
9. Occurrence and relationship of SAEs and adverse events of special interest (AESIs), medically-attended adverse events (MAAEs) (until 6 months after the last Janssen vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants.

3.7 Identification of Source Data

The following source data will be directly recorded in the Electronic Medical Record (EMR)

- Vital signs
- Serious Adverse Events
- Demographic Data
- Baseline Transplant and Followup
- Information related to the Janssen Ad26.CoV2.S vaccine administration and side effects
- Medications
- Patient Status
- Patient Graft Status
- Laboratory and biopsy results and clinical interpretation of the values
- Nephrology and Transplant related clinical visits
- Clinical visits related to Transplant

The following data will be obtained from the subject and maintained in the study files

- Study Diary
- Risk Factor Assessment and Kidney Transplant Follow Up Questionnaire
- Pre and Post Vaccination Symptoms Questionnaire
- Safety Follow Up Questions
- COVID-19 Surveillance and Evaluation
- Follow Up Safety Assessment Phone Calls

Mechanistic study results will be obtained from 3 sources:

1) Reported within SOFTLab which is the Mayo data repository for research data from clinical labs. This involves the reporting of results for the following assays:
    a. Total Immunoglobulin levels
    b. T-cell and B-cell Immunophenotyping.
    c. COVID T-cell ELISPOT
    d. T-cell repertoire.
2) Reported directly from Dr. Stegall's laboratory:
    a. Covid Memory B-cell.
3) Reported directly from Imanis Life Sciences:
    a. Neutralizing antibody.

Regardless of the source, all source documents will be stored by the Mayo study team.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

Criteria for Entry into the Study:

- Any kidney transplant recipient from Mayo Clinic who has received at least two doses of the mRNA vaccine (two or more doses of mRNA vaccine-Moderna or Pfizer) and are >28 days after most recent vaccination at the time of spike protein assessment.
- Recipients of a kidney transplant, including those transplanted with other solid organ transplants in addition to the kidney. Subjects may have received more than 1 kidney transplant.
- More than 90 days since any transplant including a kidney transplantation.
- ≥18 years of age on the day of consent.

Criteria for Entry into Segment I

- Must have a Roche Elecsys® Anti-SARS-CoV-2 S level of <250 U/mL to be eligible for Segment I.
- Platelet count of >75,000/μL on the day of vaccination with the Janssen Ad26.CoV2.S vaccine.
- Contraceptive (birth control) use should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.
- Before randomization, participants must be either:

- Not be of childbearing potential
- Of childbearing potential and practicing an acceptable effective method of contraception. Subject must agree to remain on contraception from date of consent until 3 months after the last dose of the Janssen Ad26.CoV2.S vaccine. Use of hormonal contraception should start at least 28 days before the 1st administration of the Janssen Ad26.CoV2.S vaccine. The sponsor-investigator should evaluate the potential for contraceptive method failure (for example, noncompliance, recently initiated) in relationship to the Janssen vaccination. Acceptable effective method a for this study include:
  - Hormonal contraception:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion/ligation procedure
  - vasectomized partner (the vasectomized partner should be the sole partner for that participant)
  - Sexual abstinence (defined as refraining from heterosexual intercourse from the date of consent until 3 months after the last dose of the Janssen Ad26.CoV2.S vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.).
    Note: Use of condoms is **not** considered as an acceptable contraceptive barrier method due to the failure rate of female and male condoms (Centers for Disease Control and Prevention. Reproductive Health: Contraception. https://www.cdc.gov/reproductivehealth/contraception/index.htm. Accessed 23 November 2020)
- If subject is female and of childbearing potential, she must:
  - Have a negative highly sensitive serum pregnancy test prior to vaccination.
- Participant agrees to not donate bone marrow, blood, and blood products from the first Janssen Ad26.CoV2.S vaccine administration until 3 months after the last dose of the Janssen Ad26.CoV2.S vaccine.

4.2 Exclusion Criteria

- Clinically significant acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned 1st dose of the Janssen Ad26.CoV2.S vaccine; randomization at a later date is permitted at the discretion of the sponsor-investigator.

- Has a known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the Janssen Ad26.CoV2.S vaccine; refer to the Investigative Brochure).
- Subject has received or plans to receive:
    - Licensed live attenuated vaccines –within 28 days before or after planned administration of the 1st or subsequent Janssen vaccinations.
    - Other licensed (not live) vaccines –within 14 days before or after planned administration of the 1st or subsequent Janssen vaccinations.
- Received an investigational drug within 30 days (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days of the Janssen Ad26.CoV2.S vaccine. Received investigational Immunoglobulin (Ig) or investigational monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine (including investigational Adenoviral- vectored vaccines) within 6 months before the planned administration of the 1st dose of the Janssen Ad26.CoV2.S vaccine or is currently enrolled or plans to participate in another investigational study within 3 months after the last Janssen vaccination.
  Note: Participation in an observational clinical study is allowed at the sponsor-investigator's discretion; please notify the sponsor-investigator of this decision.
  Efforts will be made to ensure inclusion of participants who have not been previously enrolled in coronavirus studies. In order to participate subject must agree and understand that they cannot enroll in other coronavirus focused studies while participating in this one.
- Is pregnant or planning to become pregnant at the time of consent and within 3 months of the last dose of the Janssen Ad26.CoV2.S vaccine.
- Has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings which, in the opinion of the sponsor-investigator, would make study participation not be in the participant's best interest (e.g., compromise the well- being) or that could prevent, limit, or confound the protocol-specified assessments.
- Has a contraindication to IM injections and blood draws.
- Has had major psychiatric illness, which in the sponsor-investigator's opinion would compromise the participant's safety or compliance with the study procedures.
- Cannot communicate reliably with the sponsor-investigator or comply with study procedures.
- In the opinion of the sponsor-investigator, is unlikely to adhere to the requirements of the study or is unlikely to complete the full course of protocol required vaccination and observation.
- History of cancer malignancy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or other malignancies with minimal risk of recurrence).
- History of acute polyneuropathy (e.g., Guillain-Barré syndrome)
- Chronic history of platelet count <75,000/µL.
- History of thrombosis with thrombocytopenia syndrome (TTS) or heparin-induced thrombocytopenia (HIT).
- History of capillary leak syndrome (CLS).
- History of myocarditis or pericarditis.

- Received pre-exposure prophylactic medications for COVID-19 that could interfere with assessments of any study-related endpoint.

4.3 Subject Recruitment, Enrollment and Screening

Kidney transplant recipients who have received at least two of the mRNA vaccines will be identified by review of their medical record to see if they preliminary fit other inclusion/exclusion criterion for the study. If they appear to be a potential subject they will be contacted via phone or the Mayo Clinic portal to determine interest in study participation. If the potential participant is interested, they will be consented in person or remotely and instructed on study procedures.

Consented subjects will submit a blood sample to determine if they fit the enrollment criterion for the anti-SARS-CoV-2 spike protein level (<250U/ml). Those with an anti-SARS-CoV-2 spike protein levels at <250U/ml will receive the Janssen Ad26.CoV2.S vaccine.

This study plans to enroll up to 1200 research subjects to obtain 400 that have low or no detectable anti-SARS-CoV-2 spike protein antibody levels. Based on prior small studies, we expect (conservatively) that at least 20% will have low, but detectable antibody levels and 30% of all patients will have no detectable levels and will meet this inclusion criteria and other inclusion criteria. Thus, we envision screening approximately 1,200 kidney transplant recipients. Screening will be completed once 400 subjects have enrolled in Segment I.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Vaccination with the Janssen Ad26.CoV2.S vaccine will be withheld from participants from Segment I for the reasons listed below. These participants must not receive any further doses of the Janssen Ad26.CoV2.S vaccine but can remain in the study for follow-up assessments of safety and immunogenicity. Additional unscheduled visits may be performed for safety/reactogenicity reasons, if needed. In case of questions, the study staff at Mayo Arizona, Florida or Rochester are encouraged to contact the sponsor-investigator.

- Any related AE, worsening of health status or intercurrent illness that, in the opinion of the sponsor-investigator, requires discontinuation from the Janssen Ad26.CoV2.S vaccine
- The participant becomes pregnant
- Withdrawal of consent to receive the Janssen Ad26.CoV2.S vaccine
- Anaphylactic reaction following vaccination with the Janssen Ad26.CoV2.S vaccine, not attributable to causes other than vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to the Janssen Ad26.CoV2.S vaccine
- Participant previously experienced TTS or HIT
- Participant previously experienced myocarditis and/or pericarditis.

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of Consent from the study
- Repeated failure to comply with protocol requirements
- Death

If a participant is withdrawn from the study, or chooses to no longer participate, no further study data will be acquired but their clinical care will continue as usual.

If a patient is withdrawn, but has already received the Janssen Ad26.CoV2.S vaccine, they will not be replaced by another patient.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Patients may be withdrawn from the study if an adverse event occurs which could be attributable to the Janssen Ad26.CoV2.S vaccine or related study procedures, or if patients choose to no longer participate in the study. Once patients are withdrawn from the study, or choose to no longer participate, no further study data will be acquired. If withdrawal occurs before study completion, the reason for withdrawal will be documented in the eCRF and in the source document.

4.5 Criteria for Temporarily Delaying Administration of Study Vaccination

The following events constitute a temporary contraindication to study vaccination:

- Clinically significant acute illness at the time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper respiratory tract infection.
- Fever (body temperature ≥38.0°C/100.4°F) within 24 hours prior to the planned time of vaccination.
- An illness which in the judgement of the sponsor-investigator may interfere with reactogenicity.
- Additional adjustment needed to immunosuppression medication.

If any of these events occur at the scheduled time for receiving the first dose of the Janssen Ad26.CoV2.S vaccine, randomization at a later date within the screening window is permitted at the discretion of the sponsor-investigator.

If randomization cannot occur within the screening window, the COVID spike protein test will be repeated. If any of these events occur at the scheduled time for the second vaccination, the vaccination can be rescheduled, as long as this is in agreement with the allowed windows (see Visit Windows in the Schedules of Activities).

If the second vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor-investigator should be contacted for further guidance.

For randomized participants who could not be administered with the Janssen Ad26.COV2.S vaccine on the day of randomization for any reason, vaccination can be administered on another day provided that vaccination occurs within the 28-day screening visit window. Baseline visit procedures should be performed prior to vaccination and within the visit window. The following study visits and procedures will be adjusted accordingly.

Participants who cannot be dosed within the 28-day screening window should be discontinued from the study and should not be rescreened.

5 Study Drug

5.1 Description

The Janssen Ad26.CoV2.S vaccine is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector that encodes a SARS-CoV-2 spike (S) protein in a stabilized conformation. The S protein on the surface of the coronavirus binds to the Angiotensin Converting Enzyme 2 (ACE2) receptor of a host cell allowing the virus to infect the cell. Vaccination with the Janssen COVID-19 Vaccine leads to humoral and cellular immune responses directed against the S protein and in particular the production of neutralizing and other functional S antibodies which may block ACE2 receptor binding to the S protein, contributing to protection against COVID-19.

COVID-19 and SARS-CoV-2

COVID-19 is an infectious disease of the respiratory tract caused by SARS-CoV-2. SARS-CoV-2 carries RNA as its genome. The genome consists of 6 major open reading frames and accessory genes coding for non-structural proteins, including the RNA-dependent RNA polymerase, proteases, and the structural proteins, including the matrix (M), envelope (E), spike (S), and nucleoprotein (N). The spike (S) protein is responsible for binding to the human cell surface receptor, followed by membrane fusion and entry.

Viral Vector-based Vaccines

Viral vector-based vaccines do not contain antigens, but rather use the body’s own cells to produce them. Adenoviruses are among the most utilized vectors for vaccine development. The viral vector is replication incompetent so the viral DNA cannot replicate and will over time be cleared from the cells/tissues, e.g. due to cell division, or due to removal of transduced cells by the immune system. Nonclinical biodistribution studies show that adenoviral vector DNA of Ad26 vaccine vectors did not distribute widely, as the vector DNA was primarily detected at the site of administration in the muscle, the draining lymph nodes and, to a lesser extent, to the spleen. Viral vector DNA can be detected in tissues at very low levels for weeks until a few months after vaccination in animal models. Antigen expression data for the S protein are not available, but in animals the expression of another antigen delivered with the Ad26 vector cannot be detected after 1-2 weeks.

Janssen selected the human adenovirus-26 (Ad26) as a vector for the SARS-CoV-2 antigen because of the substantial nonclinical and clinical evidence from Janssen's other vaccine development programs. Across Janssen programs, Ad26-based vaccines demonstrate the capacity to elicit strong humoral immune responses with both neutralizing activity and non-neutralizing antibody functionalities, and cellular immune responses involving both CD8+ T cells and CD4+ T cells, with predominantly a Th1 phenotype.

The Janssen COVID-19 Vaccine includes the following ingredients: recombinant, replication-incompetent adenovirus type 26 expressing the SARS-CoV-2 spike protein, Sodium chloride, Citric acid monohydrate, Polysorbate 80, 2-hydroxypropyl-β-cyclodextrin (HBCD), Ethanol (absolute), Sodium hydroxide and Water for injection (WFI).

5.2 Treatment Regimen

5.2.1 Immunosuppression Adjustment

Immunosuppression adjustment will occur 2 weeks prior to receiving the Janssen Ad26.CoV2.S vaccine and continue for 28 days receiving the Janssen Ad26.CoV2.S vaccine.

Given that transplant patients are maintained on immunosuppressive regimens that vary slightly, immunosuppression adjustment will need to be somewhat individualized to the patient. However, general rules can be implemented.

Two weeks prior to receiving the Janssen Ad26.COV2.s vaccine, patients randomized to immunosuppression adjustment (or offered immunosuppression adjustment in Segment II) will be considered individually and adjustments will be made by a nephrologist with knowledge of the patient's clinical situation. General rules for adjustment are as follows:

1. For patients receiving mycophenolate mofetil (MMF) or azathioprine (AZA), a calcineurin inhibitor (CNI) (typically tacrolimus or cyclosporine), and Prednisone. Adjustment will involve stopping MMF or AZA and starting 10 mg Prednisone/day. **Note**: most patients will be in this group.
2. For patients not on MMF, but on CNI and Prednisone, the CNI dose will be decreased by 50%,
3. For patients on belatacept, which is typically taken with MMF and Prednisone, MMF will be stopped, and belatacept and Prednisone will be modified to 10 mg a day.
4. Other patients are adjusted on a case-by-case basis by the sponsor-investigator and the co-investigators—ex. Tac-mTOR inhibitor—Reduce Tac by 50%.

28 days after receiving the Janssen Ad26.COV2.s vaccine, study subjects in this arm will resume their prior doses of immunosuppression and will be followed as per protocol and as clinically indicated by the transplant team.

5.2.2 **Janssen Ad26.CoV2.S Vaccine Dosing**

There are no required medications pre or post vaccination with the Janssen Ad26.COV2.s vaccine. Dosage of study drug is defined as such:

- A single 05 mL dosage administered via an intramuscular injection. Typical administration time is less than a minute.

For Segment I, vaccination with the Janssen Ad26.COV2.s vaccine will occur 2 weeks post randomization in the no change in immunosuppression medication group (see Schedule of Events 2B). For those who will have an adjustment to their immunosuppression medication (see Schedule of Events 2C) vaccination with the Janssen Ad26.COV2.s vaccine will be 2 weeks after medication adjustment.

In Segment II, vaccination with the Janssen Ad26.COV2.s vaccine will occur three weeks after the result from the anti-SARS-CoV-2 spike protein test results which will be obtained on Day 28 of Segment I. On Day 42 the subject will begin immunosuppressive adjustment and the 2nd vaccination will be on Day 56.

There is no treatment for the Initial Responder group.

5.3 Method for Assigning Subjects to Treatment Groups

Subjects will be placed in each group by their anti-SARS-CoV-2 spike protein antibody results obtained between screening and baseline:

Segment I

- Anti-SARS-CoV-2 spike protein antibody level >250 U/ml—no vaccination with the Janssen Ad26.CoV2.S vaccine, 2 year observation only
- Anti-SARS-CoV-2 spike protein antibody level >0, but <250 U/ml—vaccination with the Janssen Ad26.CoV2.S vaccine. If antibody levels remain <250 U/ml subjects will move to Segment II.
- Anti-SARS-CoV-2 spike protein antibody levels 0 U/ml—randomized to vaccination with the Janssen Ad26.CoV2.S vaccine with 1) no change in immunosuppression or 2) immunosuppression adjustment. For subjects that did not have a change in immunosuppression, if antibody levels remain <250 U/ml subjects will move to Segment II.

Segment II

- Study subjects from Segment I who received Janssen Ad26.CoV2.S without immunosuppression adjustment and their anti-SARS-CoV-2 spike protein antibody levels remain <250 U/ml, will be offered a second dose of the Janssen Ad26.CoV2.S vaccine with immunosuppression adjustment this time.

5.4 Preparation and Administration of Study Drug

The Janssen Ad26.CoV2.S vaccine is supplied in a carton of 10 single-dose vials out of which one dose of 0.5 mL will be withdrawn from administration.

Refer to the IPPI for additional guidance on study vaccine administration.

Please refer to IPPI/IFU included in the Quality Agreement containing clear instructions on shipping, preparation and storage.

- Confirm that the Janssen Ad26.CoV2.S vaccine is a colorless to slightly yellow, clear to very opalescent sterile suspension that does not contain a preservative.
- Visually inspect the Janssen Ad26.CoV2.S vaccine vials for particulate matter and discoloration prior to administration. If either of these conditions exist, the vaccine will not be administered.
- Before withdrawing each dose of vaccine, carefully mix the contents of the single-dose vial by swirling gently in an upright position for 10 seconds. Do not shake.
- Each dose is 0.5 mL. Each vial contains 1 dose. Do not pool excess vaccine from multiple vials.

The Janssen Ad26.CoV2.S vaccine will be administered by a vaccine administrator in the clinical setting. For the purposes of this protocol, a vaccine administrator will be defined as a qualified nurse, medical doctor, or otherwise qualified healthcare professional. The following administration guidelines will be followed:

- The administrator will visually inspect each dose in the dosing syringe prior to administration to:
    - Verify the final dosing volume of 0.5 mL
    - Determine if the vaccine is discolored or contains particulate matter. In this situation the vaccine would not be administered.

2. Janssen Ad26.CoV2.S vaccine will be injected intramuscularly into the deltoid muscle, preferably of the non-dominant arm. If an injection cannot be given in the deltoids due to a medical or other contraindication (for example, tattooed upper arms rendering it difficult to assess site reactogenicity), use alternative locations such as the hip, thigh or buttocks (to be avoided in overweight participants). In all circumstances, IM injections in other locations than the upper arm are not considered protocol deviations.

Currently there is no information on the co-administration of the Janssen COVID-19 vaccine with other vaccines.

5.5 Subject Compliance Monitoring

Study vaccines will be administered intramuscularly by a study vaccine administrator. The date and time of each study vaccine administration and the location used will be recorded in the eCRF. Subjects will not be allowed to administer the vaccine to themselves or others. Study subjects found

to be significantly non-compliant with study procedures will not be offered to receive the Janssen Ad26.COV2.s vaccine.

5.6 Prior and Concomitant Therapy

Information about the subject's past Pfizer-BioNTech (BNT162b2 vaccine) or Moderna (mRNA-1273) vaccine history will be recorded at Screening.

All pre-study therapies (excluding vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, and exercise regimens) administered up to 30 days before the 1st vaccination with the Janssen Ad26.CoV2.S vaccine must be recorded at baseline.

For all participants, concomitant therapies associated with an SAE, or suspected AESI meeting the criteria outlined in Section 8.2, will be collected and recorded in the eCRF from the moment of 1st vaccination with the Janssen Ad26.CoV2.S vaccine through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of 1st vaccination until 6 months after the last vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF during the entire study.

For all participants, concomitant therapies associated with COVID-19 will be captured in the electronic eCRF for the duration of the study.

Concomitant therapies associated with AEs will be collected and recorded in the eCRF from the time of 1st vaccination through 28 days after the last vaccination. If the signs and symptoms are not resolved by 28 days post-vaccination, the concomitant therapies associated with these AEs will be collected by the participants and recorded in the eCRF until they are resolved, or the participant exits the study.

Antipyretics are recommended post-vaccination for symptom relief as needed. Prophylactic antipyretic use is not encouraged; however, in some instances, it could be considered for participants with special circumstances and/or comorbidities.

Participants may not have received an investigational drug within 30 days (including investigational drugs for prophylaxis of COVID-19) or used an invasive investigational medical device within 30 days or received investigational Ig or investigational monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the 1st dose of the Janssen Ad26.CoV2.S vaccine. During the study, the use of investigational vaccines, drugs or devices is not allowed. Treatment with investigational COVID-19 drugs after diagnosis of a COVID-19 case is allowed during the follow-up period and needs to be recorded in the COVID-19 episode description.

Licensed live attenuated vaccines should be given at least 28 days before or at least 28 days after a study vaccination. Other licensed (not live) vaccines (e.g., influenza, tetanus, hepatitis A, hepatitis B, rabies) should be given more than 14 days before (or more than 14 days after, as per Exclusion

Criteria) administration of any dose of the Janssen Ad26.CoV2.S vaccine in order to avoid potential confusion of adverse reactions and potential immune interference If a vaccine is indicated in a postexposure setting (e.g., rabies or tetanus), it must take priority over the Janssen Ad26.CoV2.S vaccine. Receipt of any COVID-19 vaccine (outside the study) at any timepoint during the study must be recorded. The name and date(s) of administration of the COVID-19 vaccine should be recorded in the eCRF.

Subjects should not receive any pre-exposure prophylactic medications for COVID-19 until after completion of the Day 28 Visit for subjects in Segment I or the Day 84 Visit for subjects in Segment II. If pre-exposure prophylactic medication for COVID-19 is administered prior to these visits the investigator should contact the sponsor-investigator to discuss if the subject should be discontinued from the study.

The sponsor-investigator must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. The participant should remain in the study but receive no further study vaccination.

5.7 Packaging

The Janssen Ad26.CoV2.S vaccines will be packaged and labeled according to good manufacturing practices and local regulations. The Janssen Ad26.CoV2.S vaccines will not be packed in individual participant kits, 1 kit will contain 10 vials. Each vial is a single dose vial and will be used to dose only one participant.

5.8 Masking/Blinding of Study

Not applicable to this study.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

As per standard pharmacy procedures at Mayo Clinic.

5.9.2 Storage

All Janssen Ad26.CoV2.S vaccine must be stored in a secured location with no access for unauthorized personnel and at controlled temperatures as indicated on the clinical labels. If Janssen Ad26.CoV2.S vaccine is exposed to temperatures outside the specified temperature range, affected Janssen Ad26.CoV2.S vaccine must be quarantined and not used until further investigation.

Refer to IPPI/IFU for additional guidance on Janssen Ad26.CoV2.S vaccine preparation, handling, and storage.

Vials will be kept in the Mayo Clinic research pharmacy to prevent unintended or unauthorized use.

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed and dated by the study team.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

The procedures and treatments required at each visit are outlined in the tables below, and in the following text. Any visit not described as being performed in person will be completed via telephone, telemedicine, or the Mayo Clinic portal patient communication system. Kits will be provided to the subjects so that blood samples can be shipped to the Mayo Clinic Laboratory in Rochester, MN for clinical laboratory test analysis and Mechanistic Studies for non-face to face visits. For the convenience of the participant, visits can be completed in person if they are visiting the Mayo Clinic Transplant Center during a study day window for their clinical care.

6.1 Segment I

6.1.1 Day - 21 (-30 /+7 Days)

Potential subjects will be identified by review of their medical record. If a participant is identified by review of the report, they will be contacted via the Mayo Clinic portal, the online patient communication system, phone or e-mail (if the potential subject has already contacted the study team in this manner). Study details, procedures, risks, and benefits will be described to patients interested in participation. Subjects will be consented for study participation either via telephone or at Mayo Clinic, depending on patient preference. The participant's medical history, demographics, concomitant medications and therapies, immunosuppression medications and clinical outcomes (current health and graft status) will be collected. Subjects will complete the COVID-19 Surveillance and Evaluation questionnaire (Section 14.6). Relevant medical procedures which are performed as part of the participants clinical care up to 60 days prior to signing of consent, such as clinical laboratory results may be used for determining study eligibility.

Blood for anti-SARS-CoV-2 spike protein antibody and anti-SARS-CoV-2 nucleocapsid total antibody testing will be drawn locally and sent overnight to Mayo Clinic-Rochester Laboratory for

testing. Not all screening procedures need to occur in one day. After consent is obtained, screening procedures can be completed on any day up to the baseline visit.

Patients who meet criteria will be contacted and scheduled to receive the Janssen Ad26.CoV2.S vaccine. They will be required to travel to one of the 3 Mayo Clinic transplant centers to receive the vaccine. There will be 3 groups:

1. Low-responders (n=100)
2. Non-responders (n=300)—Randomized after obtaining evidence that anti-SARS-CoV-2 spike protein antibody levels = 0 U/mL. Patients are stratified by the number of mRNA vaccines they received (2 or more).
    a. Dosing with the Janssen Ad26.COV2.s vaccine without immunosuppression adjustment
    b. Dosing with the Janssen Ad26.COV2.s vaccine with immunosuppression adjustment.

Subjects randomized to receive immunosuppression adjustment will follow one of the regimens outlined in Section 5.2.1. If randomized to the immunosuppression group, they will be contacted via phone by a physician with instruction on the participant's new immunosuppression regimen.

Adjustments will occur 2 weeks prior to receiving the Janssen Ad26.COV2.s vaccine. In this arm, 50 patients who had T and B cell studies performed at baseline will have a second set of studies prior to receiving the Janssen Ad26.CoV2.S vaccine to determine the effect of immunosuppressive adjustment on these immune cells.

Screening study procedures can be completed at any time after consent up until the day of receiving the Janssen Ad26.CoV2.S.

6.1.2 Day -14 (+/-3 Days) Non-Responder Group Immunosuppression Change ONLY

Study team will contact the subject and document their immunosuppression medication and instruct the participant to begin their new immunosuppression medication regimen. Patient and graft status information will be recorded as well as the COVID-19 surveillance information collected.

For a subset of patients randomized to receive immunosuppression adjustment: prior to the adjustment the study team will send a kit for a local blood collection for Total Immunoglobulin levels and T-/B-cell immunophenotyping. These specimens will be shipped back to Mayo Rochester via overnight courier for testing.

6.1.3 Baseline Visit (-4/+1 Day)

Subjects will return to Mayo Clinic for an in-person visit. Prior to receiving the Janssen Ad26.COV2.s vaccine, the following study procedures will be performed:

- Serum pregnancy test for females of childbearing potential.
- Platelet count

- Mechanistic Studies
- Tacrolimus, Cyclosporine and MMF serum drug levels in subjects who are receiving these drugs or who were receiving these drugs at the time of enrollment.
- Anti-SARS-CoV-2 spike protein antibody and anti-SARS-CoV-2 nucleocapsid total antibody test
- The participant will have a nephrology consult and a complete physical exam (including review of concomitant medications and immunosuppression). The nephrologist will confirm with the IS reduction group that they have complied with their new medication regimen.
- Vital Signs (heart rate, blood pressure, temperature, pulse oximetry, height and weight).
- Asked if they are experiencing any COVID-19 symptoms or have been recently tested.

Eligible subjects will be vaccinated after these procedures have been completed. The following study procedures can be completed at any time during the visit:

- Study team will record concomitant medications and therapies.
- Study team will document immunosuppression medication
- Patient Status and Graft Status
- Risk Factor Assessment (see Section 14.5)
- Safety Follow Up Questionnaires (questions related to potential GBS, TTS, myocarditis and pericarditis symptoms)
- Kidney Transplant Follow-Up Questionnaire

To differentiate symptoms potentially related to the Janssen Ad26.COV2.S vaccine, the participant will be asked about any symptoms they may currently be experiencing prior to vaccination as well as after to differentiate potential vaccine related adverse events. Then they will receive the Janssen Ad26.COV2.S vaccine during a clinical appointment. All vaccination will be monitored post vaccine for 30 minutes for potential reactions to the vaccination.

6.1.4 **Days 0-7 Post-Vaccination**

During each study vaccination visit the study team will provide the subject with a diary that they will use to document unsolicited and solicited adverse reactions. This would include local symptoms (e.g. injection site pain, erythema, and swelling) and systemic symptoms (e.g. fatigue, headache, myalgia, nausea, and fever). In addition, each subject will be provided a thermometer and instructions for how to use in order to monitor fever post-vaccination.

On Day 3 post-vaccination the study team will perform a reminder phone call to each study participant to ensure subjects are compliant with safety event reporting on the diary (aka Diary compliance phone call on the Schedule of Events). The study team will also review and complete the safety follow up questionnaires with the subject.

On Day 7 post-vaccination the study team will perform a structured phone call with each study participant to review the information recorded by the subject in the diary (aka Safety follow-up phone call on the Schedule of Events). The study team will review and complete the safety follow up questionnaires with the subject. A study investigator will be notified if the subject reports symptoms that require further medical review, which could result in an Unscheduled Visit being conducted.

Patient will be provided a dairy to record symptoms from post-vaccination through day 7. If any solicited signs and symptoms reported in the diary are not resolved by the Day 7 contact, the subject will continue to record their daily symptoms in the diary until the Day 28 Visit or until they are resolved, whichever comes first.

Events will be followed until resolution or until clinically stable.

6.1.5 **Days 14 (+/- 7 Day) and 28 (+/- 7 Days)**

Anti-SARS-CoV-2 spike protein antibody and anti-SARS-CoV2 nucleocapsid total antibody levels will be obtained during these study event periods. Study team will record any changes to concomitant and immunosuppressant medications or therapies, as well as changes to health status to determine any potential adverse events. Blood will be collected for a platelet count and for mechanistic studies (Day 28 only). After Day 28, subjects randomized to a change in their immunosuppression medication will revert back to their original regimen. COVID-19 symptoms will be assessed to determine if the subject has experienced any COVID-19 symptoms or recently been tested. Patient and graft status information will also be collected. The study team will review and complete the safety follow up questionnaires with the subject.

If necessary, a symptom directed physical exam can be performed.

Segment II (described in Section 6.2) will begin on Day 28 for individuals whose immunosuppression regimen was not changed and continue to have low to no response levels for their COVID-19 spike protein test.

6.1.6 **Day 90 (+/-15 Days) and 180 (+/- 30 Days)**

This will be the last visit where the subject is directly contacted in Segment I, unless contact is made by the participant or the study team has follow-up queries. All updates to medications and therapies from last visit will be recorded. Patient and Graft Status of the patient as well as the COVID Surveillance and Evaluation will be recorded. Anti-SARS-CoV-2 spike protein antibody and anti-SARS-CoV-2 nucleocapsid total antibody will also be obtained during this visit. If necessary, a symptom directed physical exam can be performed.

6.1.7 **Year 1 and 2 (+/- 60 Days)**

Information for these visits will be obtained by review of the participant's medical record. This includes the participant's current medical status and any changes noted from last visit. Subjects will also have their immunosuppression medications recorded. Any SAEs, or AESIs will be documented and reported as necessary. The Patient and Graft Status CRFs will be completed. An anti-SARS-CoV-2 spike protein antibody and anti-SARS-CoV-2 nucleocapsid total antibody test will be performed at the Year 1 visit. These tests will only be performed at this time point if the antibody levels obtained at Day 180 are detectable. The Kidney Transplant Follow-Up, Safety Follow Up, and Risk Factor Assessment questionnaires will also be completed at the Year 1 follow up visit.

6.1.8 **Mechanistic Studies**

Specimen collections for mechanistic studies is detailed in section 3.1.4 Exploratory Mechanistic Immunologic Studies. This includes a table indicating the schedule of collections and testing to be performed. Samples will be collected as close to the timepoint as possible, but some variation is expected and will not be considered a deviation.

6.2 Segment II

This segment will be evaluating the dosing of the Janssen Ad26.COV2.S vaccine with immunosuppression adjustment of patients in Segment I who were maintained on their current immunosuppression and had a lack of response at Day 28. Lack of response for this study is defined as anti-SARS-CoV-2 spike protein levels <250 U/mL.

Study procedures for Segment II will proceed in the same manner and schedule as in Segment I with the absence of screening procedures and mechanistic studies excluding the anti-SARS-CoV-2 Nucleocapsid Total Antibody test. Samples collected for the anti-SARS-CoV-2 Nucleocapsid Total Antibody test will continue to be obtained and will align with the collection and timepoints noted for the anti-SARS-CoV-2 spike protein antibody test. As all subjects will experience a reduction in IS, the Nephrologist will confirm medication compliance with the adjusted IS regimen during the Nephrology consult prior to receiving the Janssen Ad26.CoV2.S on Day 56. See Schedule of Events 3: Segment II in Section 6.6 for more details on study procedures.

6.3 Initial Responders

Subjects who are randomized to this group will have had an anti-SARS-CoV-2 spike test result at screening ≥250 U/mL. As they are not categorized as having a low to non-response to their initial vaccine series, they will not be offered to receive the Janssen Ad26.CoV2.S vaccine. They will have follow up information collected to be used as a comparison to Segments I and II at Year 1 and Year 2. Blood samples will be collected for the Mechanistic Immunologic studies on Day 0, but otherwise all information collected will be by either patient contact or review of the medical record. This includes the subject's demographics, medical history, prior and concomitant medications and therapies, immunosuppression medications, COVID-19 surveillance and evaluation, patient and graft status. See Schedule of Events 1 under Section 6.6 for more details.

6.4 Unscheduled Visit

This visit will occur in Segments 1 and 2 if there are any medical event which would require follow up with a physician. This would be a clinical visit and contain a nephrology consult (if needed), a symptom directed physical exam, vital signs, and collection of the patient and graft status. This may include additional care if the sponsor-investigator believes it to be necessary for the health of the participant (COVID-19 surveillance, review of medications, etc.).

6.5 Assessment for COVID-19 Infections

Due to the high vulnerability of this patient population, they will be monitored for possible COVID-19 infection throughout their participation in the study.

6.5.1 Pre-specified Criteria for Suspected COVID-19

The criteria for suspected COVID-19 are pre-specified as follows:

- **A positive RT-PCR result for SARS-CoV-2, through a private or public laboratory independent of the study, whether symptomatic or asymptomatic**

  OR

- **New onset or worsening of any 1 of the symptoms listed below, which lasts for at least 24 hours, not otherwise explained:**
  - Headache
  - Malaise (appetite loss, generally unwell, fatigue, physical weakness)
  - Myalgia (muscle pain)
  - Chest congestion
  - Cough
  - Runny nose
  - Shortness of breath or difficulty breathing (resting or on exertion)
  - Sore throat
  - Wheezing
  - Eye irritation or discharge
  - Chills
  - Fever (≥ 38.0°C or ≥ 100.4°F)
  - Pulse oximetry value ≤95% which is a decrease from baseline.
  - Heart rate ≥90 beats/minute at rest, which is an increase from baseline
  - Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)
  - Neurologic symptoms (numbness, difficulty forming or understanding speech)
  - Red or bruised looking toes
  - Skin rash
  - Taste loss or new/changing sense of smell
  - Symptoms of blood clots: pain/cramping, swelling or redness in your legs/calves
  - Confusion
  - Bluish lips or face
  - Clinical suspicion/judgement by sponsor-investigator of symptoms suggestive for COVID-19

As several of the pre-specified criteria for suspected COVID-19 overlap with vaccine-related reactogenicity, investigators' clinical judgement is required to exclude vaccine-related events when assessing suspected COVID-19.

6.5.2 Procedures in the Event of (Suspected) COVID-19

Procedures to be performed in the event a participant experiences signs or symptoms suggesting possible COVID-19 or a participant became aware of a positive RT-PCR test result for SARS-CoV-2 outside the study context, whether symptomatic or asymptomatic, are detailed in the Schedules of Events and captured in the eCRFs as an Unscheduled visit.

6.6 Schedules of Events

Schedule of Events 1: Initial Responders, No Vaccination with Janssen Ad26.COV2.S Vaccine (COVID Spike Protein results ≥250 U/mL)

Study Event	**Day -21**	**Day 0 [a]**	**1 Year**	**2 Years**
Visit Description	Screening/ Consent			
Visit Window	-30/+7 Days		+/- 60 Days	+/- 60 Days
Informed Consent	X			
Demographics, Medical History	X			
Immunosuppressive Medication Data	X		X	X
Concomitant Medications and Therapies	X			
Anti-SARS-CoV-2 spike protein antibody test [b]	X[b]			
Anti-SARS-CoV-2 Nucleocapsid Total Antibody Test	X[b]			
COVID-19 Surveillance and Evaluation	X		X	X
Patient and Graft Status	X		X	X
Mechanistic Immunologic Studies[c]		X		

a For this cohort, Day 0 is generally defined as the point at which they are deemed to have anti-spike protein antibody levels ≥250 U/ml and thus not part of Segment I. Given that the windows of the 1 and 2 year assessments are wide, the follow up in this group will not differ from the follow-up in the other cohorts.
b Anti-SARS-CoV-2 spike protein antibody and Anti-SARS-CoV-2 Nucleocapsid Antibody tests will occur after consent has been obtained. The results of the anti-SARS-CoV-2 spike protein antibody levels will determine in which group the subject will participate**.**
c Defined in Section 3.1.4

Schedule of Events 2A: Segment I, Low Responders
(No Change in Immunosuppression Medication)

Study Event	**Day -21**	**Baseline Day 0**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**1 Year**	**2 Years**	**Unscheduled Visit[a]**
Visit Description	Screening	Janssen Ad26.COV2.s vaccine			Follow Up						Safety
Visit Window	-30 / +7 Days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A
Informed Consent	X										
Demographics, Medical History	X	X									
Concomitant Medications and Therapies	X	X			X	X					X
Immunosuppression Medications	X	X							X	X	X
Nephrology Consult		X									X (as needed)
Complete Physical Exam		X									
CBC with Diff (Platelet Count)[b]		X				X					
Tacrolimus, cyclosporine and/or MMF Drug Levels[o]		X									
Vital Signs[c]		X									X
HcG Pregnancy Test[d]		X									
Janssen Ad26.CoV2.S Dosing		X									
Risk Factor Assessment and Kidney Transplant Follow Up Questionnaire		X							X		
Anti-SARS-CoV-2 spike protein antibody test	X[e]	X[f]			X	X	X	X	X[r]		
Anti-SARS-CoV-2 Nucleocapsid Total Antibody	X[e]	X[f]			X	X	X	X	X[r]		
Mechanistic Immunologic Studies[g]		X				X			X[h]		
Safety assessment DURING vaccination											
Pre and Post Vaccination Symptoms (questionnaire)		X									
Post Vaccine Observation[i]		X									
Safety assessment AFTER vaccination											

Study Event	**Day -21**	**Baseline Day 0**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**1 Year**	**2 Years**	**Unscheduled Visit[a]**
Visit Description	Screening	Janssen Ad26.COV2.s vaccine			Follow Up						Safety
Visit Window	-30 / +7 Days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A
Subject Symptom Report[p]		Continuous									
Diary Compliance phone call			X								
Safety Follow-Up phone call[q]				X							
Symptom Directed Exam as needed					X	X	X	X			
Safety Follow Up Questionnaires[j]		X[l]	X	X	X	X			X		X
COVID-19 Surveillance and Evaluation[k]	X	X			X	X	X	X	X		X
Patient and Graft Status	X	X			X	X	X	X	X		X
MAAE Monitoring[m]		*Continuous*									
(S)AE Monitoring[n]		*Continuous*									

Study Event	Day -21	Baseline Day 0	Day 3	Day 7	Day 14	Day 28	Day 90	Day 180	1 Year	2 Years	Unscheduled Visit[a]
Visit Description	Screening	Janssen Ad26.COV2.s vaccine			Follow Up						Safety
Visit Window	-30 / +7 Days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A

a For evaluation of any potential adverse events
b Must have >75,000/μL to receive the Janssen Ad26.CoV2.S vaccine.
c Temperature, Height, Weight, Pulse oximetry, Blood Pressure, and Heart Rate
d only for females of childbearing potential
e Anti-SARS-CoV-2 spike protein antibody and anti-Nucleocapsid Antibody tests will occur after consent has been obtained. The results of the anti-SARS-CoV-2 spike protein antibody levels will determine which group the subject will participate in.
f Defined in Section 3.1.4
g will occur once at either time point for subjects who remain in Segment I. Subjects that end up in Segment II will have their last specimen collected on day 28.
h Subjects will be monitored for 30 minutes after vaccination to monitor for severe reactions
i Questions regarding thrombotic events, thrombocytopenia or Guillain-Barré syndrome (Section 14.1 and 14.2). Questions regarding myocarditis and pericarditis.
j As Described in Section 6.5
k To occur prior to vaccination on Day 0
l MAAEs are to be reported for all participants from the moment of receiving the 1st vaccination until 6 months after the last vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.
m All (S)AEs related to study procedures or non-investigational Janssen products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure. AEs leading to study discontinuation or discontinuation of study vaccination (regardless of the causal relationship) are to be reported from the moment of the 1st vaccination until completion of the participant's last study-related procedure. Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study related procedures. Special reporting situations, whether serious or non-serious, are to be recorded for each vaccination from the time of vaccination until 28 days post-vaccination. All other unsolicited AEs will be reported for each vaccination for the time of vaccination until 28 days post-vaccination.
n Tacrolimus, Cyclosporine and MMF serum drug levels in subjects who are receiving these drugs or who were receiving these drugs at the time of enrollment.
o Patient will be provided a dairy to record symptoms from post-vaccination through day 7. If any solicited signs and symptoms reported in the diary are not resolved by the Day 7 contact, the subject will continue to record their daily symptoms in the diary until the Day 28 Visit or until they are resolved, whichever comes first. A thermometer will be provided for daily temperature check.
p A study investigator will be notified if the subject reports symptoms that require further medical review and follow-up as necessary. An Unscheduled Visit conducted by a study investigator will be conducted if needed
q Obtain anti-SARS-CoV-2 spike protein antibody and anti-SARS-CoV-2 Nucleocapsid antibody levels if previous levels at Day 180 post vaccination were detectable.

Schedule of Events 2B: Segment I, Non-responders (No Change in Immunosuppression Medication)

Study Event	**Day -21**	**Day 0**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**1 Year**	**2 Years**	**Unscheduled Visit[a]**
Visit Description	Screening	Janssen Ad26.COV2.s vaccine		Follow Up							Safety
Visit Window	-30 / +7 Days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A
Informed Consent	X										
Demographics, Medical History	X	X									
Prior and Concomitant Medications and Therapies	X	X			X	X					X
Immunosuppression Medications	X	X				X	X	X	X	X	X
Nephrology Consult		X									X (as needed)
Complete Physical Exam		X									
CBC with Diff (Platelet Count)[b]		X				X					
Tacrolimus, cyclosporine and/or MMF Drug Levels[n]		X									
Vital Signs[c]		X									X
Serum Pregnancy Test[d]		X									
Janssen Ad26.CoV2.S Dosing		X									
Risk Factor Assessment and Kidney Transplant Follow Up Questionnaire		X							X		
Randomization	X[e]										
Anti-SARS-CoV-2 spike protein antibody test	X[e]	X			X	X	X	X	X[q]		
Anti-SARS-CoV-2 Nucleocapsid Total Antibody Test	X[e]	X			X	X	X	X	X[q]		
Mechanistic Immunologic Studies[f]		X				X			X[g]		
<u>Safety assessment DURING vaccination</u>											
Pre and Post Vaccination Symptoms (questionnaire)		X									
Post Vaccine Observation[h]		X									

Study Event	**Day -21**	**Day 0**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**1 Year**	**2 Years**	**Unscheduled Visit[a]**
Visit Description	Screening	Janssen Ad26.COV2.s vaccine		Follow Up							Safety
Visit Window	-30 / +7 Days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A
Safety assessment AFTER vaccination											
Subject Symptom Report[o]		Continuous									
Diary compliance phone call			X								
Safety follow-up phone call[p]				X							
Symptom Directed Exam as needed					X	X	X	X			X
Safety Follow Up Questionnaires[i]		X	X	X	X	X			X	X	X
COVID-19 Surveillance & Evaluation[j]	X	X[k]			X	X	X	X	X	X	X
Patient and Graft Status	X	X			X	X	X	X	X	X	X
MAAE Monitoring[l]		*Continuous*									
(S)AE Monitoring[m]		*Continuous*									

a For evaluation of any potential adverse events
b Must have >75,000/µL to receive the Janssen Ad26.CoV2.S vaccine.
c Temperature, Height, Weight, Pulse oximetry, Blood Pressure, and Heart Rate
d only for females of childbearing potential
e Anti-SARS-CoV-2 spike protein antibody and anti-Nucleocapsid Antibody tests will occur after consent has been obtained. The results of the anti-SARS-CoV-2 spike protein antibody levels will determine which group the subject will participate in.
f Defined in Section 3.1.4
g will occur once at either time point for subjects who remain in Segment I. Subjects that end up in Segment II will have their last specimen collected on day 28.
h Subjects will be monitored for 30 minutes after vaccination to monitor for severe reactions
i Questions regarding thrombotic events, thrombocytopenia or Guillain-Barré syndrome (Section 14.1 and 14.2). Questions regarding myocarditis and pericarditis (Section 14.7).
j As Described in Section 6.5
k To occur prior to vaccination on Day 0
l MAAEs are to be reported for all participants from the moment of receiving the 1st vaccination until 6 months after the last vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.
m All (S)AEs related to study procedures or non-investigational Janssen products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure. AEs leading to study discontinuation or discontinuation of study vaccination (regardless of the causal relationship) are to be reported from the moment of the 1st vaccination until completion of the participant's last study-related procedure. Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study related procedures. Special reporting situations, whether serious or non-serious, are to be recorded for each vaccination from the time of vaccination until 28 days post-vaccination. All other unsolicited AEs will be reported for each vaccination for the time of vaccination until 28 days post-vaccination.
n Tacrolimus, Cyclosporine and MMF serum drug levels in subjects who are receiving these drugs or who were receiving these drugs at the time of enrollment.
o Patient will be provided a dairy to record symptoms from post-vaccination through day 7. If any solicited signs and symptoms reported

Study Event	**Day -21**	**Day 0**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**1 Year**	**2 Years**	**Unscheduled Visit[a]**
Visit Description	Screening	Janssen Ad26.COV2.s vaccine		Follow Up							Safety
Visit Window	-30 / +7 Days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A

in the diary are not resolved by the Day 7 contact, the subject will continue to record their daily symptoms in the diary until the Day 28 visit or until they are resolved, whichever comes first. A thermometer will be provided for daily **temperature check.**

p A study investigator will be notified if the subject reports symptoms that require further medical review and follow-up as necessary. An Unscheduled Visit conducted by a study investigator will be conducted if needed

q Obtain anti-SARS-CoV-2 spike protein antibody and anti-SARS-CoV-2 Nucleocapsid antibody levels if previous levels at Day 180 post vaccination were detectable.

Schedule of Events 2C: Segment I, Non-Responders, Change in Immunosuppression Medication

Study Event	**Day -21**	**Day -14**	**Day 0**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**1 Year**	**2 Years**	**Unscheduled Visit[a]**
Visit Description	Screening visit		Janssen Ad26.COV2.s vaccine	Follow up								Safety
Visit Window	-30 / +7 Days	+/- 3 days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A
Informed Consent	X											
Demographics, Medical History	X		X									
Prior & Concomitant Medications and Therapies	X		X			X	X					X
Immunosuppression Medications	X	X	X			X	X	X	X	X	X	X
Nephrology Consult			X									
Complete Physical Exam			X									
CBC with Diff (Platelet Count)[b]			X				X					
Tacrolimus, cyclosporine and/or MMF Drug Levels[o]			X									
Vital Signs[c]			X									X
Serum Pregnancy Test[d]			X									
Janssen Ad26.CoV2.S Dosing			X									
Risk Factor Assessment & Kidney Transplant Follow Up Questionnaire			X							X		
Randomization	X[e]											
Immunosuppression Adjustment		X					X[f]					
Anti-SARS-CoV-2 spike protein antibody test	X[e]		X			X	X	X	X	X[r]		
Anti-SARS-CoV-2 Nucleocapsid Total Antibody Test	X[e]		X			X	X	X	X	X[r]		
Mechanistic Immunologic Studies[g]		X	X				X			X[h]		
<u>Safety assessment DURING vaccination</u>												
Pre and Post Vaccination Symptoms (questionnaire)			X									
Post Vaccine Observation[i]			X									

Study Event	**Day -21**	**Day -14**	**Day 0**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**1 Year**	**2 Years**	**Unscheduled Visit[a]**
Visit Description	Screening visit		Janssen Ad26.COV2.s vaccine	Follow up								Safety
Visit Window	-30 / +7 Days	+/- 3 days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A
Safety assessment AFTER vaccination												
Subject Symptom Report[p]			Continuous									
Diary compliance phone call				X								
Safety follow-up phone call[q]					X							
Symptom Directed Exam as needed						X	X	X	X			X
Safety Follow Up Questionnaires[j]			X	X	X	X	X			X	X	X
COVID-19 Surveillance and Evaluation[k]	X	X[l]	X			X	X	X	X	X	X	X
Patient and Graft Status	X	X	X			X	X	X	X	X	X	X
MAAE Monitoring[m]			*Continuous*									
(S)AE Monitoring[n]			*Continuous*									

a For evaluation of any potential adverse events
b Must have >75,000/µL to receive the Janssen Ad26.CoV2.S vaccine.
c Temperature, Height, Weight, Pulse oximetry, Blood Pressure, and Heart Rate
d For females of childbearing potential
e Anti-SARS-CoV-2 spike protein antibody test and anti-Nucleocapsid Antibody test will occur after consent has been obtained. The results Anti-SARS-CoV-2 spike protein antibody levels will determine into which group the subject will be placed. If randomized to receive vaccination with immunosuppression reduction, this will occur 14 days prior to vaccination (Day 0).
f Return to previous immunosuppression medication regimen
g Defined in Section 3.1.4
h Will occur once at either time point
i Subjects will be monitored for 30 minutes after vaccination to monitor for severe reactions
j Questions regarding thrombotic events, thrombocytopenia or Guillain-Barré syndrome (Section 14.1 and 14.2). Questions regarding myocarditis and pericarditis (Section 14.7).
k As Described in Section 6.5
l To occur prior to vaccination on Day 0
m MAAEs are to be reported for all participants from the moment of receiving the 1st vaccination until 6 months after the last vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.
n All (S)AEs related to study procedures or non-investigational Janssen products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure. AEs leading to study discontinuation or discontinuation of study vaccination (regardless of the causal relationship) are to be reported from the moment of the 1st vaccination until completion of the participant's last study-related procedure. Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study related procedures. Special reporting situations, whether serious or non-serious, are to be recorded for each vaccination from the time of vaccination until 28 days post-vaccination. All other unsolicited AEs will be reported for each vaccination for the time of vaccination until 28 days post-vaccination.

Study Event	**Day -21**	**Day -14**	**Day 0**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**	**Day 180**	**1 Year**	**2 Years**	**Unscheduled Visit[a]**
Visit Description	Screening visit		Janssen Ad26.COV2.s vaccine	Follow up								Safety
Visit Window	-30 / +7 Days	+/- 3 days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A

o Tacrolimus, Cyclosporine and MMF serum drug levels in subjects who are receiving these drugs or who were receiving these drugs at the time of enrollment.
p Patient will be provided a dairy to record symptoms from post-vaccination through day 7. If any solicited signs and symptoms reported in the diary are not resolved by the Day 7 contact, the subject will continue to record their daily symptoms in the diary until the Day 28 Visit or until they are resolved, whichever comes first. A thermometer will be provided for daily temperature check.
q A study investigator will be notified if the subject reports symptoms that require further medical review and follow-up as necessary. An Unscheduled Visit conducted by a study investigator will be conducted if needed
r Obtain anti-SARS-CoV-2 spike protein antibody and anti- anti-SARS-CoV-2 Nucleocapsid antibody levels if previous levels at Day 180 post vaccination were detectable.

Schedule of Events 3: Segment II[a]

Study Event	Day 28 (Segment I)	Day 42	Day 56	Day 59	Day 63	Day 70	Day 84	Day 146	Day 236	1 Year	2 Years	Unscheduled Visit[b]
Days post 2nd Janssen Ad26.COV2.s vaccine			**0**	**3**	**7**	**14**	**28**	**90**	**180**	**365**	**730**	**Safety**
Visit Window	+/- 7 Days	+/- 7 Days	-4/+1 day	+/- 1 Day	+/- 2 Day	+/- 7 Day	+/- 7 Days	+/- 15 Days	+/- 30 Days	+/- 60 Days	+/- 60 Days	N/A
Prior & Concomitant Medications & Therapies	X		X			X	X	X	X			X
Immunosuppression Medications		X	X			X	X	X	X	X	X	X
Nephrology Consult			X									
Complete Physical Exam			X									
CBC with Diff (Platelet Count)[c]			X				X					
Tacrolimus, cyclosporine and/or MMF Drug Levels[m]			X									
Vital Signs[d]			X									X
Serum Pregnancy Test[e]			X									
Janssen Ad26.CoV2.S Dosing			X									
Risk Factor Assessment and Kidney Transplant Follow Up Questionnaire			X							X		
Immunosuppression Adjustment		X					X[f]					
Anti-SARS-CoV-2 spike protein	X		X			X	X	X	X	X[p]		
Anti-SARS-CoV-2 Nucleocapsid Total Antibody Test	X		X			X	X	X	X	X[p]		
Safety assessment DURING vaccination												
Pre and Post Vaccination Symptoms (questionnaire)			X									
Post-Vaccine Observation[g]			X									
Safety assessment AFTER vaccination												
Subject Symptom Report[n]			Continuous									
Diary compliance phone call				X								
Safety follow-up phone call[o]					X							
Symptom Driven Exam (abbreviated)	X	X	X			X	X	X	X			X
Safety Follow Up Questionnaires[h]	X		X	X	X	X	X			X	X	X
COVID-19 Surveillance & Evaluation[i]	X	X	X[j]			X	X	X	X	X	X	X
Patient & Graft Status	X	X	X			X	X	X	X	X	X	X
MAAE Monitoring[k]			*Continuous*									
(S)AE Monitoring[l]	*Continuous*											

a For subjects from Segment I who do not achieve antibody levels ≥ 250 U/mL after receiving the Janssen Ad26.CoV2.S vaccine and still meet inclusion criteria (including no SAEs or AESIs associated with receiving the Janssen Ad26.COV2.s vaccine)
b For evaluation of any potential adverse events
c Must have >75,000/μL to receive the Janssen Ad26.CoV2.S vaccine
d Temperature, Height, Weight, Pulse oximetry, Blood Pressure, and Heart Rate
e Only for females of childbearing potential.
f Return to previous immunosuppression medication regimen
g Subjects will be monitored for 30 minutes after vaccination to monitor for severe reactions
h These questions will be in regards to thrombotic events, thrombocytopenia or Guillain-Barré syndrome (Section 14.2). Questions regarding myocarditis and pericarditis.
i As Described in Section 6.5
j To occur prior to vaccination on Day 0
k MAAEs are to be reported for all participants from the moment of receiving the 1st vaccination until 6 months after the last vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.
l All (S)AEs related to study procedures or non-investigational Janssen products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other SAEs are to be reported from the moment of vaccination until completion of the participant's last study-related procedure. AEs leading to study discontinuation or discontinuation of study vaccination (regardless of the causal relationship) are to be reported from the moment of the 1st vaccination until completion of the participant's last study-related procedure. Suspected AESIs are to be reported from the moment of vaccination until completion of the participant's last study related procedures. Special reporting situations, whether serious or non-serious, are to be recorded for each vaccination from the time of vaccination until 28 days post-vaccination. All other unsolicited AEs will be reported for each vaccination for the time of vaccination until 28 days post-vaccination.
m Tacrolimus, Cyclosporine and MMF serum drug levels in subjects who are receiving these drugs or who were receiving these drugs at the time of enrollment.
n Patient will be provided a dairy to record symptoms from post-vaccination through day 7. If any solicited signs and symptoms reported in the diary are not resolved by the Day 7 contact, the subject will continue to record their daily symptoms in the diary until the Day 28 Visit or until they are resolved, whichever comes first. A thermometer will be provided for daily temperature check.
o A study investigator will be notified if the subject reports symptoms that require further medical review and follow-up as necessary. An Unscheduled Visit conducted by a study investigator will be conducted if needed
p Obtain anti-SARS-CoV-2 spike protein antibody and anti-SARS-CoV-2 Nucleocapsid antibody levels if previous levels at Day 180 post vaccination were detectable.

6.7 Sample Size Determination

In the study populations, the actual response rates to receiving the Janssen Ad26.CoV2.S vaccine is not known.

We base our statistical calculations on what is suggested by the existing small, non-randomized reports in the current literature. For example, Kamar et al reported that 26/59 (44%) seronegative patients after two doses became seropositive after a third dose [8]. However, it appears that 17 of the 26 still had anti-S antibody titers <200. Thus, the response rate given the endpoint that we plan for this study (≥250 U/ml) would be 9/44 (20%) for those with no antibodies prior to receiving the Janssen Ad26.COV2.s vaccine and 60% for those with low, but non-zero, levels of antibody prior to receiving the Janssen Ad26.COV2.s vaccine.

The primary endpoint for our study is a measured anti-S antibody level of ≥250 U/ml. Power calculations are based on the comparison at the end of Trial Segment I using a two-sample, two-tailed test of the difference in two proportions. This focuses on whether or not there is a statistically significant difference in the proportion of responders between those patients who had zero antibodies at the time of receiving the Janssen Ad26.COV2.s vaccine with an adjustment in immunosuppression (N = 150) and those without an adjustment in immunosuppression (N = 150). Effect sizes are based on the square-root arcsine transformation.

Trial Segment I

These power calculations pertain to the randomized arm of **Segment I involving immunosuppression adjustment**: kidney transplant recipients with anti-SARS-CoV-2 spike protein antibody levels = 0 at baseline (i.e. after receiving 2 or more doses of mRNA vaccine) who are randomized to be maintained on their current immunosuppression vs transient immunosuppression adjustment around the time of receiving the Janssen Ad26.CoV2.S vaccine (n=150/arm).

We have performed power calculations using several different assumptions regarding the expected outcomes table below. For example, if we expect that the true response rate of 20% of patients without anti-S antibodies at baseline without an adjustment to their immunosuppression will achieve the primary endpoint after receiving the Janssen Ad26.COV2.S vaccine, then a true response rate of 37% in the patients in the altered immunosuppression group will reject the null hypothesis of an equal response rate with 90% power. Thus, 120 patients will still have low levels (<250 U/ml) and 30 will have high levels (≥250 U/ml). Of the 100 with low levels prior to receiving the Janssen Ad26.COV2.s vaccine, we expect that >90 will develop high levels.

Response rate in arm with no alteration in immunosuppression	Response rate in arm with alteration in immunosuppression	Power	Significance level (alpha)
20%	60%	1.00	0.05

10%	24%	0.9	0.05
20%	37%	0.9	0.05
30%	48%	0.9	0.05
23%	40%	0.9	0.05
32%	50%	0.9	0.05
41%	60%	0.9	0.05
52%	70%	0.9	0.05
63%	80%	0.9	0.05

Because we expect a true response rate of 20% and 60% in the patients without and with immunosuppression alteration, respectively, we acknowledge that this study is over-powered for the current enrollment targets. If these were the true response rates, 30 patients would be required for each arm to achieve 90% power. Therefore, even if there is drop out and/or misestimation of the response rates within each category then this study will be sufficiently powered for this comparison.

All tests will be carried out using two-side hypothesis tests with a significance level of 0.05 unless otherwise noted.

For **our other primary objective** (any effective response to the Janssen Ad26.CoV2.S vaccine in kidney transplant patients who had no anti-SARS-CoV-2 spike protein antibodies (<250 U/ml, but >0 U/mL) after 2 or more doses of mRNA vaccine), even a small response rate (1-2%) would be statistically significant. Power calculations pertaining to this endpoint are irrelevant (a very few number of subject will suffice). We also considered an unvaccinated control group for this arm, but in the current environment of COVID infection in the US, we decided that not offering a vaccine to patients who have already failed mRNA vaccination would be unethical. For this non-responder population receiving an additional dose of the Janssen Ad26.CoV2.S vaccine, we would consider a response rate of 20% in the group maintained on their current immunosuppression to be clinically significant. Importantly, patients in Segment I who do not respond to receiving the Janssen Ad26.COV2.s vaccine when maintained on their current immunosuppression will be offered immunosuppression adjustment (Segment II) and receive a second dose of the Janssen Ad26.CoV2.S vaccine.

We expect that response rate of a heterologous additional dose with the Janssen Ad26.COV2.s vaccine of low responders (anti-SARS-CoV-2 spike protein levels at baseline >0 but <250 U/ml) will be high. We would consider a response rate of >50% to be clinically meaningful. The heterologous additional dose with the Janssen Ad26.COV2.s vaccine of low responders was included in this protocol to allow develop data regarding a treatment option for this population of patients. Again, we considered a control group without vaccination in this population, but rejected it considering the high rates of COVID infection currently in the US.

Trial Segment II

The rate of response in prior non-responder to the heterologous additional dose with the Janssen Ad26.COV2.s vaccine who are then managed with a 4th vaccine with reduced immunosuppression is unknown. If we assume the true response rate is 60%, then of the 100 subjects in this study, on average, 60 will have high levels and 40 will have undetectable to low levels.

No data regarding the durability of the anti-SARS-CoV-2 spike protein antibody response is available from the current literature. Thus, power calculations regarding this endpoint were not developed.

6.8 Statistical Methods

In general, univariate descriptive statistics will be calculated, as appropriate for all variables including baseline values for demographic, clinical, and outcome variables. These variables will be summarized across treatment groups as well as strata of baseline antibody levels (none versus low) and compared for possible confounding of the primary and secondary comparisons. For example, what are the univariate and multivariate factors related to the initial good response to mRNA vaccination—data collected at the time of enrollment in all 1200 study subjects. Of additional interest are factors related to response to receiving the Janssen Ad26.CoV2.S vaccine as well as developing COVID infection at 2 years.

The **primary comparison (randomized trial of immunosuppression adjustment)** will focus on a chi-square test of vaccination response between those patients that did not have reduced immunosuppression versus those that did have a change in immunosuppression. Only the patients with a zero (undetectable) antibody level at the time of study enrollment will be compared.

Other analyses will focus on the overall incidence rate of reaching the primary endpoint across all patients or stratified by antibody levels (zero or low) at the time of screening. These analyses will be carried out using one-sample or two-sample chi-square tests. In addition, there is interest if possible confounding variables have any impact on reaching the primary endpoint. These analyses will focus on univariate and multivariate logistic regression models of binary response based on possible confounding variables.

Studying the durability of antibody production will utilize longitudinal analyses such mixed effects models to account for multiple (correlated) observations from the same individual. Assumptions of these models will be assessed through the residual plots.

Finally, we are interested in assessing changes in infection rate and cause-specific mortality during follow-up. We will analyze time to infection or COVID-related death using standard survival analysis procedures such as Kaplan-Meier estimation and Cox regression.

Handling of Missing Data

Queries in the Medidata Rave system will be used to identify outliers as well as missing and inconsistent data entered into the system. An example would be dates that appear out of order such as a death prior to an infection.

After data has been collected and locked as an analysis dataset, missingness will be assessed for degree as well as randomness. If the amount of missing data is small, incomplete observations will be removed from analyses of interest. On the other hand, imputation using chained equations (MICE) or random forests may be applied in the case of observations that are missing at random.

Multiplicity

There will be only a single analysis of the primary outcome across two treatment groups and therefore multiplicity is not a concern. However, for comparisons of possible confounding variables across treatment groups, multiple testing may give rise to elevated type I error. For these analyses we will consider correcting the p-values via the Benjamini-Hochberg or other methods.

Statistically significant differences on overall comparisons will be explored using multiple pair-wise comparisons of each of the *(n)* groups using Bonferroni correction for multiple comparisons. Mean scores and standard deviation for each group will be calculated. Subsequent multiple comparisons via Tukey's procedure will be set at 0.01 to control Type I error rate.

A Note on the Incidence of COVID 19 at 2 Years

The major reason for the large numbers of patients is to have a reasonable chance of demonstrating a difference in COVID-related complications in responders vs low/non-responders after receiving the Janssen Ad26.COV2.s vaccine. The risk of COVID 19 infections in patients without anti-SARS-CoV-2 spike protein antibody is unknown and the risk of COVID infection going forward in the US also is unknown. Over the past year prior to vaccination programs, the COVID infection rate in our patient population has been approximately 10% per year with death rates of approximately 2% overall per year.

The comparisons here are one-sample comparisons of Kaplan-Meier estimates of the incidence of infection or mortality versus historical incidences of 10% and 2%, respectively.

COVID Infection Rates: Using an assumed 10% infection rate per year as the null hypothesis in the 400 patients that had an undetectable or low mRNA vaccine response, an infection rate of less than 7% will result in 90% power to demonstrate statistical significance by the one-sample log-rank test.

COVID-Related Mortality: For mortality, a reduction from an annual rate of death due to COVID of 2% in the non-responders to 0.7% in the responders would result in 80% power to demonstrate statistical significance by the one-sample log-rank test.

Interim Analysis

No formal interim hypothesis testing will be considered and therefore alpha-spending or control of type 1 error is not of concern for this study. Data summaries will be used throughout the study to audit data quality, to create reports for the regulatory requirements (i.e.. IRB, DMSB, etc.) and to ensure the overall study is running smoothly.

6.9 Subject Population(s) for Analysis

The subject population for the primary analysis focus on the all-completed population, i.e. the patients who had undetectable antibody levels at the time of screening and were subsequently randomized in to either maintaining immunosuppression or altering it and completed the protocol requirements for the primary endpoint (n=300 total potential patients).

Secondary analyses will be broader and focus on the all-treated population (n=400 total patients). Patients with missing data may be excluded or their data can be imputed as mentioned above. Patients who did not have complete follow-up will be censored in any survival analyses at the time of their last follow-up.

The specific study populations are:

1. All enrolled patients (up to 1200)
    a. Up to 800 with anti-SARS-CoV-2 spike protein antibody levels ≥250 U/ml who will not be administered the Janssen Ad26.COV2.S vaccine but will be followed for 2 years for outcomes including COVID-19 infection.
    b. 400 with anti-SARS-CoV-2spike protein antibody levels <250 U/ml who will be administered the Janssen Ad26.CoV2.S vaccine.
2. All randomized population:
    a. n=300 to receive the Janssen Ad26.COV2.s vaccine with 150 to receive reduced immunosuppression and 150 to maintain current immunosuppression.
3. All-treated population:
    a. n=400.
    b. 100 patients with low anti-SARS-CoV-2spike protein levels (>0 to <250).
    c. 300 patients with no anti-SARS-CoV-2 spike protein levels (0).
4. All patients receiving two doses of the Janssen Ad26.CoV2.S vaccine
    a. Up to 250 patients from the treated population who meet entry criteria for Segment II
5. Protocol compliant population:
    a. We do not anticipate a large percentage of patients will be non-compliant with the protocol. However, the protocol is sufficiently powered to account for compliance failures.
6. All-completed populations:

a. For the treated patient populations the most important study related procedures (received Janssen Ad26.CoV2.S vaccine and follow-up testing) will be completed within 28 days.
b. Patients will be monitored up to 2 years post-enrollment which overlaps with the routine clinical monitoring of transplant patients at our institutions.

7 Safety and Adverse Events

7.1 Definitions

Adverse Event

Any untoward medical event in a patient administered a pharmaceutical product which does not necessarily have to have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including abnormal finding or lack of expected pharmacological action), symptom, or disease temporarily associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures, including laboratory test abnormalities.

Medically Attended Adverse Events (MAAEs)

MAAEs are defined as AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel. Routine study and clinical care visits will not be considered medically-attended visits. Unexpected medically-attended events will be considered MAAEs (as assessed and determined by the study physicians). New onset of chronic diseases unrelated to typical medical events that occur post kidney transplant (as assessed and determined by the study physicians) will be collected as part of the MAAEs.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include:

- death
- life threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity
- substantial disruption of the ability to conduct normal life functions
- birth defect/congenital anomaly
- Any suspected transmission of any infectious agent via administration of a medicinal product

- Is considered medically significant*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not result in death, be life-threatening or require hospitalization but may be considered a serious adverse drug experience when, based on appropriate medical judgement, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the bulleted list above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse or malignancy.

Per protocol problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data will also be reported as SAE.

SAEs or events of significant interest include: thrombotic thrombocytopenia syndrome, Guillan Barre Syndrome, myocarditis, pericarditis, acute rejection, de novo DSA or graft loss associated with immunosuppression adjustment, readmission to the hospital for any reason. These events and their sequelae will be followed for the duration of the study in participants who received the Janssen Ad26.COV2.s vaccine. AEs that are deemed related to the Janssen Ad26.COV2.s vaccine will be followed for day 28 after vaccination.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or

event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**

- Related: A problem or event is "related" if it is possibly related to the research procedures.

If the Investigator/agent of the Investigator receives safety information and is aware it involves a non-study J&J product, it will be reported to Janssen, indicating it is an incidental spontaneous report discovered during the course of the study.

Special Situations

The following special situations must be reported to Janssen with or without an associated serious adverse event (SAE):

- Drug exposure during pregnancy (paternal, maternal)
- Suspected transmission of any infectious agent via administration of the Janssen Ad26.CoV2.S vaccine.

The following special situations must be reported to Janssen

- Overdose of Janssen product(s) under study
- Exposure to Janssen product(s) under study from breastfeeding
- Suspected abuse/misuse of Janssen product(s) under study
- Inadvertent or accidental exposure to Janssen product(s) under study
- Any failure of expected pharmacological action (i.e., lack of effect) of Janssen product(s) under study
- Medication error (includes potential, intercepted or actual) involving a Janssen product (with or without patient exposure to the Janssen product(s) under study, e.g., name confusion)
- Unexpected therapeutic or clinical benefit from use of Janssen product(s) under study

These safety events may not meet the definition of an adverse event; however, the Parties agree that for reporting purposes, they are deemed to be adverse events.

Life Threatening Conditions

The cause of death of a subject in the study at any time whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

Product Quality Complaints

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, dissatisfaction related to the identity, quality, durability, reliability, or performance of distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of a Janssen product. In

addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the Janssen, and are mandated by regulatory agencies worldwide. Janssen has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. The Collaborative Study Partner agrees that Lot and/or Batch #s shall be collected, when available, for all PQC reports, including reports of failure of expected pharmacological action (i.e., lack of effect) of a Janssen Medicinal Product. A sample of the suspected product shall be maintained for further investigation if requested by the Janssen.

Any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or delivery system is considered a PQC. Not all PQCs involve a patient.

Examples of PQC include but are not limited to:

- Mislabelling or misbranding
- Information concerning microbial contamination, including a suspected transmission of any infectious agent by a product
- Any significant chemical, physical, or other changes that indicate deterioration in the distributed product
- Any foreign matter reported to be in the product
- Mixed product, e.g., two drugs are mixed-up in the packaging process
- Incorrect tablet sequence (e.g., oral contraceptive tablets)
- Insecure closure with serious medical consequences, e.g., cytotoxics, child-resistant containers, potent drugs
- Suspected counterfeit or tampered product
- Adverse Device Effects including any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation, installation, operation, or any malfunction of a medical device or combination product. This also includes any event that is a result of a use error or intentional misuse and dosing device malfunctions (e.g., auto-injector button not working, needle detaching from syringe, etc.)
- Physical defect (e.g. abnormal product odor, broken or crushed tablets, etc.)

Extraordinary Correspondence
Correspondence with a regulatory authority or ethics committee regarding a safety issue that may impact the safety or benefit-risk balance of the Janssen Ad26.CoV2.S vaccine, and/or may impact patients or public health. Examples include:

- Safety issues relating to a quality defect

- Major safety issues identified with changes in the nature, severity or frequency of known serious adverse reactions which are medically significant or the detection of new risk factors for the development of a known adverse reaction or a new serious adverse reaction.

Major safety issues identified in the context of ongoing or newly completed post-marketing studies e.g. an unexpected increased rate of fatal or life-threatening adverse events.

Preexisting Condition

A preexisting condition is one that is present at the start or prior to the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At Day 0, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery

For reports of hospitalization, details must be provided about the events leading up to and during hospitalization, such as the signs, symptoms or diagnosis. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the medical condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful
- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility).

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Surgery or procedure planned before entry into a study. [Note: Hospitalizations that were planned before the signing of ICF and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

7.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, in a separate adverse event worksheet and in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

7.2.1 COVID-19 Related Adverse Events

Identify all pertinent facts related to the COVID-19 infection including, but not limited to the following:

- Presumptive vs confirmed diagnosis. If presumptive, please update your narrative if/when diagnosis is confirmed, including timelines.
- Treatment information
- Recovery information, including timelines
- Outcome information/status

The SIC questionnaire in Section 14.3 will be utilized in situations of suspected COVID-19 infection in situations where information related to the infection is not readily available in the participant's EMR.

7.2.2 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are significant AEs that are judged to be of special interest because of clinical importance, known or suspected class effects, or based on nonclinical signals. Adverse events of special interest will be carefully monitored during the study by the sponsor-investigator.

AESIs must be reported to Janssen within 1 business day of becoming aware of the event, irrespective of seriousness (i.e., serious and non-serious AEs) or causality following the procedure described above for SAEs. Suspected AESIs will be reported from the moment of vaccination until the completion of the participant's last study related procedure.

Specific requirements for the AESI are described below.

7.2.2.1 Thrombosis with Thrombocytopenia Syndrome

As described in Section 1.5.2, Risks Related to Study Janssen Ad26.CoV2.S vaccine, TTS has been observed very rarely following vaccination with the Janssen Ad26.CoV2.S vaccine and is considered to be an AESI in this study.

TTS is a syndrome characterized by a combination of both a thrombotic event and thrombocytopenia. TTS is rare and not completely understood. Because of this, all cases of thrombosis and/or thrombocytopenia meeting the criteria below will be considered a suspected case of TTS until further adjudication can be performed. A Janssen AESI Adjudication Committee with appropriate expertise has been established to evaluate suspected AESI and determine whether it is a case of TTS. The sponsor-investigator shall be responsible for reporting any suspected AESI of TTS using the SAE form and the form detailed in Section 14.1.

Due to their immunosuppression and underlying diseases, kidney transplant recipients have fluctuations in their platelet counts below the typical reference range among the general population (>150,000/µl). A platelet count >75,000/µl is required for inclusion in this trial. The following will be considered as suspected AESIs and will be reported to the sponsor-investigator, Janssen, IRB and DSMB within 1 business day of awareness:

- Platelet count below 150,000/µl after receiving the Janssen Ad26.CoV2.S Vaccine without any identifiable alternative cause as determined by the study physicians,
- Platelet count below 150,000/µl and a decrease ≥25% from Baseline after receiving the Janssen Ad26.CoV2.S Vaccine, or
- Any thrombotic event without any identifiable alternative cause as determined by the study physicians.

Symptoms, signs, or conditions suggestive of a thrombotic event should be recorded and reported as a suspected AESI even if the final or definitive diagnosis has not yet been determined, and alternative diagnoses have not yet been eliminated or shown to be less likely at the time of the event. Follow-up information and final diagnoses, if applicable, should be submitted to the sponsor-investigator and Janssen as soon as they become available.

In the event of thrombocytopenia, study site personnel should report the absolute value for the platelet count and the reference range for the laboratory test used.

For either a thrombotic event or thrombocytopenia, testing for anti-PF4 should be performed at the local laboratory or substitute local laboratory; repeat testing may be requested for confirmation upon sponsor-investigator discretion.

Suspected AESIs will require enhanced data collection and evaluation (see Section 7.2.2). Every effort should be made to report as much information as possible about the AESI to the sponsor-investigator in a reasonable timeframe.

If an event meets the criteria for an SAE (Section 7.1), it should be reported using the same process as for other SAEs.

The form detailed in Section 14.1 is intended as a guide for assessment of the AESIs to facilitate diagnosis and determine treatment options. If the sponsor-investigator is not the treating physician, every effort should be made to collect the information requested in the form from the treating physician and enter the available information in the eCRF.

7.2.2.2 Guillain-Barré Syndrome

As described in Section 1.5.7, Guillain-Barré Syndrome, GBS has also been rarely observed following vaccination with the Janssen Ad26.CoV2.S vaccine and will also be considered an AESI in this study.

GBS is a disease that is defined as the immune system attacking the nerve cells, and commonly required hospitalization.

As there may be a potential association between GBS and the Janssen Ad26.Cov2.S vaccine, all cases of GBS will be considered an adverse event of special interest until further evaluation can be performed. The sponsor-investigator shall be responsible for reporting any suspected GBS. A suspected GBS case will be defined as someone exhibiting the following symptoms after vaccination up to 28 days after vaccination:

- Prickling, pins and needles sensations in your fingers, toes, ankles or wrists
- Weakness in your legs that spreads to your upper body
- Unsteady walking or inability to walk or climb stairs
- Difficulty with facial movements, including speaking, chewing or swallowing
- Double vision or inability to move eyes
- Severe pain that may feel achy, shooting or cramplike and may be worse at night
- Difficulty with bladder control or bowel function

- Rapid heart rate (this is already included)
- Low or high blood pressure (this is already included)
- Difficulty breathing

Subjects will be informed of the risks of GBS at consent and be educated on when to see medical help after vaccination by the study team. These symptoms, signs, or conditions suggestive of GBS will be recorded and reported as a suspected AESI even if the final or definitive diagnosis has not yet been determined, and alternative diagnoses have not yet been eliminated or shown to be less likely. Follow-up information and final diagnoses, if applicable, will be submitted to the sponsor as soon as they become available.

Suspected AESIs will require enhanced data collection and evaluation. Every effort should be made to report as much information as possible about the AESI to the sponsor in a reasonable timeframe.

If an event meets the criteria for an SAE (Section 7.1), it should be reported using the same process as for other SAEs.

If the sponsor-investigator is not the treating physician, every effort should be made to collect the information requested in the form from the treating physician and enter the available information in the eCRF.

7.2.2.3 Myocarditis and Pericarditis

As described in Section 1.5.10, Myocarditis and Pericarditis has been reported in temporal associations observed following vaccination with the Janssen Ad26.CoV2.S vaccine. It has been observed mainly following the usage of mRNA-based S-Protein Covid-19 vaccines. Myocarditis and/or pericarditis following administration is not considered an identified risk for the Ad26.COV2.S.

Myocarditis is the inflammation of the heart muscle. The inflammation can reduce the heart's ability to pump blood. Pericarditis is swelling and irritation of the thin, saclike tissue surrounding the heart (pericardium) and will also be considered an AESI in this study.

As there may be a potential association with the mRNA-based S-Protein Covid-19 vaccines, these cases are potentially related, unexpected, and serious and will all cases of Myocarditis and or Pericarditis will be considered an adverse event of special interest until further evaluation can be performed. The sponsor-investigator shall be responsible for reporting any suspected Myocarditis or Pericarditis. A suspected Myocarditis or Pericarditis case will be defined as someone exhibiting the following symptoms after vaccination up to 4-6 weeks after vaccination:

- Acute chest pain and pain that spreads to the left shoulder and neck which may get worse when coughing, lying down or taking a deep breath or get better when sitting up or leaning forward
- Cough,
- Fatigue
- General feeling of weakness or being sick
- Swelling of legs, ankles, and feet
- Flu like symptoms
- Low-grade fever
- Arrhythmias or heart palpitations,
- Light- headedness
- Shortness of breath
- Swelling of the abdomen.

If an event meets the criteria for an SAE (Section 7.1), it should be reported using the same process as for other SAEs.

7.2.3 **Pregnancy**

If a subject becomes pregnant during the study, in addition to reporting the pregnancy within 1 business day, a determination regarding the Janssen Ad26.CoV2.S vaccine discontinuation and subject discontinuation must be made by the sponsor-investigator in alignment with the protocol inclusion/exclusion criteria and in consultation with the Reference Safety Information (RSI).

The effect of the Janssen Ad26.CoV2.S vaccine on sperm is unknown, pregnancies in partners of male subjects exposed to the Janssen Ad26.CoV2.S vaccine will be reported by the Investigator within 1 business day **of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

A safety report is not considered complete until all clinical details needed to interpret the case are received.

Adverse Event Reporting Period

- (S)AEs that are related to study procedures or that are related to non-investigational Janssen products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.
    - (S)AEs not meeting the above criteria and occurring between first signing of the ICF and moment of 1st vaccination will be collected on the Medical History eCRF page as pre-existing conditions.
- All SAEs and all AEs leading to study discontinuation or discontinuation of study vaccination (regardless of the causal relationship) are to be reported from the moment of 1st vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. The sponsor-investigator will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.
- MAAEs are to be reported for all participants from the moment of 1st vaccination until 6 months after the last vaccination, except for MAAEs leading to study discontinuation which are to be reported during the entire study.
- Special reporting situations will be recorded for each vaccination from the time of vaccination until 28 days post-vaccination.
- Solicited AEs, collected through a diary, will be recorded for each vaccination from the time of vaccination until 7 day post-vaccination.
    - If these solicited signs and symptoms are not resolved by the Day 7 contact, the subject will continue to record their daily symptoms in the diary until the Day 28 Visit or until they are resolved, whichever comes first.
- All other unsolicited AEs, whether serious or non-serious, will be recorded for each vaccination from the time of vaccination until 28 days post-vaccination. Unsolicited AEs with an onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.
- All AEs will be followed until resolution or until clinically stable.

Sponsor-Investigator Reporting to Janssen

Type of report	Timelines	How to report
Serious Adverse Event	Within 1 business day of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Adverse Events of Special Interest (AESI)	Within 1 business day of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.

Reports of drug exposure during pregnancy (maternal and paternal), with or without SAE.	Within 1 business day of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Reports of Suspected transmission of any infectious agent via administration of a J&J Product, with or without an SAE	Within1 business day of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Abnormal Pregnancy Outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy)	Within 1 business day of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Special Situation (SS), if associated with an SAE	Within 1 business day of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Special Situation (not associated with an SAE)	Monthly and part of scheduled data transfers	Recorded in CRF and as agreed by the Parties
Medically Attended Adverse Events (not associated with an SAE)	Monthly and part of the scheduled data transfers	Recorded in CRF and as agreed by the Parties
Product Quality Complaints	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties.
Non-Serious Adverse Event* (*Not meeting other listed 1 business day reporting criteria e.g., special situation not associated with an SAE or MAAE)	Monthly and part of the scheduled data transfers	Recorded in CRF and as agreed by the Parties.
Follow-up information	Transmitted within the same timeframes as above i.e., if initial report was required to be submitted within 1 business day of becoming aware of follow-up information, follow-up information shall be submitted within the same timeframe.	Transmitted via same method as above i.e., if initial method of transmission was on an SAE form, follow-up information shall be transmitted in the same manner.

Study Team shall

- notify Janssen immediately in case of a suspension of recruitment or premature stop of the concerned clinical study because of a safety concern; preferably by means of a telephone contact with the Janssen Representative, alternatively by email within twenty-four (24) hours of the decision.
- provide to Janssen copies of any and all relevant extraordinary* (not including routine initial or follow-up Individual Case Safety Report submission) correspondences with health authorities and ethics committees regarding any and all serious adverse events (irrespective of the association with the Janssen Ad26.CoV2.S vaccine). Copies of such correspondence shall be provided within 24 hours of such report or correspondence being sent to applicable health authority.
  *See definitions section 7.1

Contact Information	
Janssen SAE/Pregnancy Notifications	[redacted]
Janssen PQC:	[redacted]
Janssen Phone:	Contact the study assigned Janssen Trial Manager
Janssen Fax:	[redacted]

- Provide the batch/lot number (if available). If batch/lot number is not available, it must be documented that it is not available. Without this documentation, Janssen is required to perform two follow-up attempts to obtain the batch/lot number

7.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event worksheet and entered in the research database:

- Subject's name
- Medical record number
- Disease/histology (if applicable)
- The date the adverse event occurred
- Description of the adverse event
- Relationship of the adverse event to the research (drug, procedure, or intervention*)
- If the adverse event was expected
- The severity of the adverse event (use a table to define severity scale 1-5**)
- If any intervention was necessary
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

Consider the use of a table to define the Relationship of an Event to the Research and the severity of each event.

Assessment of Causality

The relationship of an AE to the Janssen Ad26.CoV2.S vaccine is a clinical decision by the sponsor-investigator (S-I) based on all available information at the time of the completion of the CRF and is graded as follows:

1. Not Related: a reaction for which sufficient information exists to indicate the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the Janssen Ad26.CoV2.S vaccine is not reasonable or the event is c1early related to other factors such as the subject' s clinical state, therapeutic intervention or concomitant therapy. By definition, all solicited AEs at the injection site (local) will be considered related to the Janssen Ad26.CoV2.S vaccine administration.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. Probable: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfill this definition.

5. Definite: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

Severity Criteria

The revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or the most current updated version will be utilized to determine the grading scales and descriptions for AE reporting. The study team and all areas where study procedures will occur will have access to a copy of the CTCAE version 5.0 or the most current updated version, and a copy can be downloaded from the CTEP website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

The severity of solicited signs and symptoms will be graded in the diary by the subjects based on the severity assessment provided in the diary as well as assessed by the investigator. (Note: severity of the measured events will be derived from the diameter [for erythema and swelling] and the temperature measurements [for fever]).

7.3.2 Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

The sponsor-investigator must also notify the FDA (and sponsors must notify all participating investigators) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i)-(iv).

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

7.4 Unmasking/Unblinding Procedures

Not applicable to this study as open-label, unblinded prospective design.

7.5 Stopping Rules

Discontinuation of Study Vaccination

Study vaccinations will be withheld for the reasons listed below. These participants must not receive any further doses of Janssen Ad26.CoV2.S vaccine but should remain on study for follow-up with assessments of safety and immunogenicity as indicated in the Schedules of

Activities. Additional unscheduled visits may be performed for safety/reactogenicity reasons, if needed. In case of questions, the investigator is encouraged to contact the sponsor.

- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the sponsor-investigator, requires discontinuation from Janssen Ad26.CoV2.S vaccine
- The participant becomes pregnant
- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- Platelet Count <75,000 prior to receiving the Janssen Ad26.COV2.s vaccine
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to Janssen Ad26.CoV2.S vaccine
- Participant received any experimental medication (including experimental vaccines other than the Janssen Ad26.CoV2.S vaccine) or received a COVID-19 vaccine or treatment
- Withdrawal of consent to receive further study vaccination
- Participant has a molecularly confirmed SARS-CoV-2 infection based on samples collected within the study (see Section 7.2.1)
- Participant previously experienced TTS, Heparin Induced Thrombocytopenia (HIT), Myocarditis or Pericarditis.

7.6 Medical Monitoring

It is the responsibility of the sponsor-investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

7.6.1 Internal Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will been convened to assess the progress of a clinical study, the safety data, and critical immunogenicity endpoints. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. Members of the DSMB will not participate as investigators in the study under review and will not be supervised by study investigators.

Members of the DSMB will not have a direct interest in knowing or influencing trial outcome or have a financial or intellectual interest in the outcome of any studies under review.

The DSMB will include experts in transplantation, statistics, and infectious disease. The DSMB will have at least one biostatistician for each meeting review. A quorum will occur when two members are present. Without a quorum a meeting will not be held, unless alternate arrangements have been made by the Chair of the DSMB in agreement. The DSMB will review the study before initiation, at the midpoint of enrollment and at least yearly thereafter. *Ad hoc*

DSMB meetings can be initiated by a study Investigator and/or the Medical Monitor if a safety concern is identified at any time during the study. The DSMB will review study data to evaluate the safety, efficacy, study progress, and conduct of the study. If a concern is identified, the DSMB will recommend whether or not dosing should be discontinued or modified depending upon the event (type, severity, relationship to study treatment) and to recommend whether or not the study should continue.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

If a subject revokes authorization to collect or use PHI, the sponsor-investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries on paper

should be printed legibly in ink. If any entry error has been made, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

8.4 Data Management

Research material will be obtained from individually identifiable living human subjects through interactions with study members, review of medical records and blood specimens utilized for lab tests, obtained as part of the protocol. Individually identifiable patient history and medical record information will be stored under coded accession numbers. Clinical laboratory values are stored in the electronic medical record system of Mayo Clinic, requiring protected password access. These data are monitored regularly for access and a formal policy regarding protection of personal privacy is in place through Mayo Clinic. The key to identification of subjects will be maintained in a secure office environment under the direction of the sponsor-investigator.

8.5 Data Processing

A data coordinating group will monitor data collection and provide interim analyses to the Data Safety Monitoring Board. **We expect to complete Segment I enrollment within 6-9 months and have final data on the primary endpoint approximately 12 months from study start.** All patient outcome variables are tracked using registries set up in the "Healthy Planet" tool in the Electronic Health Record. For infection data, a registry flags patients as having an infection if a clinical diagnosis of COVID-19 was added to the problem list or a SARS-CoV-2 polymerase chain reaction test is positive. Those without laboratory confirmation are reviewed to ensure that this was appropriate (for example, an outside laboratory result not visible in our chart). External results could satisfy registry metrics if they could be identified within the interoperable framework for data sharing across the EHR, Care Everywhere (Epic Systems Corporation). A similar registry architecture captures data on vaccination data, populated from both EHR records, state health registries, and the health information exchange.

Data Security and Confidentiality

Source documents, CRFs and original consents will be stored in secured locations at Mayo Clinic. Clinical laboratory values are stored in the electronic medical record system requiring protected password access and approved use. Every individual who accesses a medical record has their activity tracked in the system. These data are monitored regularly for access and a formal policy regarding protection of personal privacy which is in place throughout Mayo Clinic.

Data Quality Assurance

Manual and computerized quality checks will occur during data collection and analyses and any discrepancies will require Case Report Form (CRF) review and validation of correct data.

Data Clarification Process

All queries will be logged and tracked electronically, as well as any corrections or justifications which are made, if applicable.

Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted] whichever is longer.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The Investigator will allocate adequate time for such monitoring activities. The sponsor-investigator will also ensure the monitor or other compliance, or quality assurance reviewer has access to all study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

9.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the funding sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

10 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

11 Study Finances

11.1 Funding Source

This study is financed by Janssen Research and Development, LLC, who will also be providing study drug.

11.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

12 Publication Plan

Mark D Stegall MD, as the primary investigator, will hold the primary responsibility for publication of the results of the study. Approval will need to be obtained from the sponsor-investigator and co-investigators before information is used or passed on to a third party.

The study will be registered with ClinicalTrials.gov.

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14 Attachments

14.1 TTS AESI Form

The form below represents the type of information that may be collected in case of a suspected AESI in order to help adjudicate whether the event is a case of TTS. Additional data may be requested by the sponsor for investigation of the event.

Adverse Event of Special Interest Questionnaire (AESIQ) for Thrombosis with Thrombocytopenia Syndrome

Date of Report: [dd-MMM-yyyy]

1. Adverse Event Description

Participant's clinical signs and symptoms (circle)

Leg/Calf Edema	Pain in Leg/Calf	Hemoptysis
Dyspnea	Chest Pain/Discomfort	Syncope
Tachypnoea	Tachycardia	Cough
Loss of consciousness	Headache	Seizure
Visual impairment	Weakness	Impaired speech
Confusional state	Paresthesia	Gait disturbance

Other Symptoms:

Was patient on VTE prophylaxis? YES/NO

If yes, details:

14.2 Guillain-Barré Syndrome Symptoms

Guillain-Barré Syndrome is a disease that causes your body to attack your nerves. If you have the following symptoms, please seek immediate medical attention:

- Prickling, pins and needles sensations in your fingers, toes, ankles or wrists
- Weakness in your legs that spreads to your upper body
- Unsteady walking or inability to walk or climb stairs
- Difficulty with facial movements, including speaking, chewing or swallowing
- Double vision or inability to move eyes
- Severe pain that may feel achy, shooting or cramplike and may be worse at night
- Difficulty with bladder control or bowel function
- Rapid heart rate (this is already included)
- Low or high blood pressure (this is already included)
- Difficulty breathing

14.3 Symptoms of Infection with Coranavirus-19 (SIC)

The following questions ask about symptoms people with coronavirus-19 infection may experience. Answer each question carefully by choosing 'yes' if you have experienced the symptom or 'no' if you have not experienced the symptom in the last 24 hours. If you choose 'yes', select the rating that best matches your experience.

In the last 24 hours, have you experienced…	**Please rate the severity of each symptom you experienced.**
Feeling generally unwell (run down) **Yes No** If yes, →	How severe was your **feeling (generally unwell or run down)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Fatigue (tiredness) **Yes No** If yes, →	How severe was your **fatigue (tiredness)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst Possible
Physical weakness **Yes No** If yes, →	How severe was your feeling of **physical weakness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst Possible
Cough **Yes No** If yes, →	How severe was your **cough** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst Possible
Shortness of breath (difficulty breathing) **Yes No** If yes, →	How severe was your **shortness of breath (difficulty breathing)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst Possible
Sore throat **Yes No** If yes, →	How severe was your **sore throat** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Nasal congestion (stuffy nose) **Yes No** If yes, →	How severe was your **nasal congestion (stuffy nose)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

Wheezing (whistling soundwhile breathing) **Yes No** If yes, →	How severe was your **wheezing (whistling sound while breathing)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Runny nose **Yes No** If yes, →	How severe was your **runny nose** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Sneezing **Yes No** If yes, →	How severe was your **sneezing** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Chest congestion (mucus in chest) **Yes No** If yes, →	How severe was your **chest congestion (mucus in chest)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Chest pain/ pressure/tightness **Yes No** If yes, →	How severe was your **chest pain/pressure/tightness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Muscle aches/pains **Yes No** If yes, →	How severe were your **muscle aches or pains** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Joint aches/pains **Yes No** If yes, →	How severe were the **aches or pains in your joints** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Headache **Yes No** If yes, →	How severe was your **headache** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Feeling faint **Yes No** If yes, →	How severe was your **feeling of faintness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

Problems thinking clearly/brain fog **Yes No** If yes, →	How severe were your **problems thinking clearly/brain fog** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Chills **Yes No** If yes, →	How severe were your **chills** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Skin rash **Yes No** If yes, →	How severe was your **skin rash** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Eye irritation/discharge **Yes No** If yes, →	How severe was your **eye irritation/discharge** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Diarrhea **Yes No** If yes, →	How severe was your **diarrhea** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Vomiting **Yes No** If yes, →	How severe was your **vomiting** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Nausea **Yes No** If yes, →	How severe was your **nausea** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Abdominal/ stomach pain **Yes No** If yes, →	How severe was your **abdominal/stomach pain** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Loss of appetite **Yes No** If yes, →	How severe was your **loss of appetite** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

What was your **highest temperature** in the last 24 hours?___ °C/°F

What method did you use to take your temperature?

☐ **oral** ☐ **armpit** ☐ **ear** ☐ **forehead** ☐ **rectal**

In the last 24 hours, have you experienced…
Uncontrollable body shaking/shivering*   ☐ **Yes** ☐ **No**
Decreased sense of smell*   ☐ **Yes** ☐ **No**
Decreased sense of taste*   ☐ **Yes** ☐ **No**
Red or bruised looking feet or toes*   ☐ **Yes** ☐ **No**

*Please rate the severity of your symptoms in the last 24 hours?
☐ No Symptoms
☐ Mild
☐ Moderate
☐ Severe

14.4 Risk Factor Assessment

Are you a student? ☐ Yes ☐ No
If Yes – Are you likely to return to school in person in the near future? ☐ Yes ☐ No ☐ I don't know
Are you retired? ☐ Yes ☐ No

How often do you go in person to your main workplace (other than work-from-home)?
☐ 0 days/week ☐ 1 day/week ☐ 2-4 days/week ☐ 5 or more days/week

Does your main workplace have social distancing measures in place?
☐ Yes ☐ No ☐ I don't know ☐ Not applicable
Is your main workplace cleaned on a regular basis?
☐ Yes ☐ No ☐ I don't know ☐ Not applicable
Do people in your main workplace use personal protection equipment (such as masks)?
☐ Yes ☐ No ☐ I don't know ☐ Not applicable
How do you get to work? (Check all that apply)
☐ Drive own car ☐ Carpool ☐ Rideshare (Taxi, Uber, Lyft, others)
☐ Bus ☐ Train / Subway ☐ Walk / Bike
☐ Frequent Air Travel ☐ Not applicable
On a typical day, how many people do you interact with in person at work?
☐ No one ☐ Between 1 and 10 people
☐ Between 11 and 30 people ☐ Between 31 and 50 people
☐ More than 50 people
On a typical day, how many people do you interact with in person outside of work?
☐ No one ☐ Between 1 and 10 people
☐ Between 11 and 30 people ☐ Between 31 and 50 people
☐ More than 50 people

Living Situation

Do you live in any of the following (choose all that apply):
☐ Single family home ☐ Multi-family housing (apartment building, condo)
☐ Long-term care facility ☐ Assisted-living facility
☐ Dormitory ☐ RV / Trailer
☐ Single room in a hotel ☐ Shelter
☐ Other adult group setting ☐ Staying with friends / Couch surfing
☐ No residence ☐ Tribal Lands / Reservation
☐ Other
How many people do you live with (other than yourself)?
Total people under 18 years of age
Total people between 18-64 years of age
Total people over 65 years of age
Are any of the people you live with expected to return to school in person in the near future?
☐ Yes ☐ No ☐ I don't know

Community Interactions

In the last 2 weeks, have you attended any gatherings with more than 10 people? (e.g., church, party, concert, wedding, funeral, demonstration or other event). ☐ Yes ☐ No ☐ Not applicable / Don't want to tell
If yes, approximately how many people were at the largest gathering?
☐ less than 10 ☐ 10-20 ☐ 21-50 ☐ 51-250 ☐ More than 250
Was this gathering an indoor or outdoor event?
☐ Indoor ☐ Outdoor ☐ Both
How frequently do you have visitors in your residence including people completing work inside?
☐ Daily
☐ Weekly
☐ Monthly
☐ Rarely
☐ Never
☐ N/A

Over the past month, have you been in close contact with anyone that tested positive for COVID-19?
☐ Yes ☐ No ☐ I don't know ☐ Not applicable / Don't want to tell
If yes, is this person someone that you live with?
☐ Yes ☐ No ☐ Not applicable / Don't want to tell

14.5 Kidney Transplant Follow Up Questionnaire

Kidney Transplant Follow-Up Questionnaire

General Questions	Answer	
Since your last visit, have you recently visited the hospital emergency room, urgent care facility or an afterhours clinic? ___ ___ visits (enter'00' if no visits)	Yes	No
Since your last visit, have you recently been admitted hospitalized? (Stayed in the hospital overnight)	Yes	No

	Admission Date (MM,DD,YYYY)	Reason for admission	Discharge Date (MM,DD,YYYY)
Hospitalization #1	_ _/_ _/_ _ _ _ MM/DD/YYYY		_ _/_ _/_ _ _ _ MM/DD/YYYY
Hospitalization #2	_ _/_ _/_ _ _ _ MM/DD/YYYY		_ _/_ _/_ _ _ _ MM/DD/YYYY

Have you recently been diagnosed with a new infection? Example Urinary Tract Infection (UTI), Cytomegaly Virus (CMV), etc. If Yes, When? _____ Was it treated? _____	Yes	No
Have you recently been diagnosed with any malignant cancer? If Yes, When? _____ Was it treated? _____	Yes	No
Have you recently experienced a heart attack, Transient Ischemic Attack (TIA) or stroke? If Yes, When? _____ Was it treated? _____	Yes	No
Have you had any unintended weight loss or gain in the last year? If Yes, When? _____ Was it treated? _____	Yes	No
Have you been treated for rejection or have any acute rejection episodes? If Yes, When? _____ Was it treated? _____	Yes	No
Have you been diagnosed with any major illness? If Yes, When? _____ Was it treated? _____	Yes	No

Immunosuppression Medications

Name of medication	Dose	Frequency	Time	Comments

Immunosuppression Medication Adherence

Which number best describes your medication adherence? ___

1.	Never missed a dose
2.	Missed 1-2 times a week
3.	Missed 1-2 times a month
4.	Pro-long periods. I'm unable to get my immunosuppression medications

14.6 COVID-19 Surveillance and Evaluation Questionnaire

1. Have you had close contact with a person with a LABORATORY CONFIRMED case of COVID-19? Close contact is defined by CDC as:
    1. Being within approximately 6 feet of a COVID-19 patient for a prolonged period of time (more than 5 minutes)
    2. Having direct contact with infectious secretions of a COVID-19 case (e.g. being coughed on)

    Yes/No

In the last 48 hours, have you had ANY of the following?

3. a fever of 100.5 F (38 C) or greater, OR
4. new cough, OR
5. new shortness of breath, OR
6. new sore throat, OR
7. new diarrhea, OR
8. new fast breathing (respiratory distress), OR
9. new chills, OR
10. new muscle aches (myalgias), OR
11. new loss of smell, OR
12. new change or loss of taste sensation

14.7 Myocarditis and Pericarditis Symptom Questionnaire

Subject ID_____ **Date_____**

Myocarditis is inflammation of the heart muscle. The inflammation can reduce the heart's ability to pump blood. Pericarditis is swelling and irritation of the thin, saclike tissue surrounding the heart (pericardium). Pericarditis often causes sharp chest pain.

1. Do you have any chest pain?
    a. If yes, does the pain spread to the left shoulder and neck?
    b. Get worse when coughing, lying down or taking a deep breathe?
    c. Get better when sitting up or leaning forward?

2. Do you have any fatigue (tiredness)?

3. Do you have swelling of the legs, ankles, and feet?

4. Do you have a rapid or irregular heartbeat (arrhythmias)?

5. Do you have shortness of breath at rest or during activity?

6. Do you have light-headedness or feeling like you might faint?

7. Do you have any flu-like symptoms such as headache, body aches, joint pain, fever, or sore throat?

8. Do you have a new cough?

9. Do you have pounding or a racing heartbeat (heart palpitations)?

10. Do you have swelling in your belly (abdomen)?

Please seek immediate medical attention if you develop new symptoms of chest pain.