STATISTICAL ANALYSIS PLAN

STUDY TITLE: BOOSTER EFFECTS WITH AUTOIMMUNE TREATMENTS IN PARTICIPANTS WITH POOR RESPONSE TO INITIAL COVID-19 VACCINE

PROTOCOL NUMBER: ACV01

SHORT TITLE:	COVID-19 BOOSTER VACCINE IN AUTOIMMUNE DISEASE NON-RESPONDERS
NCT#:	**NCT05000216**
CLIENT:	The National Institute of Allergy and Infectious Diseases (NIAID)
REGULATORY AGENCY IDENTIFIER NUMBER(S):	IND# 27528
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VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
0.1	02Mar2022	Initial Draft	
1.0	16Mar2022	Final Draft	

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
ACE	Autoimmunity Centers of Excellence
AE	Adverse event
CRF	Case report forms
CSR	Clinical Study Report
CV	Coefficient of variation
DAIT	Division of Allergy, Immunology, and Transplantation
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score 28 using C-reactive protein
DSMB	Data and Safety Monitoring Board
EDSS	Expanded Disability Status Scale
H-SLEDAI	Hybrid Systemic Lupus Erythematosus Disease Activity Index
IS	Immunosuppressive medications
JADAS	Juvenile Arthritis Disease Activity Score
JDM	juvenile dermatomyositis
JIA	juvenile idiopathic arthritis
LLOD	Lower Limit of Detection
MAAE	medically attended adverse event
MCAR	Missing-completely-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MS	Multiple sclerosis
MTX	Methotrexate
NCI	National Cancer Institute
NIAID	The National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOCMC	New onset chronic medical condition
PASI	Psoriasis Area and Severity Index

PDAI	Pemphigus Disease Area Index
PedsQL	Pediatric Quality of Life Inventory™
PGI-C	Patient Global Impression of Change
PtGA	Patient's Global Assessment
PGA	Physician Global Assessment
POMS	Pediatric-onset multiple sclerosis
PROMIS	Participant-Reported Outcomes Measurement Information System
PT	Preferred term
RA	Rheumatoid arthritis
RBD	Receptor binding domain
SACCC	Statistical and Clinical Coordinating Center
SAE	serious adverse event
SAP	Statistical analysis plan
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SD	Standard deviation
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus: National Assessment– Systemic Lupus Erythematosus Disease Activity Index
SLE	Systemic lupus erythematosus
SOC	System organ class
SSc	Systemic sclerosis
VRC	Vaccine Research Center
WHO	World Health Organization

2. PURPOSE OF THE ANALYSES

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol ACV01. This document provides details on study populations, how the variables will be derived, how missing data will be handled and details on statistical methods to be used to analyze the safety and efficacy data.

The SAP is based on ICH guidelines E3 and E9 (Statistical Principles for Clinical Trials).

The document will be updated over time to reflect the requirements of the adaptive study design, protocol amendments and any regulatory requests. However, the final SAP must be finalized, approved by the Client, and placed on file before database is locked. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Deviations from the final approved plan will be noted in the clinical study report.

3. PROTOCOL SUMMARY

Version 1.0 of the protocol was finalized July 9, 2021; the protocol is currently under Version 3.0 which includes several of the planned adaptive elements to ACV01, and is summarized below.

Title	Booster effects with autoimmune treatments in patients with poor response to initial COVID-19 vaccine
Short Title	**COVID-19 BOOSTER VACCINE IN AUTOIMMUNE DISEASE NON-RESPONDERS**
Clinical Phase	II
Number of Sites	**Adult population:** 15 – 20 sites in the United States (US) that are active National Institute of Allergy and Infectious Diseases (NIAID) Autoimmunity Centers of Excellence (ACE) or active subaward recipients of the NIAID ACE Network **Pediatric population:** 15 – 20 sites in the US.
IND Sponsor/Number	The National Institute of Allergy and Infectious Diseases (NIAID) / IND #27528
Study Objectives	**Hypotheses** • We hypothesize that adult and pediatric participants with autoimmune diseases requiring immunosuppressive (IS) medications who have had a sub-optimal response to an initial COVID-19 vaccine regimen may demonstrate enhanced immune response after receiving an additional homologous dose of an mRNA or vector-based vaccine. • We hypothesize that adult and pediatric participants with transient cessation of mycophenolate mofetil (MMF)/ mycophenolic acid (MPA) or methotrexate (MTX) before and after vaccination will have an enhanced immune response. • We further hypothesize that adult participants with autoimmune diseases requiring IS medications who continue to have a sub-optimal response after an initial COVID-19 vaccine regimen plus an additional homologous vaccine dose may demonstrate enhanced immune response after receiving an additional dose of an alternative COVID-19 vaccine. **Primary Objective** The primary objective is to determine the proportions of adult and pediatric participants who have a protective antibody response at 4 weeks after an additional homologous dose of a COVID-19 vaccine using the NIAID Vaccine Research Center (NIAID-VRC) MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay within arms defined by the initial COVID-19 vaccine regimen received, IS regimens, and treatment plans to either withhold or continue medications around the time of vaccination. **Secondary Objectives** Stage 1 Secondary Objectives (adult & pediatric):

	• To determine the incidence of seroconversion following an additional homologous COVID-19 vaccine dose in the subgroup of participants that are anti-COVID-19 antibody negative at Baseline. • To determine the incidence of adverse events (AEs), including medically attended adverse events (MAAEs), new onset chronic medical conditions (NOCMCs), and serious adverse events (SAEs) following an additional homologous COVID-19 vaccine dose. • To assess whether responses to an additional homologous COVID-19 vaccine dose differ with temporary cessation of IS medications around the time of vaccine. • To assess whether responses to an additional homologous COVID-19 vaccine dose differ by type of vaccine administered. • To assess whether responses to an additional homologous COVID-19 vaccine dose differ by type of cohort-defining IS medications and by disease type. • To assess whether response to an additional homologous COVID-19 vaccine dose is associated with corticosteroid dose at the time of vaccination. • To assess whether response to an additional homologous COVID-19 vaccine dose is associated with clinical parameters including disease activity, co-morbid illness, age, and sex. • To determine whether disease activity is increased following an additional homologous COVID-19 vaccine dose, and if so, whether Baseline or induced immunologic variables are associated with increased disease activity and/or vaccination response. Stage 2 Secondary Objectives (adult): • To determine the proportions of participants with a negative serologic or sub-optimal response to an additional homologous COVID-19 vaccine dose who develop a protective antibody response after receiving a subsequent alternative vaccine dose, evaluated using the NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay. • To determine the incidence of seroconversion following a subsequent alternative vaccine dose in the subgroup of participants that are anti-COVID-19 antibody negative following an additional homologous COVID-19 vaccine dose. • To determine the incidence of AEs, including MAAEs, NOCMCs, and SAEs following a subsequent alternative COVID-19 vaccine dose. • To assess whether responses to a subsequent alternative COVID-19 vaccine dose differ by type of vaccine administered. • To assess whether responses to a subsequent alternative COVID-19 vaccine dose differ by type of cohort-defining IS medications and by disease type.

	• To assess whether response to a subsequent alternative COVID-19 vaccine dose is associated with corticosteroid dose at the time of vaccination. • To assess whether response to a subsequent alternative COVID-19 vaccine dose is associated with clinical parameters including disease activity, co-morbid illness, age, and sex. • To determine whether disease activity is increased following a subsequent alternative COVID-19 vaccine dose, and if so, whether immunologic variables are associated with increased disease activity and/or vaccination response. **Exploratory Objectives:** • To evaluate whether Baseline CD19 positive B cell numbers associate with response to an additional study COVID-19 vaccine dose in the cohort that have received B cell depletion therapy. • To evaluate the association between immune response and levels of SARS-CoV-2 antibodies at Baseline. • To evaluate the levels of Baseline interferon signal or interferon gamma-inducible protein 10 (IP-10) serum levels that associate with an effective vaccine response. • To evaluate the levels of Baseline inflammatory signals that associate with an effective vaccine immune response. • To evaluate the association between immune response to an additional study COVID-19 vaccine dose and cellular and mechanistic endpoints.
Study Design	This is a randomized, multi-site, adaptive, open-label clinical trial comparing the immune response to different additional doses of COVID-19 vaccine in participants with autoimmune disease requiring IS medications. All study participants will have negative serologic or sub-optimal responses (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL) to initial COVID-19 vaccine regimen with Moderna COVID-19 Vaccine, Pfizer-BioNTech COVID-19 Vaccine, or Janssen COVID-19 Vaccine. **Adult Population:** **Adult Stage 1:** Stage 1 of this trial will enroll up to a maximum of 900 adult study participants (up to 60 participants per arm). The trial initially focused on adults with at least 1 of 5 autoimmune diseases: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), systemic sclerosis (SSc), and pemphigus. Participants will be assigned to one of 3 cohorts based on their IS regimens: • Cohort A: Receipt of MMF or MPA • Cohort B: Receipt of MTX • Cohort C: Receipt of any B cell depletion therapy within the past 18 months. *Treatment Arms:* Participants in Cohorts A, B, and C will be assigned to receive an additional dose of the same vaccine as their original vaccine series. Participants in Cohorts A and B will be randomized into two IS medication treatment plans as follows • Participants continue to take their cohort-defining IS medications without alterations in schedule and dosing. • Participants withhold their cohort-defining IS medications before and after the additional homologous vaccine dose per protocol instructions.

Schedule of Events: Visits to assess endpoints will occur at Baseline (Week 0), Week 4 ± 1 week, Week 12 ± 2 weeks, Week 24 ± 2 weeks, Week 36 ± 2 weeks, and Week 48 ± 2 weeks. A participant will be enrolled in the study for a maximum of approximately 13 months.

Adult Stage 2:
Stage 2 of this trial will include up to a maximum of 540 adult study participants (up to 60 per arm). Participants will be eligible to receive a dose of an alternative COVID-19 vaccine. Participants may have received their additional homologous vaccine dose as a Stage 1 study participant and then enter into Stage 2 ("rollover participant"), or they may have received their additional homologous dose prior to enrollment in the study ("newly recruited participant").
Participants will be allocated to 1 of 3 cohorts based on their IS regimens:

- Cohort D: Receipt of MMF or MPA
- Cohort E: Receipt of MTX
- Cohort F: Receipt of any B cell depletion therapy within the past 18 months.

Treatment Arms: Participants in Cohorts D, E, and F will receive a dose of an alternative COVID-19 vaccine compared to their previous COVID-19 vaccine doses. Participants who previously received 3 total doses of an mRNA vaccine (Moderna COVID-19 Vaccine OR Pfizer-BioNTech COVID-19 Vaccine) will receive their choice of either the Janssen vector-based COVID 19 vaccine or the other mRNA COVID-19 vaccine, and participants who previously received 2 doses of the Janssen vector-based COVID-19 vaccine will receive the Moderna COVID-19 Vaccine.
Participants in Cohorts D and E will withhold their cohort-defining IS medications before and after the alternative vaccine dose per protocol instructions. Participants in Cohort F who are taking MMF, MPA, or MTX in addition to B cell depletion therapies (BCDTs) will withhold these medications before and after the alternative vaccine dose per protocol instructions.
Schedule of Events: Visits to assess endpoints will occur at Baseline (Week 0), Week 4 ± 1 week, Week 12 ± 2 weeks, Week 24 ± 2 weeks, Week 36 ± 2 weeks, and Week 48 ± 2 weeks. A participant who enters Stage 2 after a serologic negative or sub-optimal response to their Stage 1 vaccine dose may be on study for up to a maximum of 26 months. A participant who is newly recruited to the study for entry into Stage 2 may be on study for up to a maximum of 13 months.

Pediatric Population:
The pediatric portion of this trial will enroll up to a maximum of 900 participants (5-17 years of age) with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL after receiving an initial COVID-19 vaccine regimen (up to 60 participants per arm). Vaccines will be included in this protocol as they receive EUA or approval by FDA for a given age group. Pediatric participants will have 1 of 4 autoimmune diseases: pediatric SLE, juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM), or pediatric-onset multiple sclerosis (POMS).
Participants will be assigned to one of 3 cohorts based on their IS regimens:

- Cohort A: Receipt of MMF or MPA
- Cohort B: Receipt of MTX
- Cohort C: Receipt of any B cell depletion therapy within the past 18 months.

Treatment Arms: Participants in Cohorts A, B, and C will be assigned to receive an additional dose of the same vaccine as their original vaccine series.
Participants in Cohorts A and B will be randomized into two IS medication treatment plans as follows):

- Participants continue to take their cohort-defining IS medications without alterations in schedule and dosing.

	• Participants withhold their cohort-defining IS medications before and after the additional homologous vaccine dose per protocol instructions. *Schedule of Events:* Visits to assess endpoints will occur at Baseline (Week 0), Week 4 ± 1 week, Week 12 ± 2 weeks, Week 24 ± 2 weeks, Week 36 ± 2 weeks, and Week 48 ± 2 weeks. A participant will be enrolled in the study for a maximum of approximately 13 months. **Adaptive Design:** An adaptive design will be employed such that cohorts and arms defined by additional vaccine doses and IS treatment plans may be added or modified based on emerging data from existing and new FDA Emergency Use Authorization (EUA) or approvals of COVID-19 vaccines: • New cohorts may be defined based on changes in the medication groups if it becomes obvious that certain medications are highly associated with sub-optimal serologic response to initial COVID-19 vaccine regimen. • Cohorts may limit or expand the autoimmune diseases that are eligible to be included in the clinical trial, and may include expansion cohorts of underrepresented diseases. • New cohorts may include participants whose antibody response falls to sub-optimal levels over time. • Based upon timing of the FDA EUA authorization for children of each of the COVID-19 vaccines used in this trial, the age range of the inclusion criteria may be expanded. • Allocation or randomization to treatment with new vaccines designed for COVID variants or with a protein-based vaccine may be incorporated into the design when the products become available. • Identification of additional strategies to enhance vaccine responsiveness in autoimmune diseases, including a temporary switch of immunomodulatory medications.
Primary Endpoint	The primary endpoint in the adult and pediatric populations of a protective antibody response at Week 4 will be assessed by the NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay.
Secondary and Exploratory Endpoints	**Secondary Endpoints** Secondary endpoints related to antibody response will primarily be assessed by the NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay; where applicable, they will also be assessed by the Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay. The secondary endpoints are applicable to both the adult and pediatric populations. • Seroconversion at Week 4 following additional doses of COVID-19 vaccine in the subgroup of participants that are anti-COVID-19 antibody negative at Week 0.

	• Fold increase in anti-COVID-19 antibody levels at Week 4 following an additional dose of COVID-19 vaccine in the subgroup of participants who are anti-COVID-19 antibody positive at Week 0. • Longitudinal changes in anti-COVID-19 antibody responses from Week 0 to Weeks 4, 12, 24, 36, and 48. • Longitudinal changes in neutralization and pseudo neutralization assays from Week 0 to Weeks 4, 12, 24, 36, and 48. • Changes in disease activity after receipt of additional doses of COVID-19 vaccine as measured by the Clinical Global Impression of Change (CGI-C). • Changes in disease activity after receipt of additional doses of COVID-19 vaccine as measured by the Physician Global Assessment (PGA). • Changes in disease activity after receipt of additional doses of COVID-19 vaccine as measured by the following disease-specific assessments: o Adult population disease assessments: o Hybrid Systemic Lupus Erythematosus Disease Activity Index (H-SLEDAI) and Thanou modified Safety of Estrogens in Lupus Erythematosus: National Assessment– Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Flare Index for SLE o Disease Activity Score 28 using C-reactive protein (DAS28-CRP) for RA o Flare assessment for SSc (including patient reported flare assessment) o Pemphigus Disease Area Index (PDAI) for pemphigus o Physician-assessed relapse for MS o Pediatric population disease assessments: o JIA: ▪ JADAS10 for polyarthritis, enthesitis related to JIA, oligoarthritis, and psoriatic arthritis ▪ Psoriasis Area and Severity Index (PASI) for psoriatic arthritis o SLEDAI-2K and Childhood-onset SLE Criteria for Global Flare [1] for pediatric SLE o Childhood Myositis Assessment Scale (CMAS) and JDM Disease Activity Score (DAS) for JDM o Physician-assessed relapse for MS for POMS

	• Changes in patient-reported outcomes as measured by:
	  ○ Participant-Reported Outcomes Measurement Information System (PROMIS) 29 (adults only)
	  ○ Pediatric Quality of Life Inventory™ (PedsQL) (pediatrics only)
	  ○ Patient Global Assessment (PtGA)
	  ○ Patient Global Impression of Change (PGI-C)
	• The proportion of participants who experience the following safety events:
	  ○ Any Grade 1 or higher AEs related to the additional doses of COVID-19 vaccine
	  ○ Any SAEs, MAAEs, NOCMCs
	  ○ Any SARS-CoV-2 infection
	Exploratory Endpoints
	• Changes in autoantibody levels after COVID-19 vaccination between Week 0, and Weeks 4, 12, 24, 36, and 48.
	• Assessments of cellular and mechanistic response, including
	  ○ Immune cell population profiling over time
	  ○ Antigen-specific T cell responses
	  ○ Antigen-specific memory B cell responses
	  ○ Total IgG responses
	  ○ B cell and T cell repertoire
	  ○ Changes in gene expression profile modules
	  ○ Plasma levels of soluble mediators

Accrual Objective	**Adult Population:** In Stage 1, 15 arms are planned within cohorts defined by categories of IS medications such that a maximum of 900 participants are to be randomized/allocated. In Adult Stage 2, 9 arms are planned to evaluate the immune response to a subsequent alternative COVID-19 vaccine dose such that a maximum of 540 participants (either rollover or newly recruited) are to be allocated. **Pediatric Population:** A total of 15 arms are planned within cohorts defined by categories of IS medications such that a maximum of 900 participants are to be randomized/allocated (up to 300 participants for each vaccine to receive FDA EUA in pediatric participants). In all populations and stages, 40 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤50 U/mL will be targeted for each arm, with a total of 60 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL randomized or allocated to each arm. In each arm, the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results ≤50 U/mL will be capped at 40 participants, and the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results >50 U/mL and ≤200 U/mL will be capped at 40 participants.

Study Duration	Study duration for Adult Stage 1, Adult Stage 2 newly recruited, or pediatric participant: 13 months Study duration for Adult 2 participant rolling over from Stage 1: maximum of 26 months
Treatment Description	All participants will receive one dose of the following: • mRNA COVID-19 vaccine : Moderna OR • mRNA COVID-19 vaccine : Pfizer-BioNTech OR • vector-based COVID-19 vaccine : Janssen
Inclusion/Exclusion Criteria – Adult Stage 1	**Inclusion Criteria:** Individuals who meet all of the following criteria are eligible for randomization/allocation as study participants in Adult Stage 1: 1. Individuals 18 years of age or older that meet classification criteria for SLE, SSc, RA, MS, or pemphigus. 2. Participants must meet the 2019 ACR/EULAR[2] or 2012 SLICC classification criteria for SLE [3], the 2010 ACR/EULAR classification criteria for RA [4], the 2013 EULAR/ACR classification criteria for SSc [5], the 2017 McDonald [6] criteria for MS, and the international consensus criteria for pemphigus [7]. a. If a participant has been diagnosed with more than one autoimmune disease, the participant will be assessed based on the disease that is selected for study entry. 3. Willing and able to sign informed consent. 4. Documented full COVID-19 vaccination (Centers for Disease Control and Prevention [CDC] card or documentation in medical records) that was completed at least 4 weeks prior and no more than 52 weeks prior to the Screening visit. 5. Negative or suboptimal serologic response to initial COVID-19 vaccine regimen, defined as an Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL - at Screening visit. a. Initial COVID-19 vaccine regimen is defined as either: i. 2 doses of the Pfizer-BioNTech COVID-19 Vaccine ii. 2 doses of the Moderna COVID-19 Vaccine 6. Must be currently taking one of the following IS medications with or without additional disease-related medications: MMF (minimum of 1000 mg per day)/MPA (minimum of 720 mg per day), MTX (minimum of 7.5mg per week), or B cell depleting agents within the past 18 months (such as rituximab, ocrelizumab, ofatumumab). a. If taking MMF/MPA or MTX, the participant must have initiated therapy at least 8 weeks prior to randomization and be taking the same medications (regardless of dose) as at the time of the initial COVID-19 vaccine regimen. Note: Participants who withheld their IS medications around their initial vaccinations are eligible to participate. b. If enrolling in the B cell depleting therapy cohort, the participant must have received an anti-CD20 or an anti-CD19 B cell depleting therapy in the past 18 months.

7. No changes in background IS medications, including MMF/MPA or MTX, in the 8 weeks prior to Screening, excluding the following:
    a. HCQ,
    b. Intraarticular steroids,
    c. The addition of prednisone at ≤10mg per day or prednisone at any dose when given for ≤3 days, and
    d. Corticosteroid bursts for non-autoimmune disease-related conditions, such as asthma or COPD, are permitted.

Exclusion Criteria:

Individuals who meet any of these criteria are not eligible for randomization/allocation as study participants in Adult Stage 1:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.
2. History of severe allergic reaction to the initial COVID-19 vaccine regimen, to any component of any of the COVID-19 vaccines, or to polyethylene glycol (PEG).
3. New diagnosis of malignancy that will require chemotherapy or immunotherapy, or ongoing treatment for a malignancy with chemotherapy or immunotherapy.
4. Active disease (per the Investigator's decision) resulting in inability to hold the IS therapy in the MMF/MPA or MTX arms of the study.
    a. The potential impact of temporarily holding medication for participants with a recent mild disease flare within 4 weeks should be carefully considered.
5. Active disease during the Screening period resulting in:
    a. An increase/addition of IS medications, or
    b. A suggestion of MS relapse per the investigator
6. Recent or current SARS-CoV-2 infection defined as:
    a. Documented SARS-CoV-2 infection in the past 30 days (from the day the participant is diagnosed by positive test to Screening).
    b. Positive result on a molecular COVID-19 test at Screening.
7. Receipt of a COVID-19 vaccine booster prior to Screening with the Moderna COVID-19 Vaccine, Pfizer-BioNTech COVID-19 Vaccine, or Janssen COVID-19 Vaccine.
8. Inflammatory myocarditis/pericarditis following initial COVID-19 vaccine regimen.
9. Participants with active, ongoing chronic infections, including participants with evidence of:
    a. Human Immunodeficiency Virus (HIV)
    b. Hepatitis B as indicated by surface antigen

	c. Hepatitis C as indicated by anti-hepatitis C antibody positivity; if a participant is Hepatitis C antibody positive, they will be eligible to participate in the study if he/she is negative for viral load at Screening. *Note: Participants are permitted to be on chronic prophylactic antimicrobial therapy.* 10. Participants with common variable immunodeficiency disease, as well as any participants currently receiving immune globulin replacement therapy. 11. Participants who received licensed or investigational monoclonal antibodies or plasma products directed against SARS-CoV-2 within 30 days of Screening. 12. Participants who have received any live vaccines within 2 months of the anticipated study vaccine dose or who will have need of a live vaccine at any time during the study. 13. Currently pregnant or breastfeeding. 14. Participants who are planning a pregnancy during the course of the trial. 15. Hemoglobin (Hgb) <8.0 g/dL (80 g/L) 16. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study. 17. Other investigational chemical agent within 30 days or other investigational biologic agent within 8 weeks or 5 half-lives (whichever is longer) of Screening. 18. Concurrent treatment with cyclophosphamide, cladribine, alemtuzumab, or mitoxantrone. 19. Participants currently on any type of dialysis, or who have received a solid organ transplant. 20. Prisoners or participants who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness. 21. Taking both MMF/MPA and MTX. 22. Receiving other investigational B cell depleting therapy as part of a clinical trial within 18 months of Screening, unless drug assignment is known and the participant received an anti-CD20 or CD19 drug. 23. Participants with active systemic infections who have received systemic antimicrobials within the 14 days prior to Screening.
Inclusion/Exclusion Criteria – Adult Stage 2 Newly Recruited Participants	**Inclusion Criteria:** Individuals who meet all of the following criteria are eligible for enrollment as participants in Stage 2:

	1. Individuals 18 years of age or older that meet classification criteria [1-6] for SLE, SSc, RA, MS, or pemphigus If a participant has been diagnosed with more than one autoimmune disease, the participant will be assessed based on the disease that is selected for study entry. 2. Willing and able to sign informed consent. 3. Documented full COVID-19 vaccination (CDC card or documentation in medical records). 4. Received an additional homologous COVID-19 vaccine dose (documented by CDC card or in medical records) that was completed at least 4 weeks prior and no more than 48 weeks prior to the Stage 2 Screening visit. 5. Negative or suboptimal serologic response to the additional homologous COVID-19 vaccine in one of the qualifying regimens, defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) negative result or positive result of ≤200 U/mL within 4 weeks of the Stage 2 Baseline/Week 0 visit. The regimens of COVID-19 vaccination that qualify are as follows: a. 3 full doses of the Pfizer-BioNTech COVID-19 Vaccine b. 3 full doses of the Moderna COVID-19 Vaccine c. 2 full doses of the Janssen COVID-19 Vaccine 6. Must be currently taking one of the following IS medications with or without additional disease-related medications: MMF (minimum of 1000 mg per day)/MPA (minimum of 720 mg per day), MTX (minimum of 7.5mg per week), or B cell depleting agents within the past 18 months (such as rituximab, ocrelizumab, or ofatumumab). a. If taking MMF/MPA or MTX, the participant must have initiated therapy at least 8 weeks prior to allocation and be taking the same medications (regardless of dose) as at the time of the initial COVID-19 vaccine regimen. Note: Participants who withheld their IS medications around their initial vaccinations are eligible to participate. b. If enrolling in the B cell depleting therapy cohort, the participant must have received an anti-CD20 or an anti-CD19 B cell depleting therapy in the past 18 months. 7. No changes in background IS medications, including MMF/MPA or MTX, in the 4 weeks prior to Stage 2 Screening, excluding the following: a. HCQ, b. Intraarticular steroids, c. The addition of prednisone at ≤10mg per day or prednisone at any dose when given for ≤3 days, and

d. Corticosteroid bursts for non-autoimmune disease-related conditions, such as asthma or COPD, are permitted.

Exclusion Criteria:

Individuals who meet any of these criteria are not eligible for randomization/allocation as study participants in Stage 2:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.
2. History of severe allergic reaction to any previous COVID-19 vaccines, to any component of any of the COVID-19 vaccines, or to PEG.
3. New diagnosis of malignancy that will require chemotherapy or immunotherapy, or ongoing treatment for a malignancy with chemotherapy or immunotherapy.
4. Active disease (per the Investigator's decision) resulting in inability to hold the IS therapy in the MMF/MPA or MTX arms of the study.
    a. The potential impact of temporarily holding medication for participants with a recent mild disease flare within 4 weeks should be carefully considered.
5. Active disease during the Stage 2 Screening period resulting in:
    a. An increase/addition of any IS medications, or
    b. A suggestion of MS relapse per the investigator.
6. Recent or current SARS-CoV-2 infection defined as:
    a. Documented SARS-CoV-2 infection in the past 30 days (from the day the participant is diagnosed by positive test to Stage 2 Screening).
    b. Positive result on a molecular COVID-19 test at Stage 2 Screening.
7. Receipt of an additional heterologous COVID-19 vaccine dose prior to Stage 2 Screening, i.e., a participant cannot have received a mixture of mRNA vaccines or both mRNA and Janssen COVID-19 vaccines in any order or combination.
8. Inflammatory myocarditis/pericarditis following any COVID-19 vaccine doses.
9. Participants with active, ongoing chronic infections including participants with evidence of:
    a. HIV.
    b. Hepatitis B as indicated by surface antigen.
    c. Hepatitis C as indicated by anti-hepatitis C antibody positivity; if a participant is Hepatitis C antibody positive, they will be eligible to participate in the study if he/she is negative for viral load at Stage 2 Screening.

	Note: Participants *are permitted to be on chronic prophylactic antimicrobial therapy.* 10. Participants with common variable immunodeficiency disease, as well as any participants currently receiving immune globulin replacement therapy. 11. Participants who received licensed or investigational monoclonal antibodies or plasma products directed against SARS-CoV-2 within 30 days of Stage 2 Screening. 12. Participants who have received any live vaccines within 2 months of the anticipated study vaccine dose or who will have need of a live vaccine at any time during the study. 13. Currently pregnant or breastfeeding. 14. Female participants who are planning a pregnancy during the course of the trial. 15. Hemoglobin (Hgb) <8.0 g/dL (80 g/L) 16. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study. 17. Other investigational chemical agent within 30 days or other investigational biologic agent within 8 weeks or 5 half-lives (whichever is longer) of Stage 2 Screening. 18. Concurrent treatment with cyclophosphamide, cladribine, alemtuzumab, or mitoxantrone. 19. Participants currently on any type of dialysis, or who have received a solid organ transplant. 20. Prisoners or participants who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness. 21. Taking both MMF/MPA and MTX. 22. Receiving other investigational B cell depleting therapy as part of a clinical trial within 18 months of Screening, unless drug assignment is known and the participant received an anti-CD20 or CD19 drug. 23. Participants with active systemic infections who have received systemic antimicrobials within the 14 days prior to Stage 2 Screening.
Inclusion/Exclusion Criteria – Adult Stage 2 Rollover Participants	**Inclusion Criteria:** Individuals who meet all of the following criteria are eligible to continue as participants in Stage 2: 5. Negative or suboptimal serologic response to the additional homologous COVID-19 vaccine in one of the qualifying regimens, defined as an Elecsys® Anti-SARS-CoV-

2 S (RBD) negative result or positive result of ≤200 U/mL within 4 weeks of the Stage 2 Baseline/Week 0 visit.

The regimens of COVID-19 vaccination that qualify are as follows:

a. 3 full doses of the Pfizer-BioNTech COVID-19 Vaccine

b. 3 full doses of the Moderna COVID-19 Vaccine

c. 2 full doses of the Janssen COVID-19 Vaccine

6. Must be currently taking one of the following IS medications with or without additional disease-related medications: MMF (minimum of 1000 mg per day)/MPA (minimum of 720 mg per day), MTX (minimum of 7.5mg per week), or B cell depleting agents within the past 18 months (such as rituximab, ocrelizumab, ofatumumab).

    a. If taking MMF/MPA or MTX, the participant must have initiated therapy at least 8 weeks prior to allocation and be taking the same medications (regardless of dose) as at the time of the initial COVID-19 vaccine regimen. Note: Participants who withheld their IS medications around their initial vaccinations are eligible to participate.

    b. If enrolling in the B cell depleting therapy cohort, the participant must have received an anti-CD20 or an anti-CD19 B cell depleting therapy in the past 18 months.

7. No changes in background IS medications, including MMF/MPA or MTX, in the 4 weeks prior to Stage 2 Baseline/Week 0 visit, excluding the following:

    a. HCQ,

    b. Intraarticular steroids,

    c. The addition of prednisone at ≤10mg per day or prednisone at any dose when given for ≤3 days, and

    d. Corticosteroid bursts for non-autoimmune disease-related conditions, such as asthma or COPD, are permitted.

Exclusion Criteria:

Individuals who meet any of these criteria are not eligible to continue as participants in Stage 2*:*

2. History of severe allergic reaction to any previous COVID-19 vaccines, to any component of any of the COVID-19 vaccines, or to PEG.

3. New diagnosis of malignancy that will require chemotherapy or immunotherapy, or ongoing treatment for a malignancy with chemotherapy or immunotherapy.

4. Active disease (per the Investigator's decision) resulting in inability to hold the IS therapy in the MMF/MPA or MTX arms of the study.

[redacted]

	a. The potential impact of temporarily holding medication for participants with a recent mild disease flare within 4 weeks should be carefully considered. 5. Active disease during the Stage 2 Screening period resulting in: a. An increase/addition of any IS medications, or b. A suggestion of MS relapse per the investigator. 6. Recent or current SARS-CoV-2 infection defined as: a. Documented SARS-CoV-2 infection in the past 30 days (from the day the participant is diagnosed by positive test to Stage 2 Screening). b. Positive result on a molecular COVID-19 test at Stage 2 Screening or Stage 2 Baseline/Week 0. 8. Inflammatory myocarditis/pericarditis following any COVID-19 vaccine doses. 11. Participants who received licensed or investigational monoclonal antibodies or plasma products directed against SARS-CoV-2 within 30 days of Stage 2 Screening. 13. Currently pregnant or breastfeeding. 14. Female participants who are planning a pregnancy during the course of the trial. 15. Hemoglobin (Hgb) <8.0 g/dL (80 g/L) 16. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study. 17. Other investigational chemical agent within 30 days or other investigational biologic agent within 8 weeks or 5 half-lives (whichever is longer) of Stage 2 Screening. 18. Concurrent treatment with cyclophosphamide, cladribine, alemtuzumab, or mitoxantrone. 19. Participants currently on any type of dialysis, or who have received a solid organ transplant. 20. Prisoners or participants who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness. 23. Participants with active systemic infections who have received systemic antimicrobials within the 14 days prior to Stage 2 Baseline/Week 0.
Inclusion/Exclusion Criteria – Pediatric Participants	**Inclusion Criteria:** Individuals who meet all of the following criteria are eligible for enrollment randomization/allocation as participants in the pediatric portion of the study:

1. Individuals 5-17 years of age that meet classification criteria for SLE, JIA, POMS, or JDM. Note: Juvenile idiopathic arthritis includes the following conditions: polyarticular JIA (both RF + and -), oligoarticular persistent and oligoarticular extended JIA, psoriatic arthritis, and enthesitis related JIA.
    a. Participants must meet the 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups [8], the International League of Associations for Rheumatology (ILAR) classification for JIA [4], the 2017 McDonald [6] criteria for MS, or the Bohan and Peter criteria or the 2017 EULAR/ACR classification criteria for JDM.
    b. If a participant has been diagnosed with more than one autoimmune disease, the participant will be assessed based on the disease that is selected for study entry.
2. Parents/guardians of pediatric participants must be willing and able to sign informed consent. Participants, ages 7-17, must be willing and able to sign assent.
3. Documented full COVID-19 vaccination (CDC card or documentation in medical records) that was completed at least 4 weeks prior and no more than 52 weeks prior to the Screening visit.
4. Negative or suboptimal serologic response to initial COVID-19 vaccine regimen, defined as an Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL at Screening visit.
    a. Initial COVID-19 vaccine regimen is defined as:
        i. 2 doses (as appropriate to age) of the Pfizer-BioNTech COVID-19 Vaccine

        The following vaccines have yet to receive EUA in pediatric populations. If EUA occurs for younger ages, the participants receiving age-appropriate regimens of the following COVID-19 vaccines may be enrolled into the study:

        ii. Moderna COVID-19 Vaccine
        iii. Janssen COVID-19 Vaccine
5. Must be currently taking one of the following IS medications with or without additional disease-related medications: MMF (minimum of 250 mg per day)/MPA (minimum of 360 mg per day), MTX (minimum of 5 mg per week), or B cell depleting agents within the past 18 months (such as rituximab, ocrelizumab, or ofatumumab).
    a. If taking MMF/MPA or MTX, the participant must have initiated therapy at least 8 weeks prior to randomization and be taking the same medications (regardless of dose) as at the time of the initial COVID-19 vaccine regimen. Note: Participants who withheld their IS medications around their initial vaccinations are eligible to participate.

b. If enrolling in the B cell depleting therapy cohort, participant must have received an anti-CD20 or an anti-CD19 B cell depleting therapy in the past 18 months.

6. No changes in background IS medications, including MMF/MPA or MTX, in the 8 weeks prior to Screening, excluding the following:
    a. HCQ,
    b. Intraarticular steroids,
    c. The addition of prednisone at ≤10mg per day or prednisone at any dose when given for ≤3 days, and
    d. Corticosteroid bursts for non-autoimmune disease-related conditions, such as asthma or COPD, are permitted

Exclusion Criteria:

Individuals who meet any of these criteria are not eligible for randomization/allocation as study participants*:*

1. Inability or unwillingness of a participant to give assent or of a parent/guardian to give written informed consent, or of either to comply with study protocol.
2. History of severe allergic reaction to the initial COVID-19 vaccine regimen, or any component of any of the COVID-19 vaccines, or to PEG.
3. New diagnosis of malignancy that will require chemotherapy or immunotherapy, or ongoing treatment for a malignancy with chemotherapy or immunotherapy.
4. Active disease (per the Investigator's decision) resulting in inability to hold the IS therapy in the MMF/MPA or MTX arms of the study.
    a. The potential impact of temporarily holding medication for participants with a recent mild disease flare within 4 weeks should be carefully considered.
5. Active disease during the Screening period resulting in:
    a. an increase/addition of any IS medications, or
    b. a suggestion of MS relapse per the investigator
6. Recent or current SARS-CoV-2 infection defined as:
    a. Documented SARS-CoV-2 infection in the past 30 days (from the day the participant is diagnosed by positive test to Screening).
    b. Positive result on a molecular COVID-19 test at Screening.
7. Receipt of a COVID-19 vaccine booster prior to Screening.
8. Inflammatory myocarditis/pericarditis following initial COVID-19 vaccine regimen.

9. Participants with active, ongoing chronic infections, including participants with evidence of:
    a. HIV.
    b. Hepatitis B as indicated by surface antigen.
    c. Hepatitis C as indicated by anti-hepatitis C antibody positivity; if a participant is Hepatitis C antibody positive, they will be eligible to participate in the study if he/she is negative for viral load at Screening.

    Note: Participants *are permitted to be on chronic prophylactic antimicrobial therapy.*
10. Participants with common variable immunodeficiency disease, as well as any participants currently receiving immune globulin replacement therapy.
11. Participants who received licensed or investigational monoclonal antibodies or plasma products directed against SARS-CoV-2 within 30 days of Screening.
12. Participants who have received any live vaccines within 2 months of the anticipated study vaccine dose or who will have need of a live vaccine at any time during the study.
13. Currently pregnant or breastfeeding (postmenarchal females must have a negative urine pregnancy test at Screening)
14. Hemoglobin (Hgb) <8.0 g/dL (80 g/L)
15. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
16. Other investigational chemical agent within 30 days or other investigational biologic agent within 8 weeks or 5 half-lives (whichever is longer) of Screening.
17. Concurrent treatment with cyclophosphamide.
18. Participants currently on any type of dialysis, or who have received a solid organ transplant.
19. Prisoners or participants who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be allowed to participant in this study.
20. Taking both MMF/MPA and MTX.
21. Other investigational B cell depleting therapy as part of a clinical trial within 18 months of Screening, unless drug assignment is known and the participant received an anti-CD20 or CD19 drug.
22. Participants with active systemic infections who have received systemic antimicrobials within the 14 days prior to Screening.

Study Stopping Rules	0BIf any of the events listed below occur, the DSMB chair will be notified, and a review of safety data will be performed to determine if enrollment in the study, randomization/allocation, and/or administration of investigational study medication should be halted. If two weeks has elapsed and the DSMB has not met, then no new participants will be consented, allocated or randomized until after the DSMB completes review of the safety data. **Adult Participants:** Any of the following adverse events in adult participants attributable to the vaccine will trigger an *ad hoc* DSMB Safety Review: • Death related to vaccine. • Life-threating adverse event (Grade 4) related to vaccine. • Permanent or severe disability related to vaccine. • Occurrence of a Grade 3 or higher, vaccine-related SAE of the same type in 3 or more of the study participants who have received a study treatment. *Note: Only SAEs occurring between Day 1 and the Week 24 study visit will* be counted. • Occurrence of severe flare or relapse after an additional homologous COVID-19 vaccine dose given at Stage 1, defined as within 12 weeks of the Stage Baseline/Week 0 visit (vaccination), in 3 of the first 10 participants or 30% thereafter, defined as follows. • Occurrence of severe flare or relapse after a subsequent alternative COVID-19 vaccine dose given at Stage 2, defined as within 12 weeks of the Stage 2 Baseline/Week 0 visit (vaccination), in 3 of the first 10 participants or 30% thereafter. **Pediatric Participants:** Any of the following adverse events in pediatric participants attributable to the vaccine will trigger an *ad hoc* DSMB Safety Review: • Death related to vaccine • Life-threatening AE (Grade 4) related to vaccine • Permanent or severe disability related to vaccine • Occurrence of a Grade 3 or higher, vaccine-related SAE of the same type in 3 or more of the study participants who have received a study treatment. Note: Only SAEs occurring between Day 1 and the Week 24 study visit will be counted. • Occurrence of severe flare or relapse, between Baseline/Week 0 (vaccination) and the Week 12 visit, in 3 of the first 10 participants or 30% thereafter.

4. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study:

- Categorical variables will be summarized using counts (n) and percents (%) and will be presented in the form n (%).
- Moment statistics including mean will be reported at 1 more significant digit than the precision of the original data. The standard deviation will be reported at 2 more significant digits than the precision of the original data. The level of precision may be modified on specific displays based on clinical judgement.
- Order statistics including median, min, and max will be reported to the same level of precision as the original observations. If any values are calculated to have more significant digits, then the value should be rounded so that it is the same level of precision as the original data.
- Following SAS default rules, the median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Test statistics including t and z test statistics will be reported to two decimal places.
- P-values will be reported to 3 decimal places if greater than 0.001; if less than 0.001, then they will be reported as '<0.001'. P-values and significant levels will be reported as 0.05 rather than .05. A p-value will be reported as "1.000" only if it is exactly 1.000 without rounding. A p-value will be reported as "0.000" only if it is exactly 0.000 without rounding.
- No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider the digit to the right of last significant digit; if <5 then round down, and if ≥5 then round up.
- In general, listings will be displayed by treatment arm and subject and will be sorted in the order that columns are displayed, starting with the first column on the left.
- All analyses will be performed using the SAS System version 9.4 or higher.

5. ANALYSIS SAMPLES

Analysis samples for ACV01 for each study stage (Stage 1, Stage 2) and age group (Adult, Pediatric) will be defined as follows:

- **Vaccinated population**: will be defined as all participants who are randomized or allocated and receive study vaccine in the study. For all endpoints, participants will be evaluated by the actual vaccine received. In Cohorts A and B, participants will be analyzed in subgroups defined by randomized assignment to continue or withhold IS medications in the primary analysis.
- **Per protocol populations**: will be defined as the subgroup of participants in the vaccinated population who adhere to the treatment plan for IS medications defined in Section 7.1.1 Protocol-mandated Medications and have no major protocol deviations or ineligible entry criteria that would impact the vaccine response assessment at Week 4.
- **Safety population**: will be defined as all participants who initiate the treatment plan for IS medications or receive an additional dose of vaccine.

6. STUDY SUBJECTS

6.1. Disposition of Subjects

The disposition of participants will be summarized in tables and listed for each study stage (Stage 1, Stage 2) and age group (Adult, Pediatric). A CONSORT diagram outlining the flow of participants in the study will also be created. The numbers and percentages of participants randomized/allocated, in each analysis sample, and receiving vaccine, as well as reasons for early termination from the study, will be presented. For participants who were randomized/allocated but did not receive an additional dose of vaccine, the reasons for not receiving vaccine will also be presented. For Stage 2 of the study, the numbers and percentages of participants who are newly recruited vs. rollovers from Stage 1 will be summarized. Study disposition will also be summarized by site.

6.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for all analysis samples by study arm. Characteristics to be summarized include:

- Age, race, ethnicity, sex, body weight at screening, height
- Disease type and duration
- Roche Elecsys® Anti-SARS-CoV-2 S result at screening; both as a continuous variable and categorical: negative (≤0.79 U/mL) vs. positive (>0.79 U/mL); additionally, categorized as ≤0.79 U/mL, >0.79 U/mL through 50 U/mL, >50 U/mL through 200 U/mL, >200 U/mL
- History of prior SARS-CoV-2 infection at Screening
- Time (in weeks) from previous vaccine series
- Additional IS medications
- Steroid dose
- For Stage 2: previous vaccine series
- Medication dose for or Cohort A: MMF or MPA and Cohort B: MTX
- For Cohort C and Cohort F: B cell depletion therapy:
    - Type of B cell depletion therapy
    - Time (in weeks) from last dose of b cell depletion therapy to vaccine.
    - CD19+ B cells

6.3. Prior and Concomitant Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary: WHO-Drug Global v2021-March. Medications will be reported on both the *Immunosuppressive Medication* and *Concomitant Medications* case report forms (CRFs).

The number and percentage of participants receiving IS medications will be presented overall and by medication class. Immunosuppressive medications will also be summarized by disease type. When reporting the number of subjects receiving the medication, a subject will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of subjects in the analysis population. Medications will also be listed.

The numbers and percentages of participants receiving the following concomitant medications will be presented overall and by medication class:

- SARS-CoV-2 vaccines or live vaccines (of any kind) administered outside of the study.
- Monoclonal antibodies administered for (a) pre-exposure prevention of COVID-19, (b) post-exposure prevention of COVID-19, or (c) treatment of COVID-19 infection.

6.4. Medical History

Analysis details will be provided in subsequent versions of the SAP.

7. STUDY OPERATIONS

7.1. Protocol Deviations

Protocol deviations will be listed by site with information such as date of deviation, category, description and reason for deviation, and corrective action taken. Protocol deviations will be summarized overall and by site in tabular format by type of deviation.

7.2. Randomization and Allocation

When employed in any population, randomization will be accomplished through a password-protected, web-based randomization system. The investigators, clinic personnel, and participants will not be blinded to randomized treatment assignments. Statistical and project staff at the Statistical and Clinical Coordinating Center (SACCC) and the DAIT Medical Monitor and Project Manager will be unblinded to individual treatment assignments as well. Laboratories performing assays for this protocol will be blinded to the identity and group assignment of biological materials to be studied.

7.2.1. Adult Stage 1

Participants who sign the informed consent form and meet all eligibility criteria for Stage 1 will be assigned to cohorts defined by IS medication and by the initial COVID-19 vaccine regimen received. Participants in Cohort C will be allocated to continuing to take their prescribed IS medications throughout the trial. Participants in Cohorts A and B will be randomized in a balanced fashion (1:1), within the cohorts defined by IS medication and initial COVID-19 vaccine regimen, to one of the available IS medication treatment plans (continue cohort-defining IS vs. withhold cohort-defining IS). Randomization will be performed using a permuted block design stratified by disease type.

A total of 60 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL will be randomized or allocated to each arm. In each arm, the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results ≤50 U/mL will be capped at 40 participants, and the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results >50 U/mL and ≤200 U/mL will be capped at 40 participants.

7.2.2. Adult Stage 2

Participants who have signed the informed consent form and meet all eligibility criteria for Stage 2 will be allocated to cohorts defined by IS medication and by the initial COVID-19 vaccine regimen received. Participants who received either the Moderna COVID-19 Vaccine or Pfizer-BioNTech COVID-19 Vaccine will be allocated to the Stage 2 Arm that corresponds to their choice of either the Janssen vector-based COVID-19 vaccine or the other mRNA COVID-19 vaccine. Participants who received the Janssen COVID-19 Vaccine will be allocated to the Stage 2 Arm that corresponds to the Moderna COVID-19 Vaccine. Participants in Cohort D will withhold their MMF/MPA, participants in Cohort E will withhold their MTX, and any participants in Cohort F (B cell depletion therapy) who are also taking MMF/MPA or MTX will withhold these medications. No randomization will be employed.

A total of 60 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL will be allocated to each arm. In each arm, the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results ≤50 U/mL will be capped at 40 participants, and the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results >50 U/mL and ≤200 U/mL will be capped at 40 participants.

7.2.3. Pediatric Population

Participants and their legal guardian(s) who sign the consent and assent forms, as appropriate to age, and meet all eligibility criteria for the pediatric portion of the trial will be assigned to cohorts defined by IS medication and by the initial COVID-19 vaccine regimen received. Participants in Cohort C will be allocated to continuing to take their prescribed IS medications throughout the trial. Participants in Cohorts A and B will be randomized in a balanced fashion (1:1), within the cohorts defined by IS medication and initial COVID-19 vaccine regimen, to one of the available IS medication treatment plans (continue IS vs. withhold IS). Randomization will be performed using a permuted block design stratified by disease type.

A total of 60 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL will be randomized or allocated to each arm. In each arm, the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results ≤50 U/mL will be capped at 40 participants, and the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results >50 U/mL and ≤200 U/mL will be capped at 40 participants.

7.3. Measures of Treatment Compliance

The number of participants who receive study vaccine will be summarized by arm.

In study arms that withhold IS medications around the time of vaccination, the total number of days, the number of days prior to vaccine, and the number of days post-vaccine that IS medications are withheld will be summarized.

[redacted]

8. ENDPOINT EVALUATION

8.1. Overview of Efficacy Analysis Methods

8.1.1. Multicenter Studies

Study participants will be recruited from 15-20 study sites for each of the adult and pediatric groups. Study data will be analyzed as a whole, and no formal accommodation for site-to-site variation will be made.

8.1.2. Assessment Time Windows

Additional details will be provided in subsequent versions of the SAP.

8.1.3. Timing of Analyses

The primary analysis will be evaluated independently within each arm (defined by age, cohort, vaccine, and IS treatment plan) in the vaccinated population, and will be conducted overall, in all participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL at the Screening visit, and in the subgroup of participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤50 U/mL at the Screening visit. Each analysis will occur after the evaluable participants assigned to that arm have completed the Week 4 study visit or are withdrawn from the study.

8.1.4. Multiple Comparisons/Multiplicity

The primary analysis will be evaluated independently within each arm, and p-values will not be adjusted for multiple comparisons.

All secondary analyses will be conducted in an exploratory fashion, with any p-values and confidence intervals presented as descriptive statistics with no adjustments for multiple comparisons.

8.2. Primary Endpoint

The primary endpoint of a protective antibody response will be the proportion of participants who reach the laboratory-defined threshold for the NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay at Week 4. The Wu-1 full-length spike protein will be used in determining a protective antibody response in the primary analysis; the RBD protein will be used in secondary analyses of antibody response; and N proteins will be used in supportive analyses as evidence of COVID infection.

8.2.1. Computation of the Primary Endpoint

The proportion of participants who reach the laboratory-defined threshold for the NIAID-VRC MSD 3 plex assay at Week 4 will be summarized by arm overall, in all participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL at the Screening visit, and in the subgroup of participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤50 U/mL at the Screening visit.

For concentrations that are below the Lower Limit of Detection (LLOD), numeric values equivalent to LLOD/2 are assigned before and for all descriptive reporting. Concentrations that are above the Upper Limit of Quantification are reported without adjustments.

Participants with missing Week 4 anti-COVID-19 antibody response data with a documented COVID infection prior to Week 4 will be considered as not having a protective antibody response. All other participants missing Week 4 anti-COVID-19 antibody response data will be considered to be missing-completely-at-random (MCAR).

8.2.2. Primary Analysis of the Primary Endpoint

The primary analysis will be evaluated independently within each arm (defined by stage, age, cohort, vaccine, and IS treatment plan) in the vaccinated population. The proportion of participants meeting a protective antibody response criteria will be reported in each arm with 90% Clopper-Pearson confidence intervals and analyzed using a one-sided exact test with alpha = 0.05 against the null hypothesis that the probability of achieving a protective immune response is ≤0.25. P-values will not be adjusted for multiple comparisons.

The primary analysis will be conducted in all participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL at the Screening visit, and in the subgroup of participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤50 U/mL at the Screening visit. Each analysis will occur after the evaluable participants assigned to that arm have completed the Week 4 study visit or are withdrawn from the study.

8.2.3. Sensitivity Analyses of the Primary Analysis

A sensitivity analysis will be performed on the per protocol population.

8.2.4. Secondary Analyses of the Primary Endpoint

Descriptive statistics will be used to summarize antibody response to the additional homologous vaccine dose on a continuous scale, including median, minimum, and maximum, interquartile range, geometric mean, CV of the geometric mean, and 95% confidence intervals. Summary statistics, including 25th percentile, mean, median, and 75th percentile, will be plotted for each visit by treatment arm. Geometric mean and CV of the geometric mean will be computed as follows:

Geometric mean = exp(mean on $\log_e$ scale).

%CV geometric mean = $\sqrt{\exp\left((SD\ on\ log_e\ scale)^2\right) - 1}\ x\ 100$

Primary and secondary analyses will be repeated for the RBD proteins to summarize antibody response to the additional homologous vaccine dose on a continuous scale. Supportive analyses will use descriptive statistics to summarize N protein levels as evidence of COVID infection.

In the final analysis, supportive analyses will also use a multivariable regression model on the entire vaccinated population in order to estimate the rates of vaccine response within and across arms (age group, cohort, vaccine, and IS treatment plan group) using the logistic link function, and including baseline covariates for disease type (SLE, RA, MS, SSc, and pemphigus in adults

and JIA, pediatric SLE, JDM, and POMS in pediatrics) and immune response to the initial COVID-19 vaccine regimen (anti-COVID-19 antibody negative or positive).

Estimates of the average antibody response and variance within and across cohorts will be obtained from a multivariate general linear regression model. Based on published data on the assays, it is anticipated that log-transformation of assay values will allow for Gaussian assumptions to hold, but alternative Box-Cox transformations of the data may be explored to stabilize the variance.

The primary and supportive analyses will also be replicated on the Per protocol population and using alternative strategies for missing data. Additional analysis details will be provided in subsequent versions of the SAP.

8.3. Secondary Endpoints

8.3.1. Seroconversion at Week 4

Seroconversion at Week 4, following additional doses of COVID-19 vaccine, will be assessed in the subgroup of participants in the vaccinated population that are anti-COVID-19 antibody negative at Week 0. Seroconversion will be assessed separately with (a) the NIAID-VRC MSD 3 plex assay and (b) the Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay.

The subgroup of participants that are anti-COVID-19 antibody negative at Week 0 will be defined as having a result less than or equal to the positive threshold value listed below at the Week 0/Baseline visit.

Seroconversion will be defined as a having a result greater than the positive threshold value listed below at the Week 4 visit. Seroconversion will be defined in a similar fashion for subsequent follow-up visits through Week 48 as well. Participants with missing anti-COVID-19 antibody response data will be considered to be MCAR.

The following positive thresholds will be used:

Assay	Test	Positive Threshold
NIAID-VRC MSD 3 plex	Wu-1 full-length spike	1,204.71 AU/mL
NIAID-VRC MSD 3 plex	RBD	517.86 AU/mL
Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay	COVID-19 Spike Domain Antibody	0.79 U/mL

The proportions who seroconvert within arms will be summarized using 95% Clopper-Pearson confidence intervals in preliminary analyses. In the final analysis, comparisons of rates of seroconversion across arms and subgroups will use a two-sample Binomial exact test with nominal two-sided alpha = 0.05.

Supportive analyses will evaluate seroconversion of N protein levels in the NIAID-VRC MSD 3 plex assay (Threshold = 9,779.62 AU/ml) as evidence of COVID infection.

8.3.2. Fold Increase in anti-COVID-19 Antibody Levels at Week 4

Fold increase in anti-COVID-19 antibody levels will be assessed for the subgroups of participants in the vaccinated population that are anti-COVID-19 antibody positive at Week 0 using separately (a) the NIAID-VRC MSD 3 plex assay and (b) the Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay.

The subgroup of participants that are anti-COVID-19 antibody positive at Week 0 will be defined as having a result greater than the positive threshold value listed below at the Week 0/Baseline visit.

The following positive thresholds will be used:

Assay	Test	Positive Threshold
NIAID-VRC MSD 3 plex	Wu-1 full-length spike	1,204.71 AU/mL
NIAID-VRC MSD 3 plex	RBD	517.86 AU/mL
Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay	COVID-19 Spike Domain Antibody	0.79 U/mL

Participants with missing anti-COVID-19 antibody response data will not be imputed.

Fold improvement for each assay will be defined as follows and will be defined in a similar fashion for subsequent follow-up visits through Week 48 as well:

$$\text{Fold improvement} = \frac{\text{anti-COVID-19 Antibody Response}_{\text{Week 4}}}{\text{anti-COVID-19 Antibody Response}_{\text{Baseline}}}$$

Descriptive statistics will be used to summarize fold increase in anti-COVID-19 antibody levels at Week 4, including median, minimum, and maximum, geometric mean, CV of the geometric mean, and 95% confidence intervals.

Supportive analyses will evaluate fold increase in N protein levels in the NIAID-VRC MSD 3 plex assay (Threshold = 9,779.62 AU/ml) as evidence of COVID infection.

8.3.3. Longitudinal Changes in anti-COVID-19 Antibody Responses

Longitudinal changes in anti-COVID-19 antibody responses will be analyzed from Week 0 to Weeks 4, 12, 24, 36, and 48 and will be summarized over time by study visit using descriptive statistics. This endpoint will not be evaluated in preliminary analyses. Additional analysis details will be provided in subsequent versions of the SAP.

8.3.4. Longitudinal Changes in Neutralization and Pseudo Neutralization Assays

Longitudinal changes in neutralization and pseudo neutralization assays will be assessed from Week 0 to Weeks 4, 12, 24, 36, and 48 and will be summarized by study visit using descriptive statistics. This endpoint will not be evaluated in preliminary analyses. Additional analysis details will be provided in subsequent versions of the SAP.

8.3.5. Changes in Diseases Activity using CGI-C

Changes in disease activity after receipt of additional doses of COVID-19 vaccine will be assessed as measured by the CGI-C. In preliminary analyses, the change in CGI-C from Week 0 to Week 4 will be summarized in each study population using descriptive statistics. Analysis details will be provided in subsequent versions of the SAP.

8.3.6. Changes in Diseases Activity using PGA

Changes in disease activity after receipt of additional doses of COVID-19 vaccine will be assessed as measured by the PGA. This endpoint will not be evaluated in preliminary analyses. Analysis details will be provided in subsequent versions of the SAP.

8.3.7. Changes in Disease Activity as Measured by Disease-Specific Assessments

Longitudinal changes in disease activity will not be evaluated in preliminary analyses. The proportion of participants who meet the definition for disease-specific flares by Week 4 will be summarized in preliminary analyses.

8.3.7.1. H-SLEDAI and SELENA-SLEDAI Flare Index

Disease activity for SLE participants will be measured by the (H-SLEDAI and SELENA-SLEDAI Flare Index for SLE. Analysis details will be provided in subsequent versions of the SAP.

8.3.7.2. DAS28-CRP

Disease activity for RA participants will be measured by the DAS28-CRP for RA. Analysis details will be provided in subsequent versions of the SAP.

8.3.7.3. Flare assessment for SSc

Disease activity for SSc participants will be measured using the flare assessment for SSc (including patient-reported flare assessment). Analysis details will be provided in subsequent versions of the SAP.

8.3.7.4. PDAI

Disease activity for pemphigus participants will be measured using the PDAI for pemphigus. Analysis details will be provided in subsequent versions of the SAP.

8.3.7.5. Physician-assessed relapse for MS

Disease activity for MS participants will be measured using the physician-assessed relapse for MS. Analysis details will be provided in subsequent versions of the SAP.

[redacted]

8.3.7.6. JADAS-10

Disease activity for JIA participants will be measured using the JADAS-10 for polyarthritis, enthesitis related to JIA, oligoarthritis, and psoriatic arthritis. Analysis details will be provided in subsequent versions of the SAP.

8.3.7.7. PASI

Disease activity for JIA participants will also be measured using the PASI for psoriatic arthritis. Analysis details will be provided in subsequent versions of the SAP.

8.3.7.8. SLEDAI-2K and Childhood-onset SLE Criteria for Global Flare

Disease activity for pediatric SLE will be measured using the SLEDAI-2K and Childhood-onset SLE Criteria for Global Flare [1] for pediatric SLE. Analysis details will be provided in subsequent versions of the SAP.

8.3.7.9. CMAS

Disease activity for JDM will be measured using the CMAS for JDM. Analysis details will be provided in subsequent versions of the SAP.

8.3.7.10. JDM DAS

Disease activity for JDM will be measured using the JDM DAS for JDM. Analysis details will be provided in subsequent versions of the SAP.

8.3.7.11. Physician-assessed relapse for POMS

Disease activity for POMS will be measured using the physician-assessed relapse for MS for POMS. Analysis details will be provided in subsequent versions of the SAP.

8.3.8. Changes in Patient-reported Outcomes

8.3.8.1. PROMIS 29

Changes in the PROMIS 29 will be assessed in the adult population. Analysis details will be provided in subsequent versions of the SAP.

8.3.8.2. PedsQL

Changes in the PedsQL will be assessed in the pediatric population. Analysis details will be provided in subsequent versions of the SAP.

8.3.8.3. PtGA

Changes in the PtGA will be assessed in the adult and pediatric populations. Analysis details will be provided in subsequent versions of the SAP.

8.3.8.4. PGI-C

Changes in the PGI-C will be assessed in the adult and pediatric populations. Analysis details will be provided in subsequent versions of the SAP.

8.4. Other Endpoints

Analysis details will be provided in subsequent versions of the SAP.

8.5. Examination of Subgroups

Analysis details will be provided in subsequent versions of the SAP.

[redacted]

9. SAFETY EVALUATION

9.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 5 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site.

9.2. Adverse Events

For this study, solicited AEs are predefined local and systemic events for which the participants will be specifically questioned, and which will be noted by these participants. An AE is considered "unsolicited" when it is collected through an open-ended question and is not specified as a solicited AE. An MAAE is defined as a hospitalization, emergency room visit, or an otherwise unscheduled visit to or from medical personnel for any reason; and considered related to study vaccine. A NOCMC is defined as any new ICD diagnosis (per current International Statistical Classification of Diseases and Related Health Problems) that is applied to the study participant during the course of the study, after receipt of the vaccine, that is expected to continue for at least 3 months and requires continued health care intervention. An AE is considered "serious" if, in the view of either the investigator or Sponsor (DAIT/NIAID), it results in any of the following outcomes: death, life-threatening, hospitalization, persistent or significant incapacity, congenital anomaly or birth defect, or is considered an important medical event. See protocol Section 12.2 for more details on AE definitions.

The collection periods and reporting for AEs are as follows:

- Solicited AEs (all grades) will be collected from Day 1 (vaccine administration) through 7 days post study vaccination using the MyOwnMed vaccine reaction diary.
    - Investigators are responsible for reporting solicited AEs in the electronic data capture system (EDC) in the following special cases:
        - If a solicited AE is also an SAE or MAAE must be entered in EDC to capture additional information about the event.
        - If a solicited AE, previously reported in MyOwnMed, is found to be ongoing at Day 7 (post vaccination), the solicited AE must be entered in EDC so it can be followed to resolution, with or without sequelae.
        - Unsolicited AEs (unrelated to reactogenicity) that are entered into the Vaccine Reaction Diary and are also identified during the Week 1 visit are to be reported in EDC
- Unsolicited AEs will be collected as follows and reported in EDC:
    - Any unsolicited AEs that are Grade 3 or higher will be collected from randomization/allocation through vaccination administration.
    - All unsolicited AEs (all grades) will be collected from Day 1 through Day 28.

  - Any flares of a secondary autoimmune disease will be reported as an unsolicited AE (all grades) and will be collected from Day 1 through the end of the participant's study participation.

- SAEs, MAAEs, and NOCMCs will be collected from Day 1 through the end of the participant's study participation, regardless of the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) grade, and reported in EDC.
- COVID-19 diagnoses (all grades) confirmed by molecular COVID-19 testing will be collected from Day 1 through the end of the participant's study participation and reported in EDC.

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 24.0).

Grading criteria are defined as follows:

- Solicited AEs: Participants will grade solicited AEs using a 0-3 (no symptom, mild, moderate, and severe) participant symptom rating scale as outlined in the Vaccine Reaction Diary instructions.
- Allergic reactions: The investigator will grade severity of systemic allergic reactions on a scale of 1 to 5 according to criteria set forth in the Consortium of Food Allergy Research (CoFAR) Grading Scale modified for use in adults only (See Protocol Section 20.2 CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0).
- Liver Function Abnormalities: Liver function abnormalities will be graded using alternative criteria, which are based on the NCI-CTCAE version 4.0, and are defined relative to the upper limit of normal (ULN) as defined in Protocol Section 12.3.1 *Grading Criteria*.
- All other events: The study site will grade the severity of all other AEs experienced by the study participants according to the criteria set forth in the NCI-CTCAE version 5.0 as deemed appropriate for the 5 adult autoimmune diseases and 4 pediatric autoimmune diseases, and use of background IS medications of interest in this trial.

If the start date of an AE is incomplete or missing, it will be assumed to have occurred on or after the first dose of investigational product, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment

If a subject experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of subjects experiencing the events, a subject will only be counted once if they experience at least one event within the particular SOC or preferred term. Percentages will be based on the number of subjects in the safety population. The tabular summaries will be sorted by descending frequency by SOC and preferred term (PT) in the treatment group arm.

Summary tables will be reported for treatment emergent adverse events unless otherwise indicated. An overall summary table will include:

- Total number of events, and number and percentage of subjects experiencing at least one event for the following categories:
  - AEs
  - SAEs
  - AEs related to study vaccine
  - AE leading to study vaccine discontinuation
  - AE leading to death
  - MAAEs
  - NOCMCs
  - SARS-CoV-2 infections
  - Solicited Adverse Events
  - AEs by severity

AEs classified by MedDRA SOC and preferred term will be summarized for each treatment group for each of the following:

- All AEs
- All Related AEs
- All SAEs
- All AEs leading to study drug discontinuation
- AEs by severity
- AEs by relationship to study drug

Listings of all AEs, MAAEs, and NOCMCs will be provided for the safety population.

9.2.1. Solicited Adverse Events

Participants are provided access to an electronic 7-day diary to aid in recording solicited local and systemic reactions to the vaccine, as well as symptoms of a potential allergic reaction, unsolicited AEs, and concomitant medications, including start and stop dates. The diary includes instructions for participants on how to take an oral temperature and how to measure injection site reactions. A paper copy of the diary may be provided for participants who do not have a device to access the electronic diary or as a backup collection tool. A member of the study team will review the information in the diary with the participant, including how to use and access the electronic diary, and will record adverse events on the CRF page as appropriate based on review of the diary.

Summary displays based on the maximum severity of solicited symptoms reported over the 7-day period will be presented in tables and graphically by study arm. Summaries of the diary entries over the 7-day period will also be presented by study arm.

9.3. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Serious AEs classified by MedDRA SOC and PT will be summarized for each treatment group and overall for each of the following:

- All serious AEs

[redacted]

- Serious AEs by severity
- Serious AEs by relationship to study drug

Rules for counting SAEs in summary tables are the same as those applied to AEs reported in Section 9.3.

All SAEs and SAEs resulting in death will be presented in data listings for subjects in the safety population. A separate display listing will be created for all deaths summarizing the time to death and cause of death.

9.4. Clinical Laboratory Evaluation

Analysis details will be provided in subsequent versions of the SAP.

9.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

9.5.1. Vital Signs

Analysis details will be provided in subsequent versions of the SAP.

9.5.2. Physical Examinations

Analysis details will be provided in subsequent versions of the SAP.

9.5.3. Other Safety Measures

Analysis details will be provided in subsequent versions of the SAP.

[redacted]

10. OTHER ANALYSES

Analysis details will be provided in subsequent versions of the SAP.

[redacted]

11. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the NIAID DSMB. The NIAID Autoimmune DSMB is chartered to review safety data and to make recommendations to NIAID regarding continuation, termination, or modification of the study. The DSMB will review the safety data within 6 months after the first participant is treated, and an initial review should occur no later than after this first arm has closed to enrollment and all participants completed 4 weeks of follow up. Following the initial review, the DSMB will review the safety data approximately every 6 months during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs, SAEs, MAAEs, NOCMCs, and increases in autoimmune disease activity (flares/relapses).

The DSMB chair will be informed of any IND Safety Reports in a timely manner in order to make a recommendation for an ad hoc full board review and /or protocol suspension. In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the NIAID medical monitor or protocol co-chairs to warrant review, or when an event occurs that could contribute to a stopping rule.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

1. The protocol specifies that the analysis of primary and secondary endpoints will be evaluated independently within each arm (defined by age, cohort, vaccine, and IS treatment plan) and conducted in (1) all participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL at the Screening visit, and (2) in the subgroup of participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤50 U/mL at the Screening visit. Each analysis of the primary endpoint will occur after the evaluable participants assigned to that arm and subgroup have completed the Week 4 study visit or are withdrawn from the study. For the purposes of this document, we refer to analyses at this timepoint as preliminary, and a final analysis will occur once all participants have completed or withdrawn from the study.

   If at the point of each preliminary analysis, a definition of a protective antibody response using a laboratory-defined threshold for responses within the NIAID-VRC MSD 3 plex assay is unavailable, the primary analysis of primary and secondary endpoints will not be performed, and only the secondary analysis to summarize antibody response on a continuous scale using descriptive statistics will be performed.

2. Protocol Section 13.4.4, *Analyses of Secondary and Other Endpoint(s)*, notes "The incidence of seroconversion following additional vaccine doses of COVID-19 vaccine will be evaluated in the subgroups of participants that are anti-COVID-19 antibody negative at baseline using separately, (a) NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N) assay with thresholds <1204.7 and 517.9 proteins AU/mL, respectively, and (b) the Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay with a threshold <0.80 U/mL." Seroconversion will not be assessed using the N proteins test as it is a measure of natural infection rather than vaccine response.

13. REFERENCES

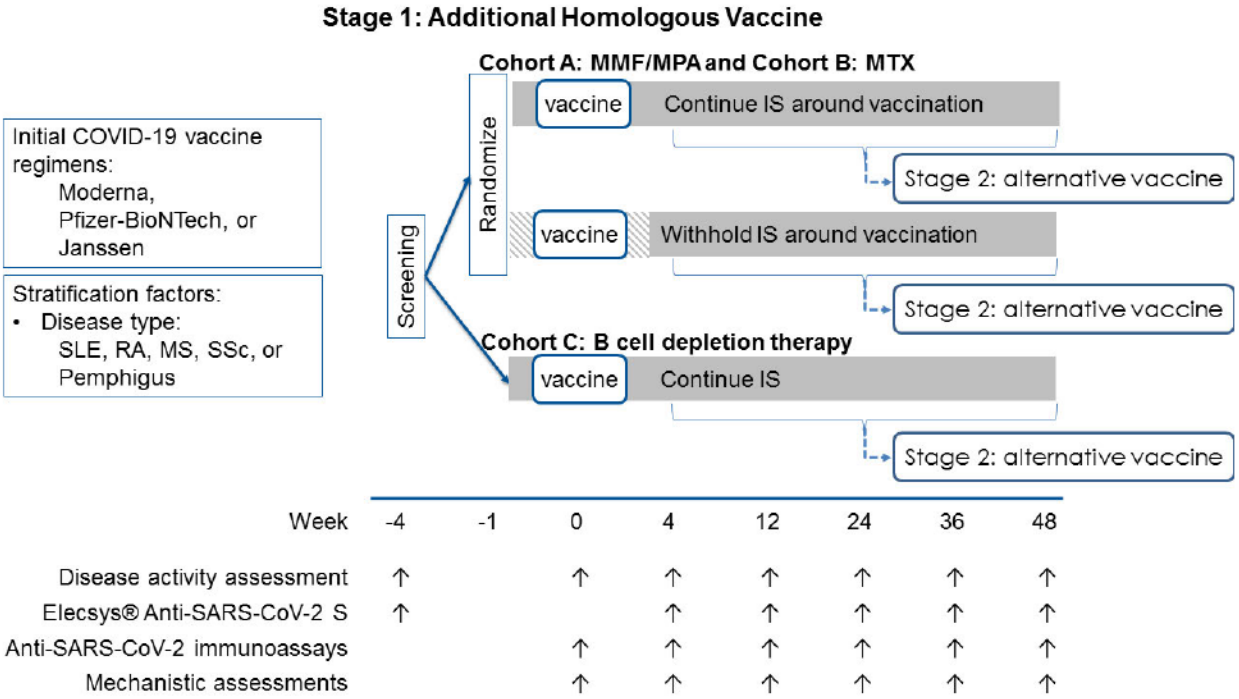
NA.

[redacted]

14. APPENDIX

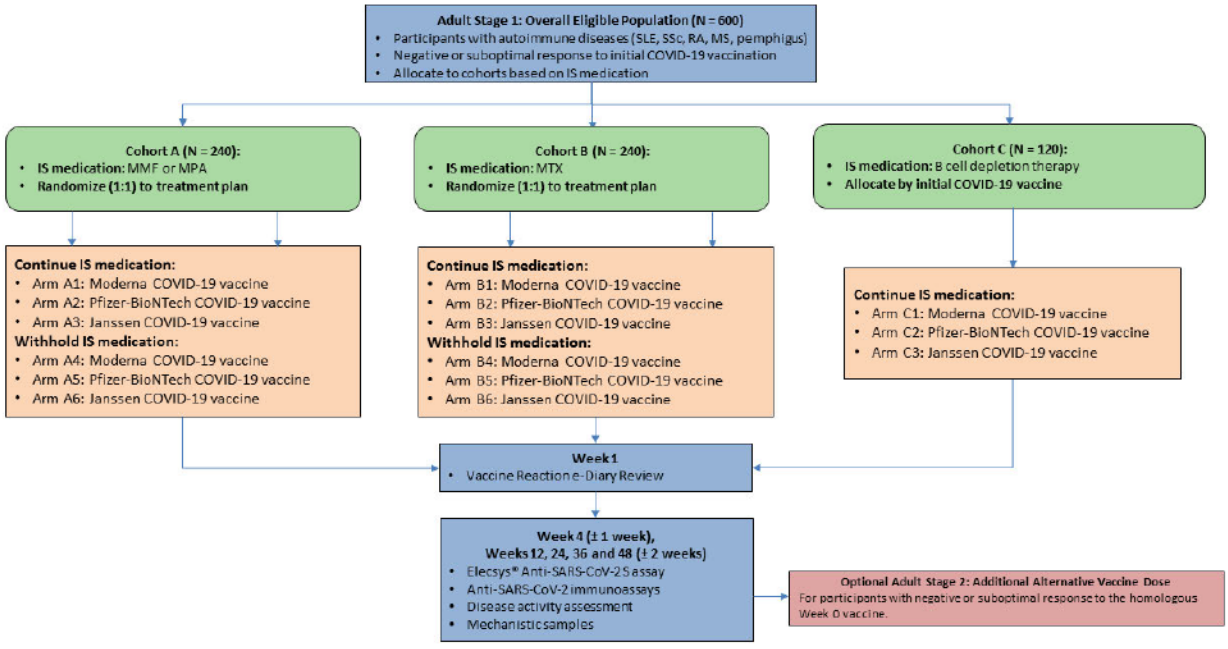
14.1. Study Flow Chart

Figure 1. Participant Flow Diagram for Adult Stage 1



IS = immunosuppressive medications; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MS = multiple sclerosis; MTX = methotrexate; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis

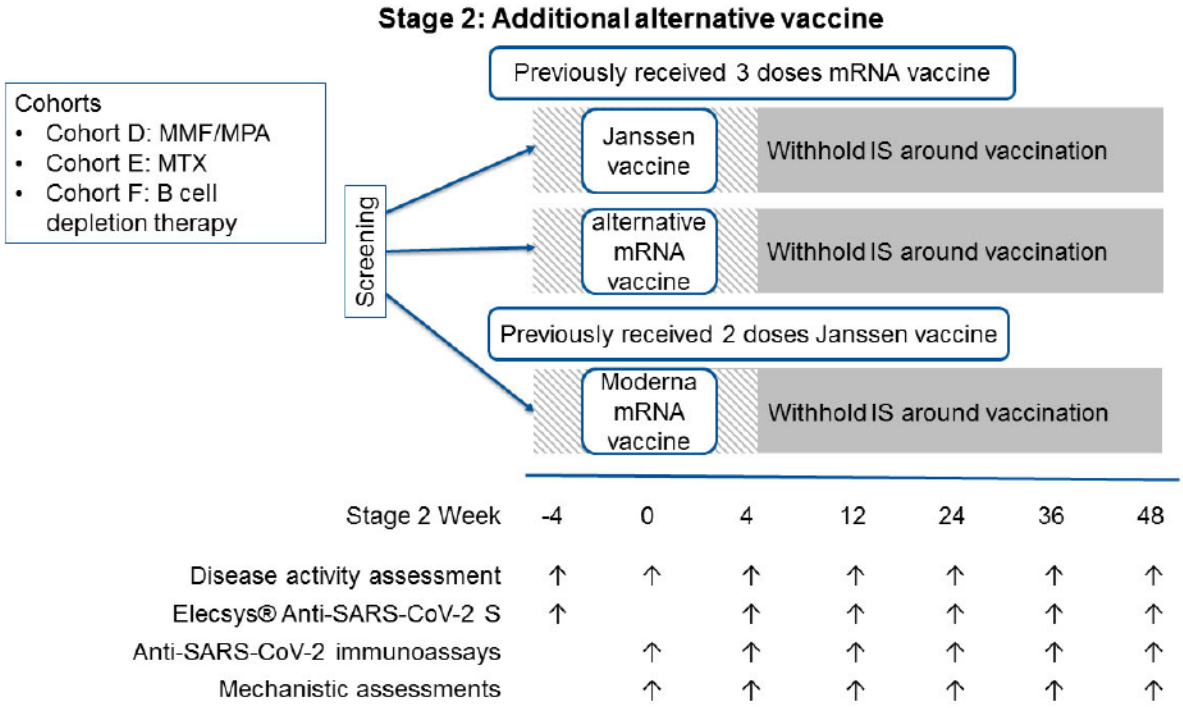
Figure 2. Study Flow for Adult Stage 1



IS = immunosuppressive medication

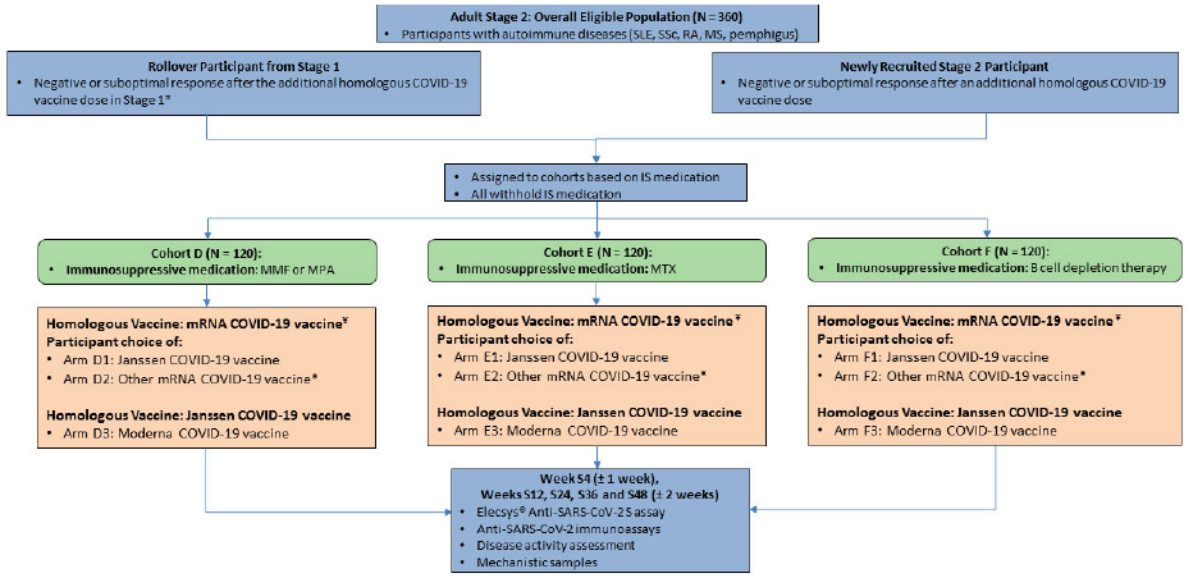
[redacted]

Figure 3. Participant Flow Diagram for Adult Stage 2



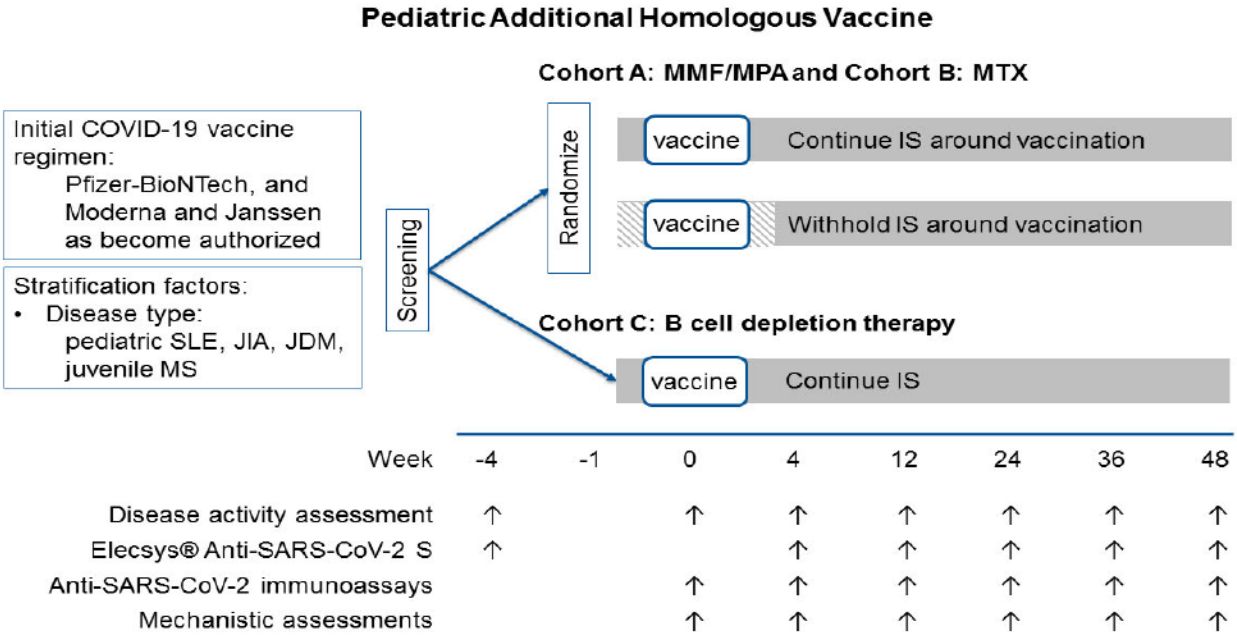
IS = immunosuppressive medications; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MS = multiple sclerosis; MTX = methotrexate; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis

Figure 4. Study Flow for Adult Stage 2



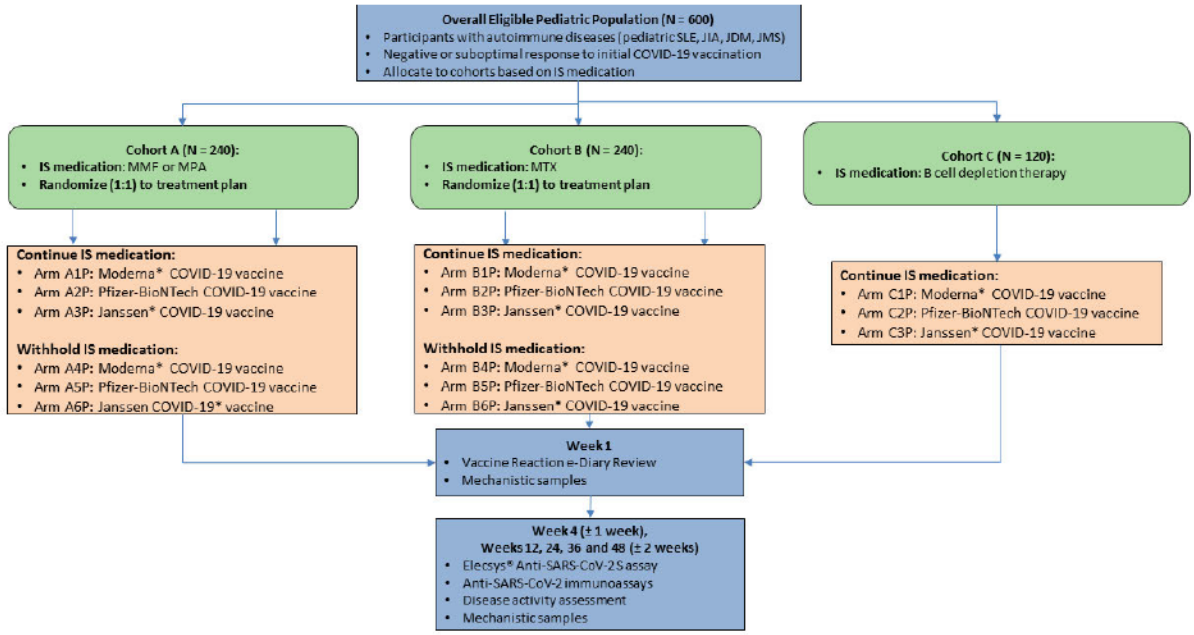
IS = immunosuppressive; MMF = mycophenolate mofetil; MPA = mycophenolic acid
* Additional homologous vaccine dose is defined as a third dose of the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, or a second dose of the Janssen COVID-19 Vaccine.
¥ Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, whichever was not received for the initial regimen and additional homologous dose.

Figure 5. Participant Flow Diagram for Pediatric Participants



IS = immunosuppressive medications; JDM = juvenile dermatomyositis; JIA = juvenile idiopathic arthritis; POMS = pediatric-onset multiple sclerosis; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MTX = methotrexate; SLE = systemic lupus erythematosus

Figure 6. Study Flow Diagram for Pediatric Participants



IS = immunosuppressive medication
*Treatment arm will be opened for enrollment when authorization or approval of these vaccines is granted for the pediatric population(s).

14.2. Schedule of Events

See protocol Section 20.1, *Schedules of Events*, for more details.

[redacted]

15. ATTACHMENTS

NA.

[redacted]

ACKNOWLEDGEMENT AND SIGNATURE SHEET

Approved:	Approved:
[redacted] Principal Biostatistician	[redacted] Principal Statistical Scientist
Signature and Date	Signature and Date
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Judith James, MD, PhD Protocol Co-Chair	Meggan Mackay, MD, MS Protocol Co-Chair
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DocuSigned by: Judith James Signer Name: Judith James Signing Reason: I approve this document Signing Time: 16-Mar-2022 | 2:14:19 PM EDT 01C3137148084E71A42CA9A2B9E2A802	DocuSigned by: Meggan Mackay Signer Name: Meggan Mackay Signing Reason: I approve this document Signing Time: 17-Mar-2022 | 12:45:25 PM EDT 2464E5AFBC954423A68E6337D94689E5

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Approved:	Approved:
Natasha Mckerran Ruth, MD Protocol Co-Chair	Tracey Wright, MD Protocol Co-Chair
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Signer Events	Signature	Timestamp
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Meggan Mackay mmackay@northwell.edu MD Security Level: Email, Account Authentication (Required)	Meggan Mackay Signature Adoption: Pre-selected Style Signature ID: 2464E5AF-BC95-4423-A68E-6337D94689E5 Using IP Address: 69.27.229.130 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/16/2022 12:21:14 PM Resent: 3/17/2022 12:35:07 PM Viewed: 3/17/2022 12:45:00 PM Signed: 3/17/2022 12:45:45 PM
Electronic Record and Signature Disclosure: Accepted: 12/3/2021 10:28:55 AM ID: a9f3ff03-031d-4ff7-930e-d639278d301f		
Natasha Mckerran Ruth ruthn@musc.edu Security Level: Email, Account Authentication (Required)	DocuSigned by: Natasha Mckerran Ruth Signer Name: Natasha Mckerran Ruth Signing Reason: I approve this document Signing Time: 16-Mar-2022 | 1:42:52 PM EDT CDE71CEB76764AB4BD23AF440A9CEC2E Signature Adoption: Pre-selected Style Signature ID: CDE71CEB-7676-4AB4-BD23-AF440A9CEC2E Using IP Address: 76.23.125.236 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/16/2022 12:21:15 PM Viewed: 3/16/2022 1:42:20 PM Signed: 3/16/2022 1:43:02 PM
Electronic Record and Signature Disclosure: Accepted: 3/16/2022 1:42:20 PM ID: e799f907-edc7-4fb5-a123-9d974d4c468c		

Signer Events	Signature	Timestamp
Stacy Ardoin stacy.ardoin@nationwidechildrens.org Security Level: Email, Account Authentication (Required)	Stacy Ardoin Signature Adoption: Pre-selected Style Signature ID: 6695E7A3-F92C-4B16-94DA-1BFC14F98F68 Using IP Address: 69.24.144.18 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/16/2022 12:21:15 PM Resent: 3/17/2022 12:35:07 PM Viewed: 3/20/2022 12:24:02 PM Signed: 3/20/2022 12:24:50 PM
Electronic Record and Signature Disclosure: Accepted: 3/20/2022 12:24:02 PM ID: 1e81ac1d-6965-4b21-a997-a3300d5a3f9d		
Tracey B. Wright, MD tracey.wright@utsouthwestern.edu Security Level: Email, Account Authentication (Required)	DocuSigned by: Tracey B. Wright, MD Signer Name: Tracey B. Wright, MD Signing Reason: I approve this document Signing Time: 16-Mar-2022 | 1:13:41 PM EDT 7EFC6823A13941DCA79C34B24E62EFE5 Signature Adoption: Pre-selected Style Signature ID: 7EFC6823-A139-41DC-A79C-34B24E62EFE5 Using IP Address: 129.112.109.53 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/16/2022 12:21:16 PM Viewed: 3/16/2022 1:12:08 PM Signed: 3/16/2022 1:13:45 PM
Electronic Record and Signature Disclosure: Accepted: 3/16/2022 1:12:08 PM ID: d91b8622-a08f-4f76-9280-e78d8d642f28		
Virginia Pascual vip2021@med.cornell.edu MD Security Level: Email, Account Authentication (Required)	DocuSigned by: Virginia Pascual Signer Name: Virginia Pascual Signing Reason: I approve this document Signing Time: 16-Mar-2022 | 12:23:47 PM EDT 600745241B59467B82ED5ED47F214D2D Signature Adoption: Pre-selected Style Signature ID: 60074524-1B59-467B-82ED-5ED47F214D2D Using IP Address: 96.224.244.124 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/16/2022 12:21:16 PM Viewed: 3/16/2022 12:23:00 PM Signed: 3/16/2022 12:23:56 PM
Electronic Record and Signature Disclosure: Accepted: 3/16/2022 12:23:00 PM ID: ee99b2af-8977-42f1-8228-adeffb1ca95e		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	3/16/2022 12:21:16 PM
Certified Delivered	Security Checked	3/16/2022 12:23:00 PM
Signing Complete	Security Checked	3/16/2022 12:23:56 PM
Completed	Security Checked	9/23/2022 3:45:26 PM
Payment Events	**Status**	**Timestamps**
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ACKNOWLEDGEMENT AND SIGNATURE SHEET

Approved:	Approved:
[redacted]	[redacted]
Signature and Date	Signature and Date

Approved:	Approved:
[redacted]	[redacted]
Signature and Date	Signature and Date

Approved:	Approved:
Judith James, MD, PhD Protocol Co-Chair	Meggan Mackay, MD, MS Protocol Co-Chair
Signature and Date	Signature and Date

[redacted]

Approved:	**Approved:**
Dinesh Khanna, MBBS, MSC Protocol Co-Chair	Amit Bar-Or, MD, FRCPC Protocol Co-Chair
Signature and Date	Signature and Date
	 March 16 2022

Approved:	**Approved:**
Virginia Pascual, MD Protocol Co-Chair	Stacy Ardoin, MD Protocol Co-Chair
Signature and Date	Signature and Date

Approved:	**Approved:**
Natasha Mckerran Ruth, MD Protocol Co-Chair	Tracey Wright, MD Protocol Co-Chair
Signature and Date	Signature and Date

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