ACV01

BOOSTER EFFECTS WITH AUTOIMMUNE TREATMENTS IN PATIENTS WITH POOR RESPONSE TO INITIAL COVID-19 VACCINE

COVID-19 BOOSTER VACCINE IN AUTOIMMUNE DISEASE NON-RESPONDERS

[v7.0/13DEC2022]

IND# *27528*

IND SPONSOR: The National Institute of Allergy and Infectious Diseases (NIAID)

NIAID Funding Mechanism: Autoimmunity Centers of Excellence (ACE) Cooperative Agreement

Investigational Agents: Pfizer-BioNTech COVID-19 Vaccine (BNT162b2), Moderna COVID-19 Vaccine (mRNA-1273), Sanofi-GSK COVID-19 Vaccine (Monovalent [B.1.351] CoV2 preS dTM-AS03), and Janssen (AD26.COV2.S.) COVID-19 Vaccine

Network: Autoimmunity Centers of Excellence

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SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: ACV01	**Version Number/Date:** V7.0 13DEC2022
Protocol Title: **Booster** effects with autoimmune treatments in participants with poor response to initial COVID-19 Vaccine	
IND Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
Return Signed Form to: *The original signature page must be kept for your records. Return an electronic PDF copy of the signed signature page (*as described below) to the* [redacted]	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) document titled *Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

*[*The site Principal Investigator should sign and date at the indicated location below. A written signature/date is acceptable (e.g., scanned and sent via email as a PDF version). An electronic signature is also acceptable (e.g., sent via email as a PDF version).]*

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Version History

Protocol Version	Protocol Date	Summary of Revisions
1.0	09Jul2021	Initial version
2.0	06Dec2021	• Administrative updates, expansion of Elecsys® Anti-SARS-CoV-2 S specimen collection to Weeks 12 – 48/Early Termination. • Extension of entry criteria time limits to account for expanded enrollment period. • Vaccine risks updated to match current EUA factsheets for healthcare providers. • Additional information added regarding the collection of solicited adverse events.
3.0	04Jan2022	• Addition of adult Stage 2 (with heterologous additional vaccine dose) and pediatric population (with homologous additional vaccine dose). • Elecsys® Anti-SARS-CoV-2 S entry criterion increased from a result ≤ 50 U/mL to 200 U/mL for adult stage 1, adult Stage 2, and pediatric study eligibility. Treatment arm sample size increased to 60/treatment arm in response to this change. • Vaccine risks updated to match current EUA factsheets for healthcare providers. • Closure of Janssen COVID-19 vaccine treatment arms in adult Stage 1. • Prohibited medications section updated to include guidance for use of monoclonal antibodies for pre-exposure prophylaxis.

4.0	29Jul2022	• Administrative updates
		• Pediatric Updates
		  ○ Removal of MMT8 from pediatric schedule of events and Section 8.
		  ○ Note added to Exclusion #10:
		  ▪ Note: Participants on IVIG therapeutically may enter the study provided they have sufficiently quiet disease that they can withhold their IVIG from 8 weeks prior to the Screening visit through 4 weeks after vaccination.
		• Expansion of adult Stage 2 criteria to allow participants who have received more than 3 doses of the same mRNA vaccine and a mixture of mRNA vaccine doses to enter the study.
		• Addition of the Sanofi-GSK protein-based COVID-19 Vaccine to the list of available vaccine options for adult Stage 2 (with associated background, risks, investigational agent, and safety information).
		• Removal of Janssen as an alternative dose option for adult Stage 2.
		• Study design revised to allow participants who received an alternative mRNA vaccine dose and have a Roche Elecsys result ≤200 U/mL at a post-Baseline visit to re-enter Stage 2 and restart the Stage 2 schedule of events.
		• Vaccine formulation information updated to reflect the current EUA factsheets and FDA Approvals.
		• Section 7.3, *Prohibited Medications*, updated to separate COVID-19 vaccine and other vaccine guidance.

5.0	19Aug2022	• Administrative updates
		• Updates to both pediatric and adult populations:
		  ○ Revisions to entry criteria, study risks, vaccine eligibility criteria, safety events, and study stopping rules, and related to pericarditis/myocarditis.
		  ○ Revisions to vaccine formulation information to match current EUAs/FDA approvals.
		• Pediatric Updates
		  ○ Addition of pediatric Stage 2 (with heterologous additional vaccine dose)
		  ○ Expansion of entry criteria to allow enrollment of 2-4 year olds.
		  ○ Addition of Moderna COVID-19 vaccine investigational agent information for 2 -17 year olds and Pfizer COVID-19 vaccine investigational agent information for 2-4 year olds.
		  ○ Removal of infectious disease testing (HIV, Hepatitis B, and Hepatitis C).

6.0	11Nov2022	• Administrative updates • Protocol updated to note the closure of all Adult Stage 1 treatment arms on 15 August 2022. • Addition of Omicron bivalent vaccines for use as additional doses and discontinuation of use of monovalent vaccines where applicable. • Revisions to vaccine formulation information to match current EUAs/FDA approval. • Extension of Roche Elecsys entry criterion to include participants with a low vaccine response. • Extension of treatment arm sample size from 60 participants per treatment arm to 80 participants per treatment arm.
7.0	13Dec2022	• Addition of Omicron bivalent vaccine for use in young pediatric participants and discontinuation of use of monovalent vaccines.

Protocol Synopsis

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). **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 suboptimal response (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL) 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 pediatric participants with autoimmune diseases requiring IS medications who have a low immune response (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result >200 U/ml and ≤2500 U/mL) after an initial COVID-19 vaccine regimen may demonstrate enhanced immune response after receiving an additional dose of an additional homologous COVID-19 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 hypothesize that adult and pediatric participants with autoimmune diseases requiring IS medications who continue to have a suboptimal response after an initial COVID-19 vaccine regimen plus additional vaccine doses may demonstrate enhanced immune response after receiving an additional dose of an alternative COVID-19 vaccine. • We hypothesize that adult and pediatric participants with autoimmune diseases requiring IS medications who have a low immune response after an initial COVID-19 vaccine regimen plus additional vaccine doses 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 and 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 assess the immune response following an additional homologous COVID-19 vaccine dose in the subgroup of participants that had a low immune response following a previous COVID-19 vaccine dose. • 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 and pediatric): • To determine the proportions of participants with a negative serologic or suboptimal response to a previous COVID-19 vaccine administration 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 assess the immune response following a subsequent alternative vaccine dose in the subgroup of participants that had a low immune response following a previous COVID-19 vaccine dose. • 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 a previous 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 (adult and pediatric)** • 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 (BCDT). • 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 suboptimal responses (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL) or a low immune

	response (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result >200 U/ml and ≤2500 U/mL) to their previous doses of 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 BCDT 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 COVID-19 vaccine as their original vaccine series. The trial initially enrolled participants who were vaccinated with the Pfizer-BioNTech COVID-19 Vaccine, the Moderna COVID-19 Vaccine, and the Janssen COVID-19 Vaccine. ***Update:*** Arms to receive an additional homologous vaccine dose after an initial Janssen COVID 19 Vaccine were closed to enrollment after the CDC updated its recommendations to express a clinical preference for individuals to receive an mRNA COVID-19 vaccine over the Janssen COVID-19 vaccine. All Adult Stage 1 treatment arms were closed to enrollment on 15 August 2022. Participants in Cohorts A and B will be randomized into 2 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 960 adult study participants (up to 80 per arm) with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL after previous COVID-19 vaccine administration (at least 3 doses of mRNA vaccine(s) or 2 doses of the Janssen COVID-19 Vaccine). Participants will be eligible to receive a dose of an alternative COVID-19 vaccine. Participants may have received their previous COVID-19 vaccine prior to enrollment in the study (“newly recruited participant”), or they may have received their previous COVID-19 vaccine as a study participant and then (re-) enter into Stage 2 (“rollover participant”).

	Participants can also roll over into Stage 2 via two pathways: • Stage 1 participant rolls over to Stage 2 • Stage 2 participant rolls over to a different Stage 2 treatment arm 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 BCDT 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. Originally, participants who previously received 3 total doses of a single mRNA vaccine (Moderna COVID-19 Vaccine OR Pfizer-BioNTech COVID-19 Vaccine) received 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 received the Moderna COVID-19 Vaccine. ***Update**:* Beginning with v4.0 of the protocol, this trial will not utilize the Janssen vector-based COVID-19 vaccine. Participants who previously received 3 total doses of a single mRNA vaccine will receive their choice of an alternative mRNA COVID-19 vaccine or the Sanofi-GSK protein-based COVID-19 vaccine. Participants who previously received 4 or more doses of a single mRNA vaccine or 3 or more doses of a mixture mRNA vaccines (Moderna COVID-19 Vaccine AND Pfizer-BioNTech COVID-19 Vaccine, in any order or combination) will receive the Sanofi-GSK protein-based COVID-19 vaccine. Beginning with v6.0 of the protocol, bivalent versions of the mRNA vaccines, Moderna and Pfizer-BioNTech COVID-19 vaccines, replaced original monovalent versions. 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 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 is newly recruited to the study for entry into Stage 2 may be on study for up to a maximum of 13 months. A participant who enters Stage 2 after a serologic negative, suboptimal, or low immune response to their Stage 1 vaccine dose may be on study for up to a maximum of 26 months. Rollover participants will discontinue follow-up as part of Stage 1 upon rollover into Stage 2. A participant who rolls over to a different Stage 2 treatment arm 2 after a serologic negative, suboptimal, or low immune response to another Stage 2 vaccine dose may be on study for up to a maximum of 38 months. **Pediatric Population** **Pediatric Stage 1:**

	The pediatric portion of this trial will enroll up to a maximum of 800 participants (2-17 years of age) with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL after receiving an initial COVID-19 vaccine regimen (up to 80 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 1 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 BCDT 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. Based on FDA EUA status, pediatric participants were initially eligible to receive the Pfizer-BioNTech COVID-19 Vaccine only. ***Update:*** Beginning with v6.0 of the protocol, bivalent versions of the mRNA vaccines, Moderna and Pfizer-BioNTech COVID-19 vaccines, replaced original monovalent versions. Participants in Cohorts A and B will be randomized into 2 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. **Pediatric Stage 2:** Stage 2 of this trial will include up to a maximum of 480 pediatric study participants (up to 80 per arm) with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL after previous COVID-19 vaccine administration (an age-appropriate EUA-authorized or FDA-approved initial COVID-19 vaccine regimen plus 1 additional dose of the same vaccine as shown in Table 8). All participants (2-17 years of age) who previously received doses of the Pfizer-BioNTech COVID-19 Vaccine are eligible to receive an age-appropriate dose of the Moderna COVID-19 Vaccine. Participants 12 through 17 years of age who previously received doses of the Moderna COVID-19 vaccine are eligible to receive an age-appropriate dose of the Pfizer-BioNTech COVID-19 Vaccine. Participants will be eligible to receive a dose of an alternative COVID-19 vaccine. Participants may have received their previous COVID-19 vaccine as a study participant and then enter into Stage 2 (“rollover participant”), or they

	may have received their previous COVID-19 vaccine 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 (± other rheumatic disease medications, including biologics)
	  ○ Participants who are taking MMF or MPA (without additional B cell depleting medications or MTX) will be placed in this cohort.
	• Cohort E: Receipt of MTX (± other rheumatic disease medications, including biologics)
	  ○ Participants who are taking MTX (without additional B cell depleting medications or MMF/ MPA) will be placed in this cohort.
	• Cohort F: Receipt of B cell depletion therapy within the past 18 months (± other rheumatic disease medications)
	  ○ Participants taking B cell depletion medications, regardless of whether they are also taking MMF or MTX, will be placed in this cohort.
	
	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 age-appropriate doses of a single mRNA vaccine (Moderna COVID-19 Vaccine OR Pfizer-BioNTech COVID-19 Vaccine, as noted above) will receive the other mRNA COVID-19 vaccine. Table 8 describes the age-appropriate qualifying COVID-19 vaccine regimen for participation in Pediatric Stage 2.
	
	Update: Beginning with v6.0 of the protocol, bivalent versions of the mRNA vaccines, Moderna and Pfizer-BioNTech COVID-19 vaccines, replaced original monovalent versions.
	
	Participants in Cohorts D and E will withhold their cohort-defining IS medications before and after the alternative vaccine dose per protocol instructions (see Section 7.1.1 Protocol-mandated Medications).
	
	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 instruction (see Section 7.1.1 Protocol-mandated Medications).
	
	All potential treatment arms for Pediatric Stage 2 are detailed in Table 9.
	
	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. Participant and study flow diagrams for Stage 2 are provided in Figure 7 and Figure 8, respectively.
	
	A participant who enters Stage 2 after a serologic negative, suboptimal, or low immune response to their Stage 1 vaccine dose may be on study for up to a maximum of 26 months. Rollover participants will discontinue follow-up as part of Stage 1 upon rollover into Stage 2. 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. **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 suboptimal or low immune 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 suboptimal or low immune response 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 COVID-19 vaccines 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:
    - Adult population disease assessments:
        - 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
        - Disease Activity Score 28 using C-reactive protein (DAS28-CRP) for RA
        - Flare assessment for SSc (including patient reported flare assessment)
        - Pemphigus Disease Area Index (PDAI) for pemphigus
        - Physician-assessed relapse for MS
    - Pediatric population disease assessments:
        - JIA:
            - JADAS10 for polyarthritis, enthesitis related to JIA, oligoarthritis, and psoriatic arthritis
            - Psoriasis Area and Severity Index (PASI) for psoriatic arthritis
        - SLEDAI-2K and Childhood-onset SLE Criteria for Global Flare [1] for pediatric SLE
        - Childhood Myositis Assessment Scale (CMAS) and JDM Disease Activity Score (DAS) for JDM
        - 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	The Adult Stage 1 portion of this trial will enroll up to a maximum of 900 participants. The Pediatric Stage 1 portion will enroll up to a maximum of 800 participants. The Adult Stage 2 portion of the trial will enroll up to a maximum of 960 participants. The Pediatric Stage 2 portion will enroll up to a maximum of 480 participants. In Adult Stage 2 and Pediatric Stages 1 and 2, a total of 80 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL randomized or allocated to each arm. In each arm, the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results ≤200 U/mL will be capped at 40 participants, and the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results >200 U/mL and ≤2500 U/mL will be capped at 40 participants.
Study Duration	Study duration for Adult Stage 1, Adult Stage 2 newly recruited, Pediatric Stage 1, or Pediatric Stage 2 newly recruited participant: 13 months Study duration for Adult Stage 2 or Pediatric Stage 2 participant rolling over from Stage 1: maximum of 26 months Study duration for Adult Stage 2 participant re-entering Stage 2: maximum of 38 months
Treatment Description	All participants will receive at least 1 dose of the following: • mRNA COVID-19 vaccine: Moderna OR • mRNA COVID-19 vaccine: Pfizer-BioNTech OR • vector-based COVID-19 vaccine: Janssen (Protocol v1.0-v3.0) • protein-based COVID-19 vaccine: Sanofi-GSK (Adult Stage 2 only)

	Participants who qualify may rollover from Stage 1 to Stage 2 to receive an alternative vaccine dose. Adult participants who qualify may re-enter Stage 2 to receive the protein-based COVID-19 vaccine (Sanofi-GSK).
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 BCDT cohort, the participant must have received an anti-CD20 or an anti-CD19 BCDT in the past 18 months. 7. No changes in background IS medications, including MMF/MPA or MTX, in the 4 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 BCDT 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 Adult 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 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 a previous COVID-19 vaccine administration 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, or a low immune response defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 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 doses of the Pfizer-BioNTech COVID-19 Vaccine b. 3 doses of the Moderna COVID-19 Vaccine c. 2 doses of the Janssen COVID-19 Vaccine d. 4 or more doses of a single mRNA vaccine (Pfizer-BioNTech COVID-19 Vaccine OR Moderna COVID-19 Vaccine) e. 3 or more doses of a mixture of mRNA vaccines (Pfizer-BioNTech COVID-19 Vaccine OR 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, 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 BCDT cohort, the participant must have received an anti-CD20 or an anti-CD19 BCDT 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 Adult 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 the COVID-19 vaccine, or to any component of the COVID-19 vaccine, that is to be administered in Stage 2, including polysorbate for participants receiving the Sanofi-GSK COVID-19 Vaccine, 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 a mixture of Janssen COVID-19 vaccines and mRNA COVID-19 vaccines (in any order or combination) prior to Stage 2 Screening.
8. Inflammatory myocarditis/pericarditis within 6 weeks of 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 BCDT 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 were previously enrolled in Adult Stage 1 or Adult Stage 2 will have met some inclusion and exclusion criteria at that time. Only a subset of

	the criteria for (re-)entering Adult Stage 2 will be assessed in rollover participants at the time of screening for Stage 2. Individuals who meet all of the following criteria are eligible to (re-)enter Adult Stage 2: 4. Received an additional COVID-19 vaccine dose that was completed at least 4 weeks prior and no more than 48 weeks prior to the Stage 2 vaccination. 5. Negative or suboptimal serologic response to a previous COVID-19 vaccine administration 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, or a low immune response defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 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 doses of the Pfizer-BioNTech COVID-19 Vaccine b. 3 doses of the Moderna COVID-19 Vaccine c. 2 doses of the Janssen COVID-19 Vaccine d. 4 doses of a combination of mRNA vaccines (i.e., Pfizer-BioNTech COVID-19 Vaccine, 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 7.5 mg 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 BCDT cohort, the participant must have received an anti-CD20 or an anti-CD19 BCDT 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 (re-)enter Adult Stage 2*:* 2. History of severe allergic reaction to the COVID-19 vaccine, or to any component of the COVID-19 vaccine, that is to be administered in Stage 2, including polysorbate for participants receiving the Sanofi-GSK COVID-19 Vaccine, 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 or Stage 2 Baseline/Week 0. 8. Inflammatory myocarditis/pericarditis within 6 weeks of 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 for Pediatric Stage 1	**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 2-17 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 and participants ages 14 – 17 must be willing and able to sign informed consent. Participants, ages 7-13, must be willing and able to sign assent. 3. Documented EUA-authorized or FDA-approved COVID-19 doses (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 EUA-authorized or FDA-approved COVID-19 vaccine doses, defined as an Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL, or a low immune response defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 U/mL, within 4 weeks of the Stage 1 Baseline/Week 0 visit Initial COVID-19 vaccine regimen is defined as: i. Pfizer-BioNTech COVID-19 Vaccine (2 through 4 years of age): 3 age-appropriate doses

ii. Pfizer-BioNTech COVID-19 Vaccine (5 through 17 years of age): 2 age-appropriate doses

iii. Moderna COVID-19 Vaccine (2 through 17 years of age): 2 age-appropriate doses.

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 BCDT cohort, participant must have received an anti-CD20 or an anti-CD19 BCDT 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 <0.15mg/kg/dose 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 participants in the pediatric portion of the study*:*

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 within 6 weeks of any COVID-19 vaccine doses. 9. Participants with active, ongoing chronic infections. *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. *Note: Participants on IVIG therapeutically may enter the study provided they have sufficiently quiet disease that they can withhold their IVIG from 8 weeks prior to the Screening visit through 4 weeks after vaccination.* 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 BCDT 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.
Inclusion/Exclusion Criteria – Pediatric Stage 2 Newly Recruited Participants	**Inclusion Criteria:** Individuals who meet all of the following criteria are eligible for enrollment as participants in Pediatric Stage 2: 1. Individuals 2-17 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 all pediatric participants and participants ages 14 – 17 must be willing and able to sign informed consent. Participants ages 7-13 must be willing and able to sign assent. 3. Documented full COVID-19 vaccination (CDC card or documentation in medical records). 4. Received an additional 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 homologous doses of 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, or a low immune response defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 U/mL, within 4 weeks of the Stage 2 Baseline/Week 0 visit. Initial COVID-19 vaccine regimen is defined as:

a. Pfizer-BioNTech COVID-19 Vaccine (2 through 5 years of age): 4 full, age-appropriate doses of the Pfizer-BioNTech COVID-19 Vaccine

b. Pfizer-BioNTech COVID-19 Vaccine (5 through 17 years old): 3 full, age-appropriate doses of the Pfizer-BioNTech COVID-19 Vaccine

Note: Participants who are 5 years old and previously received the Pfizer-BioNTech COVID-19 Vaccine may have received either age-appropriate regimen. See Section 3.1.2.2, Pediatric Stage 2, *for additional details.*

c. Moderna COVID-19 Vaccine (12 through 17 years of age): 3 full, age-appropriate 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 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 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 BCDT cohort, participant must have received an anti-CD20 or an anti-CD19 BCDT in the past 18 months.
7. No changes in background IS medications, including MMF/MPA or MTX, in the 4 weeks prior to Screening, excluding the following:
    a. HCQ,
    b. Intraarticular steroids,
    c. The addition of prednisone at <0.15mg/kg/dose 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 enrollment as participants in Pediatric Stage 2:

1. Inability or unwillingness of a participant to give assent or consent; 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 vaccine, that is to be administered in Stage 2, 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 an additional heterologous COVID-19 vaccine dose prior to Stage 2 Screening, i.e., a participant cannot have received a mixture of mRNA vaccines. 8. Inflammatory myocarditis/pericarditis within 6 weeks of any COVID-19 vaccine doses. 9. Participants with active, ongoing chronic infections. *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. *Note: Participants on IVIG therapeutically may enter the study provided they have sufficiently quiet disease that they can withhold their IVIG from 8 weeks prior to the Screening visit through 4 weeks after vaccination.* 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 BCDT 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.
Inclusion/Exclusion Criteria – Pediatric Stage 2 Rollover Participants	**Inclusion Criteria:** Individuals who meet all of the following criteria are eligible for enrollment as participants in Pediatric Stage 2: 4. Received an additional COVID-19 vaccine dose that was completed at least 4 weeks prior and no more than 48 weeks prior to the Stage 2 vaccination. 5. Negative or suboptimal serologic response to a previous COVID-19 vaccine administration 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, or a low immune response defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 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. Pfizer-BioNTech COVID-19 Vaccine (2 through 5 years of age): 4 full, age-appropriate doses of the Pfizer-BioNTech COVID-19 Vaccine b. Pfizer-BioNTech COVID-19 Vaccine (5 through 17 years old): 3 full, age-appropriate doses of the Pfizer-BioNTech COVID-19 Vaccine *Note: Participants who are 5 years old and previously received the Pfizer-BioNTech COVID-19 Vaccine may have received either age-appropriate regimen. See*

	Section 3.1.2.2, Pediatric Stage 2, *for additional details.* c. Moderna COVID-19 Vaccine (12 through 17 years of age): 3 full, age-appropriate 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 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 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 BCDT cohort, participant must have received an anti-CD20 or an anti-CD19 BCDT 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, excluding the following: a. HCQ, b. Intraarticular steroids, c. The addition of prednisone at <0.15mg/kg/dose 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 enrollment as participants in Pediatric Stage 2: 2. History of severe allergic reaction to the initial COVID-19 vaccine regimen, or any component of any of the COVID-19 vaccine, that is to be administered in Stage 2, 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 or Stage 2 Baseline/Week 0. 8. Inflammatory myocarditis/pericarditis within 6 weeks of 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 Screening. 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 Stage 2 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. 22. Participants with active systemic infections who have received systemic antimicrobials within the 14 days prior to Stage 2 Baseline/Week 0.

Study Stopping Rules	If any of the events listed below occur, other than myocarditis/pericarditis, 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. For any NCI-CTCAE Grade 2 or higher myocarditis or pericarditis that occurs within 6 weeks of vaccine administration, the DSMB chair be notified of the event within 3 business days from when the AESI was reported to DAIT/NIAID (see Section 12.5.2). The DSMB chair will adjudicate whether an expedited, ad hoc safety review by the full DSMB is required. **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 within 24 weeks of a Day 1 visit will be counted.* • Occurrence of a Grade 2 or higher myocarditis or pericarditis within 6 weeks of vaccine administration. *Note: the DSMB chair will be notified within 3 business from when the AESI is reported to DAIT/NIAID.* • 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. • 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 a Grade 2 or higher myocarditis or pericarditis within 6 weeks of vaccine administration. *Note: the DSMB chair will be notified within 3 business days from when the AESI is reported to DAIT/NIAID.* • 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.

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Glossary of Abbreviations

ACE	Autoimmunity Centers of Excellence
ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCDT	B-cell depletion therapy
CAP	College of American Pathologists
CAPA	Corrective and Preventative Action
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CI	confidence interval
CK	creatine kinase
CMAS	Childhood Myositis Assessment Scale
CMP	comprehensive metabolic panel
CoFAR	Consortium of Food Allergy Research
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CSVT	cerebral sinus venous thrombosis
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score 28 using C-reactive protein
DMG	dimyristoyl glycerol
DSMB	Data and Safety Monitoring Board
DSPC	1,2,-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate

EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FSS	Functional Systems Score
GBS	Guillain Barré Syndrome
GCP	Good Clinical Practice
H-SLEDAI	Hybrid Systemic Lupus Erythematosus Disease Activity Index
HCQ	hydroxycholoroquine
Hgb	hemoglobin
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IgG	immunoglobulin G
ILAR	International League of Associations for Rheumatology
IND	Investigational New Drug
IP-10	interferon gamma-inducible protein 10
IRB	Institutional Review Board
IS	immunosuppressive
JADAS	Juvenile Arthritis Disease Activity Score
JAK	Janus kinase
JDM	juvenile dermatomyositis
JIA	juvenile idiopathic arthritis
MAAE	medically attended adverse event
MMF	mycophenolate mofetil
MOP	Manual of Procedures
MPA	mycophenolic acid
mRNA	messenger ribonucleic acid
modRNA	nucleoside-modified messenger RNA
MS	multiple sclerosis
MTX	methotrexate
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health

NOCMC	new onset chronic medical condition
OMRF	Oklahoma Medical Research Foundation
PASI	Psoriasis Area and Severity Index
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
PDAI	Pemphigus Disease Area Index
PedsQL	Pediatric Quality of Life Inventory™
PEG	polyethylene glycol
PGI-C	Patient Global Impression of Change
PtGA	Patient's Global Assessment
PGA	Physician Global Assessment
PI	[Site] Principal Investigator
pIMD	potential immune-mediated diseases
POMS	pediatric-onset multiple sclerosis
PROMIS	Participant-Reported Outcomes Measurement Information System
RA	rheumatoid arthritis
RBD	receptor binding domain
S	pre-fusion stabilized spike glycoprotein
SACCC	Statistical and Clinical Coordinating Center
SAE	serious adverse event
SAR	suspected adverse reaction
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
SLICC	Systemic Lupus International Collaborating Clinics
SSc	systemic sclerosis
SUSAR	serious unexpected suspected adverse reaction
TNF	tumor necrosis factor
TTS	thrombosis with thrombocytopenia syndrome
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VAERS	Vaccine Adverse Event Reporting System
VP	viral particles

VRC	Vaccine Research Center
WBC	white blood cell
WHO	World Health Organization

1. Background and Rationale

1.1 Background and Scientific Rationale

Autoimmune disease afflicts up to 1 in 12 Americans and disproportionately afflicts the minority communities most severely impacted by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic. For example, systemic lupus erythematosus (SLE) is a top 10 medical cause of death in African American and Hispanic women between the ages of 15 and 45 [9]. Many of these autoimmune diseases have higher rates of co-morbidities associated with increased severe COVID-19 disease and death, such as obesity, hypertension, and cardiovascular disease. These co-morbidities may result from underlying disease processes or a requirement for immunosuppressive (IS) medications including prednisone, anti-metabolite drugs, or B-cell targeting therapies [10, 11]. Increased disease severity and death rates from COVID-19 in systemic autoimmune disease patients have been reported [12]. Whether this increased risk of severe SARS-CoV-2 infection is attributable to underlying autoimmune disease, background IS medication, or both is unknown. Data is scarce but some studies have associated mycophenolate mofetil (MMF), rituximab, and corticosteroid use with increased risk of poor outcomes [13]. For example, in a French cohort of 1,090 rheumatic and autoimmune disease patients, severe disease was more frequent after adjusting for potential confounding factors (effect size 3.26; 95% confidence interval [CI] 1.66-6.40, p = 0.0006) with rituximab use. Furthermore, more patients died in the rituximab group (21%) than in the patients not taking rituximab (7%) [14], although it may be that patients on rituximab have more severe autoimmune disease with underlying organ damage. Autoimmune disease patients on IS medications harbor higher viral loads of SARS-CoV-2 and have prolonged viral shedding, potentially serving as ongoing sources of community infection. Unfortunately, based upon their underlying medical conditions, immunomodulatory medications, and co-morbid health conditions, very few autoimmune disease patients were studied in the COVID-19 vaccine trials even though they may be some of the patients who most need protection (category 1b for vaccines based upon the National Academy of Medicine report [15]).

Early case reports show that a significant number of individuals taking IS medications respond poorly or not at all to COVID-19 vaccination. Approximately 26% of 123 chronic inflammatory rheumatic disease patients had undetectable SARS-CoV-2 receptor binding domain (RBD) antibody response (Roche Elecsys® enzyme immunoassay) 3 weeks after their first messenger ribonucleic acid (mRNA) vaccine dose. Following the second dose of an mRNA vaccine in this cohort, significant improvement was seen with only 6% of 404 patients having persistent undetectable SARS-CoV-2 RBD antibody [16]. However, those taking MMF or rituximab were at much higher risk of not mounting a detectable response or having a very low SARS-CoV-2 RBD antibody response [17]. Another report has demonstrated diminished overall serologic response in 133 adults with chronic inflammatory diseases particularly in those treated with B-cell depletion, glucocorticoids, or antimetabolites including methotrexate [18]. In another preliminary study of 113 autoimmune disease patients after receiving both doses of mRNA vaccine, a 3-fold lesser response in anti-S immunoglobulin G (IgG) titers (p = 0.009) and COVID-19 neutralization (p <0.0001) was observed in patients compared to immunocompetent controls. Again, diminished responses were most pronounced in patients taking B cell depletion therapies (BCDTs), corticosteroids, Janus kinase (JAK) inhibitors, and methotrexate (MTX) [18]. A smaller study of autoimmune disease patients (which excluded patients on rituximab or MMF based upon concerns about non-response) [19], showed that all 26 patients made antibodies after vaccination; however, on average, antibody levels were less than half of levels in healthy control patients. Particular IS medications that may impact autoimmune disease patient immune responses to vaccination (including B cell depletion, MMF, and calcineurin inhibitors) are also commonly used in transplant recipients, other inflammatory diseases, and specific malignancies and have been associated with poor vaccine response. A study of SARS-CoV-2 vaccination in Multiple Sclerosis (MS) patients undergoing treatment with anti-CD20 confirmed that serologic responses were substantially attenuated (or undetectable), while T-cell responses (including spike-protein antigen-specific T-cell responses) were relatively intact [20]. Among 436 transplant recipients, only 76 (17%) mounted a detectable antibody response 3 weeks after receiving the first dose of mRNA vaccine, and poor response was associated with use of anti-metabolite therapy (mycophenolate and azathioprine, p = 0.001) [21] as well as older age.

Recent studies have indicated that administration of a vaccine booster dose increases antibody response in solid organ transplant recipients. A recent report describes the humoral response in a group of 101 solid organ transplant recipients who were given three doses of the Pfizer–BioNTech COVID-19 Vaccine [22]. Among the patients who were seronegative before the third dose, 44% were seropositive at 4 weeks after the third dose, and no serious adverse events (SAEs) or

acute rejection episodes were reported. A case series has also been reported describing antibody responses and vaccine reactions in recipients of solid organ transplants who had a suboptimal response to standard COVID-19 vaccination and subsequently received a third dose of vaccine (Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, or Janssen COVID-19 Vaccine). The antibody titers increased after the third dose in one third of patients who had negative antibody titers and in all patients who had low-positive antibody titers [23]. These data suggest that administration of a third dose of COVID-19 vaccine to immunocompromised individuals improves the immunogenicity of the vaccine with no safety signals identified.

Vaccination of autoimmune disease patients may also present efficacy challenges relative to non-autoimmune patients for disease-intrinsic reasons. Autoimmune disease patients are more likely to have pre-existing antibodies against RNA, RNA-binding proteins, DNA, and adenovirus strains, several of which could potentially limit the effectiveness of the related vaccines. In addition, based upon their underlying immune dysregulation, autoimmune disease patients may be stimulated to enhanced autoreactivity instead of toward protective vaccine responses.

In addition, recently published data, consistent with the investigators experience, show that many autoimmune disease patients have significant vaccine hesitancy, based upon concerns regarding efficacy and perceived unknown safety in patients like them. In a survey of 1,531 participants, including 1,266 autoimmune disease patients enriched in SLE and rheumatoid arthritis (RA) patients, only 53% of patients reported being vaccinated or reported they would be vaccinated [24]. Within the autoimmune disease communities and patient groups, concerns are raised regarding whether a mRNA-based vaccine will be safe in those autoimmune diseases where RNA-protein complexes drive autoimmune disease pathogenesis, and whether the early infrequent autoimmune/autoinflammatory and thrombotic adverse events (AEs) that paused adenoviral-based vaccines could be harbingers of heightened concerns about autoimmune disease SAEs in individuals genetically pre-disposed to autoimmune disorders.

Vaccines using more established technologies, such as adjuvanted protein-based vaccines, may be more palatable to vaccine-hesitant individuals. Sanofi-GlaxoSmithKline (GSK) has an AS03-adjuvanted COVID-19 vaccine currently under development. While this vaccine has not been used in patients with autoimmune disease, the safety of protein or polysaccharide subunit vaccines with adjuvant, including commonly used vaccines for Hepatitis B, Pneumococcus, meningococcus, Haemophilus influenzae, and varicella zoster is well-established in this population [25]. Of note, an increased risk of narcolepsy, particularly in Sweden, was observed after an influenza vaccination campaign with Pandemrix (an AS03-adjuvanted H1N1 pandemic influenza vaccine) in 2009-2010. A similar risk of narcolepsy was not identified in other countries with AS03- or MF59-adjuvanted H1N1 pandemic influenza vaccines except for Taiwan where the incidence increased after wild-type H1N1 virus circulated in the country [26]. An EMA report in 2016 concluded that: “Based on the evidence generated so far, a hypothesis that takes into account the potential role of antigen is more likely to explain the increased risk of narcolepsy observed with Pandemrix than hypotheses that are based on a direct role for the AS03 adjuvant” [27].

Additional knowledge about vaccination approaches to optimize efficacy and minimize AEs is critical to understand and to communicate to autoimmune disease patients, as they could greatly benefit from COVID-19 vaccination.

1.2 Clinical Trial Design and Rationale

1.2.1 Initial Trial Design - Additional Homologous Vaccine Dose

This clinical trial was initially designed to assess antibody responses to an additional homologous COVID-19 vaccine dose and identify methods for improving COVID-19 vaccine responses in patients with 1 of 5 autoimmune diseases. The diseases included in the trial (SLE, RA, MS, pemphigus, and systemic sclerosis [SSc]) were chosen based on prevalence rates, use of background medications of interest, and/or availability of pre-existing cohorts among the current Autoimmune Centers of Excellence (ACE) associated institutions. The medications of interest, MMF/ mycophenolic acid (MPA), MTX, and B cell depleting drugs, are used commonly in these patient populations and have been associated with poor vaccine response as described above. Only autoimmune disease patients with a negative or suboptimal serologic response to the initial COVID-19 vaccine regimen will be included in this clinical trial. Using the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, Ruddy et al [17] demonstrated that while many patients with autoimmune diseases have apparently robust antibody to COVID-19 vaccines (median response >250 U/ml) that some, particularly in that study those treated with mycophenolate and B cell depletion, have poor responses (8 U/ml and <0.4 U/ml, respectively).

Data observations presented in the paper suggest that using 50 U/ml is a reasonable threshold for defining a subgroup of patients who may benefit the most from an additional dose. This threshold is the same as chosen for the companion National Institute of Allergy and Infectious Disease (NIAID)-supported study in solid organ transplantation (COVID19-TB-02). Additional studies in healthy populations have shown average responses to primary vaccination ranging from 2,079 U/ml to 4,435 U/ml, and the reported ranges of immune response were all >250 U/ml [28-30]. Only autoimmune disease patients with a 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 the Screening visit will be eligible to be included in this trial. The trial will also investigate whether transiently withholding IS therapies has an impact on vaccine response. The study will address important public health issues by determining which patients with autoimmune diseases are at increased risk for suboptimal responses to COVID-19 vaccines and identifying safe and effective strategies to enhance their immune response to COVID-19 vaccines. The planned mechanistic studies will provide critical information about the efficacy of an additional homologous vaccine dose in autoimmune patients on other components of immune response such as B and T cell responses, and whether baseline molecular signatures may predict response.

The NIAID ACE Network includes nine institutions with large autoimmune disease patient cohorts, strong infrastructures for autoimmune disease vaccine clinical trials, talented basic immunologists at the forefront of understanding vaccine immune responses, cutting-edge immune-based technologies, and a history of collaborating on projects that transcend the expertise and capabilities of any single center.

1.2.2 Alternative Vaccine Dose Adaptation

Some immunocompromised individuals will not develop a robust immune response to an additional full dose of homologous vaccine and therefore remain at risk to develop severe COVID-19. Early data suggest an additional vaccine dose may be effective in eliciting an immune response in kidney transplant recipients on IS medications [31]. In a study of 92 kidney transplant recipients with suboptimal immune responses after the third vaccine dose, 54.3% of participants reached a threshold of 143 BAU/mL on anti-spike IgG titers after a fourth dose was administered. As autoimmune patients on IS therapies have a similar risk of suboptimal immune responses, an additional dose of vaccine may be an effective method of eliciting a robust immune response. The Centers for Disease Control and Prevention (CDC) has recently endorsed the use of an additional dose of a COVID-19 vaccine in immunocompromised individuals [32].

Recent data suggest that a heterologous vaccine dose following the initial vaccine series is both safe and efficacious in healthy individuals. Heterologous boosters of all vaccines were found to be immunogenic and the “fold increases from baseline in both binding and neutralizing antibody titers were similar or greater after heterologous boosts compared to homologous boosts.” Reactogenicity did not differ from prior evaluations of the Moderna, Pfizer-BioNTech, and Janssen COVID-19 vaccines and did not differ between patients receiving the heterologous and homologous boosts [33].

Per the Sanofi-GSK vaccine press release (February 23, 2022), in participants who had received a primary series of an already authorized mRNA or adenovirus vaccine (i.e., different platforms), the Sanofi-GSK booster vaccine (prototype CoV2 preS dTM [D614] vaccine [5 mcg] with AS03) induced a significant increase in neutralizing antibodies of 18- to 30-fold across vaccine platforms and age groups. When the Sanofi-GSK vaccines were used as a 2-dose primary series followed by a booster dose, neutralizing antibodies increased 84- to 153-fold compared to pre-boost levels [34]. Under the alternative vaccine adaptation, participants who agree to receive a fourth dose of vaccine will receive an alternative vaccine dose.

Originally, participants who previously received 3 total doses of a single mRNA vaccine (Moderna COVID-19 Vaccine OR Pfizer-BioNTech COVID-19 Vaccine) received their choice of either the Janssen vector-based COVID-19 vaccine or the other mRNA COVID-19 vaccine.

Beginning with v4.0 of the protocol, this trial will not utilize the Janssen vector-based COVID-19 vaccine. Participants who previously received 3 total doses of a single mRNA vaccine will receive a choice of an alternative mRNA COVID-19 vaccine or the Sanofi-GSK protein-based COVID-19 vaccine. Participants who previously received 4 or more doses of a single mRNA vaccine or 3 or more doses of a mixture mRNA vaccines (Moderna COVID-19 Vaccine AND Pfizer-BioNTech COVID-19 Vaccine) will receive the Sanofi-GSK protein-based COVID-19 vaccine.

Participants who previously received 2 doses of the Janssen vector-based COVID-19 vaccine will receive the Moderna COVID-19 Vaccine. This alternative Moderna dose will be a full vaccine dose, not a reduced vaccine booster dose.

Beginning with v6.0 of the protocol, bivalent versions of the mRNA vaccines, Moderna and Pfizer-BioNTech COVID-19 vaccines, replaced original monovalent versions. In addition, autoimmune disease patients with a negative or suboptimal serologic response to the initial COVID-19 vaccine regimen (defined as an Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL at the Screening visit), or with a low immune response (defined as an Elecsys® Anti-SARS-CoV-2 S result >200 U/ml and ≤2500 U/mL at the Screening visit) are eligible to receive an additional or homologous or alternative vaccine dose. The threshold of Roche Elecsys® anti-RBD assay ≤2500 U/ml SARS-CoV-2 S antibody concentration has been chosen based on a study of immunosuppressed organ transplant candidates, which showed that low anti-RBD titers after the third dose of mRNA-1273 was associated with low prevalence of Omicron BA.1 neutralizing antibodies [35]. In addition, a recent study using a cohort of health-care workers estimated that subsequent Omicron BA.4/5 neutralizing titers may be as much as 5-fold lower [36].

Cohort-defining IS medications (MMF/MPA and MTX) will be held by all participants around the time of vaccination, as appropriate, in an effort to improve the likelihood of a robust response to the alternative vaccine.

1.2.3 Pediatric Adaptation

While children have more often experienced mild disease from SARS-CoV-2 infection, severe disease occurs resulting in admission to the intensive care unit and death [37].COVID-NET data revealed a significant increase in hospitalization during the recent Delta variant surge, with approximately 10 times higher rates of admission of unvaccinated adolescents compared to those who were vaccinated [38].

There are limited reports of the impact of SARS-CoV-2 infection in children with rheumatic disease. A recent study described SARS-CoV-2 infection and related outcomes in a large cohort of children with rheumatic disease on immunomodulatory medications [39]. In the cohort of 262 subjects in which juvenile idiopathic arthritis (JIA) and SLE/other connective tissue diseases were the most common diagnoses, there was an estimated 13% rate of SARS-CoV-2 infection. Half of the IgG-positive subjects had no symptoms, and those taking immunomodulatory medications were not more likely to be IgG positive. Infected subjects had mild disease with no deaths or no one requiring hospitalization. Sengler et al. evaluated the clinical features and outcomes in children with rheumatic disease from the National Paediatric Rheumatology Database from Germany [40]. A diagnosis of JIA was the most common in their cohort of 76 children, and 76% were treated with IS medications. The majority of subjects had testing due to COVID exposure, while only approximately one third experienced any symptoms. A total of 76% of subjects developed symptoms of SARS-CoV-2, and the majority (96%) had mild symptoms. Two children were hospitalized, one of whom died from cardiorespiratory failure. Further study of the deceased patient suggested a possible underlying immunodeficiency and not a rheumatic disease as the correct diagnosis. Most (78%) patients with symptoms reported full recovery by approximately 4 weeks. The authors were not able to comment on the impact of medication exposure and co-morbidities on manifestations of SARS-CoV-2 infections in this population.

In adolescents 12 to 18 years of age, vaccination has been found very effective in preventing COVID-19 hospitalization, with an effectiveness estimate of 93% [41]. This effectiveness rate was determined during the period of time when the Delta variant was pervasive and having a significant impact on the pediatric population. Of the 464 hospitalized adolescents studied, 72% were reported to have at least one underlying condition, and of those, a small proportion (2%) had a non-oncologic IS disorder. Most hospitalized patients (97%) were unvaccinated, and all of those who were admitted to the intensive care unit or died were unvaccinated.

COVID-19 vaccination is recommended for all individuals with autoimmune and inflammatory rheumatic disease consistent with the age restrictions of the vaccine Emergency Use Authorizations (EUAs) or FDA approvals [42]. Rigorous studies of the impact of IS therapy on COVID-19 vaccination response in children with rheumatic disease are needed to guide the clinician in effective counsel and management of this population. There is one published study of the clinical impact of COVID-19 vaccination in adolescent patients with JIA treated with tumor necrosis factor (TNF) inhibitors [43]. This study enrolled 21 patients with inactive JIA between 16 and 21 years of age. Following vaccination, patients were monitored for AEs and changes in disease activity, as measured by the Juvenile Arthritis Disease Activity Score-27 (JADAS-27). Most patients (74%) experienced localized reactions, but systemic reactions did occur rarely (19% of

patients) after the second vaccine. Patients did not have disease when vaccinated and did not experience any disease flare.

Studies in other pediatric populations receiving immunomodulatory medications have demonstrated the impact of treatment on vaccine response. In a study of 33 children with Inflammatory Bowel Disease (IBD) treated with infliximab or vedolizumab, the spike protein receptor binding domain IgG level was significantly greater after vaccination compared to IBD subjects who experienced SARS-CoV-2 infection [44]. In a study of 25 adolescent renal transplant patients on a variety of IS medications including steroids, Mycophenolate, azathioprine, and calcineurin inhibitors, 52% were positive for spike antibody following vaccination [45]. Improved vaccine response was noted at lower doses of mycophenolate.

Under this adaptation, pediatric participants (2-17 years of age) with 1 of 4 autoimmune diseases (pediatric SLE, JIA, juvenile dermatomyositis [JDM], or pediatric-onset multiple sclerosis [POMS]) will receive additional COVID-19 vaccine doses. On 29 October 2021, EUA was granted for the Pfizer COVID-19 Vaccine for a 2-dose primary series in children 5 to 11 years old, and on 06 January 2022, EUA was granted for a third dose in immunocompromised children in this age group. Thus, an additional homologous COVID-19 vaccine dose has been included in this protocol in a design similar to that previously described for adults. On 17 June 2022, the FDA authorized emergency use of the Moderna COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine for use in children as young as 6 months of age. In response to these authorizations, the study's age of entry has expanded to include children ages 2 through 17, thus capturing a broader range of children with autoimmune diseases. Additionally, with the authorization of the Moderna COVID-19 Vaccine for children, the study can now offer an alternative vaccine to pediatric participants if they do not respond to the additional homologous dose. On 08 December 2022, the FDA authorized emergency use of bivalent versions of the mRNA vaccines, Moderna COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, as a booster dose in children as young as 6 months of age.

1.3 Rationale for Selection of Investigational Product

This trial originally utilized the 3 COVID-19 vaccines that had received EUA for adults from the United States (US) Food and Drug Administration (FDA): the Moderna and Pfizer-BioNTech mRNA vaccines; and the Janssen vector-based COVID-19 Vaccine.

At the time of this protocol's release, the following EUAs and FDA approvals are in place for COVID-19 vaccination in the US for the vaccines listed above:

*Table 1. FDA Emergency Use Authorizations and FDA Approvals of COVID-19 Vaccines**

Product Name	Authorization/Approval	Manufacturer	ACV01 Nomenclature
COMIRNATY® (COVID-19 Vaccine, mRNA)	FDA Approved for ages 12 and older as a primary series dose	Pfizer, Inc. & BioNTech Manufacturing GmbH	Pfizer-BioNTech COVID-19 Vaccine
Pfizer-BioNTech COVID-19 Vaccine	EUA for ages 6 months through 11 years as a primary series dose	Pfizer, Inc. & BioNTech Manufacturing GmbH	Pfizer-BioNTech COVID-19 Vaccine
Pfizer-BioNTech COVID-19 Vaccine, Bivalent	EUA for ages 6 months and older as a booster dose and as the last shot in the primary series	Pfizer, Inc. & BioNTech Manufacturing GmbH	Pfizer-BioNTech COVID-19 Vaccine, Bivalent

Product Name	Authorization/Approval	Manufacturer	ACV01 Nomenclature
SPIKEVAX™ (COVID-19 Vaccine, mRNA)	FDA Approved for ages 18 and older as a primary series dose	Moderna US, Inc.	Moderna COVID-19 Vaccine
Moderna COVID-19 Vaccine	EUA for ages 6 months through 17 years as a primary series dose	Moderna US, Inc.	Moderna COVID-19 Vaccine
Moderna COVID-19 Vaccine, Bivalent	EUA for ages 6 months and older as a booster dose	Moderna US, Inc.	Moderna COVID-19 Vaccine, Bivalent
Janssen COVID-19 Vaccine	EUA for ages 18 and older as a primary series dose and a booster dose in certain limited situations	Janssen Biotech, Inc.	Janssen COVID-19 Vaccine

*Information regarding the most recent EUAs for COVID-19 vaccinations can be found here:COVID-19 Vaccine EUA Recipient/Caregiver Fact Sheets | CDC. Information regarding the most recent FDA approvals for COVID-19 vaccinations can be found here: COVID-19 Vaccines | FDA

Beginning with v4.0 of the protocol, this trial will not utilize the Janssen vector-based COVID-19 vaccine. The Monovalent (B.1.351) CoV2 preS dTM-AS03 adjuvanted COVID-19 vaccine from Sanofi Pasteur and GSK, referred to as the Sanofi-GSK COVID-19 Vaccine in this protocol, will be offered as a heterologous vaccine to provide an alternative choice to adult participants who did not mount a robust immune response to previous doses of a mRNA vaccine.

1.4 Clinical Studies

Overall, 15,419 participants aged 18 years or older received at least one dose of the Moderna COVID-19 Vaccine in 3 clinical trials [46, 47]. A Phase 3 randomized, placebo-controlled, observer-blind clinical trial to evaluate the efficacy, safety, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older is ongoing in the US (NCT04470427). The primary efficacy analysis population (referred to as the Per-Protocol Set) included 28,207 participants who received 2 doses (at 0 and 1 month) of either Moderna COVID-19 Vaccine (n = 14,134) or placebo (n = 14,073) and had a negative baseline SARS-CoV-2 status. The median length of follow up for efficacy for participants in the study was 9 weeks post Dose 2. There were 11 COVID-19 cases in the Moderna COVID-19 Vaccine group and 185 cases in the placebo group, with a vaccine efficacy of 94.1% (95% confidence interval of 89.3% to 96.8%). Among all participants in the Per-Protocol Set analysis, which included COVID-19 cases confirmed by an adjudication committee, no cases of severe COVID-19 were reported in the Moderna COVID-19 Vaccine group compared with 30 cases reported in the placebo group (incidence rate 9.138 per 1,000 person-years). One PCR-positive case of severe COVID-19 in a vaccine recipient was awaiting adjudication at the time of the analysis. Adverse reactions reported in a clinical trial following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site [48]. Pediatric response to the Moderna vaccine was evaluated in 2 studies [49]. In the KidCOVE study, 4,016 pediatric participants ages 6 through 11 received 2 doses of the Moderna COVID-19 vaccine (50 µg per dose) or placebo. The estimated vaccine efficacy for this study was 88% (95% confidence interval of 70.0% - 95.8%). This dose was associated with low-grade, transient adverse events (AEs) and no vaccine-related serious adverse events (SAEs), multi-system inflammatory syndrome, pericarditis, or myocarditis events were reported at the time of the initial report [50]. The second study evaluated 3,732 participants, ages 12- 17 who were randomly assigned to receive either 2 doses of the Moderna COVID-19 vaccine or placebo. No SAEs were reported, and the most common solicited AEs included injection site pain, headache, and fatigue. No cases of COVID-19 with an onset of 14 days after the second dose were reported in the Moderna group [51]. Data for these older pediatric ages groups as well as children 6 months through 5

years were presented to the Vaccines and Related Biological Products Advisory Committee in June 2022 [49, 52]. Immune responses in subsets of each age group were generally comparable to those seen in adult participants. Among approximately 5,400 children, the vaccine was 50.6% effective in preventing COVID-19 in participants 6 through 23 months of age 36.8% effective in preventing COVID-19 in participants 2 through 5 years of age. No severe cases of COVID-19 were observed. Across all pediatric age cohorts, adverse reactions included pain, redness and swelling at the injection site, fever and axillary swelling/tenderness. In participants 6 through 36 months of age, side effects also included irritability/crying, sleepiness, and loss of appetite. In participants 37 months through 5 years of age, side effects also included fatigue, headache, muscle ache, chills, nausea/vomiting and joint stiffness. The safety of the bivalent form of the Moderna COVID-19 Vaccine is based on a clinical study that evaluated a booster dose of Moderna's bivalent COVID-19 vaccine (Original and Omicron BA.1). Adverse reactions following a booster dose included pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, axillary swelling/tenderness, nausea/vomiting, erythema at the injection site, swelling at the injection site, and fever [48].

The safety and efficacy of the Pfizer-BioNTech COVID-19 Vaccine has been evaluated in 2 clinical studies [53, 54]. The BNT162-01 study (NCT04380701) was a phase 1/2 trial that enrolled 60 participants, 18 through 55 years of age. Study C459001 (Study 2) is an ongoing phase 1/2/3 study that has enrolled approximately 44,000 participants, 12 years of age or older that were randomized equally and received 2 doses of Pfizer-BioNTech COVID-19 Vaccine or placebo separated by 21 days. The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the Pfizer-BioNTech COVID-19 Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. At the time of the analysis of Study 2 for the EUA, 37,586 participants 16 years of age or older (18,801 Pfizer-BioNTech COVID-19 Vaccine and 18,785 placebo) have been followed for a median of 2 months after the second dose of Pfizer-BioNTech COVID-19 Vaccine. Overall, there were 8 COVID-19 cases in the Pfizer-BioNTech COVID-19 Vaccine group and 162 cases in the placebo group, with a vaccine efficacy of 95% (95% CI 90.3-97.6). Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy[55]. Data were presented to the Vaccines and Related Biological Products Advisory Committee for children 5 through 11 years in October 2021 [56, 57], and for children 6 months through 4 years in June 2022 [49, 52]. In both age groups, immune responses were generally comparable to those seen in adult participants. In a preliminary analysis of approximately 2,000 participants ages 5 through 11 years, the vaccine was 90.7% effective in preventing COVID-19. No cases of severe COVID-19 were observed. Among 860 participants ages 2 through 4 years, the vaccine was 82.4% effective in preventing COVID-19. One hospitalization for severe COVID-19 was observed. Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in participants ages 5 through 17 years include injection site pain, redness and swelling, fatigue, headache, muscle and/or joint pain, chills, fever, swollen lymph nodes, nausea, and decreased appetite. For participants 6 months through 4 years of age included irritability, decreased appetite, fever, headache, chills and pain, tenderness, redness and swelling at the injection site. The safety of the bivalent form of the Pfizer-BioNTech COVID-19 Vaccine is based on a clinical study which evaluated a booster dose of Pfizer-BioNTech's bivalent COVID-19 vaccine (Original and Omicron BA.1). Adverse reactions following a booster dose included injection site pain, fatigue, headache, muscle pain, chills, joint pain, injection site swelling, fever, injection site redness, lymphadenopathy, nausea, malaise, pain in extremity, rash, and decreased appetite [58].

In an ongoing, global, multicenter, randomized trial, 44,325 participants (age 18 and older) were randomized to receive a single dose of the Janssen COVID-19 Vaccine or a saline placebo (NCT04505722). The primary efficacy analysis population of 39,321 individuals (19,630 in the Janssen COVID-19 Vaccine group and 19,691 in the placebo group) included 38,059 SARSCoV-2 seronegative individuals at Baseline and 1,262 individuals with an unknown serostatus. The median length of follow up for efficacy for individuals in the study was 8 weeks post vaccination. Vaccine efficacy for the co-primary endpoints against moderate to severe/critical COVID-19 in individuals who were seronegative or who had an unknown serostatus at Baseline was 66.9% (95% CI 59.0-73.4) at least 14 days after vaccination and 66.1% (95% CI 55.0-74.8) at least 28 days after vaccination. Vaccine efficacy against severe/critical COVID-19 at least 14 days after vaccination was 76.7% (95% CI 54.6-89.1) and 85.4% (95% CI 54.2-96.9) at least 28 days after vaccination. As of the primary analysis cut-off date of January 22, 2021, there were no COVID-19-related deaths reported in Janssen COVID-19 Vaccine recipients compared to 5 COVID-19-related deaths reported in placebo recipients, who were SARS-CoV-2 PCR

negative at Baseline. Adverse reactions reported in a clinical trial following administration of the Janssen COVID-19 Vaccine include injection site pain, headache, fatigue, nausea, fever, injection site erythema, and injection site swelling. In clinical studies, severe allergic reactions, including anaphylaxis, have been reported following the administration of the Janssen COVID-19 Vaccine [59].

The Phase 3 trial VAT00008 (NCT04904549), sponsored by Sanofi, is evaluating a 10 µg antigen formulation of a SARS-CoV-2 adjuvanted, recombinant, protein-based vaccine for efficacy, immunogenicity, and safety compared to a placebo. Stage One of the trial is assessing the efficacy of a vaccine formulation containing the spike protein from the original D614 (parent) virus in more than 10,000 participants aged 18 years and older who are randomized to receive 2 doses of 10 µg vaccine or placebo at Day 1 and Day 22 across sites in the US, Asia, Africa, and Latin America. Enrollment recently completed for a second stage in the trial evaluating a bivalent formulation that contains the spike protein of both the original virus and the B.1.351 (Beta) variant. The Phase 3 trial follows positive initial results from a Phase 2 clinical trial (VAT00002; NCT04762680) [60]. In that trial, the COVID-19 vaccine candidate was administered to 722 adults to assess the safety, reactogenicity, and immunogenicity of 2 doses and to identify an optimal dosing for use as a booster. Results showed strong rates of neutralizing antibody response with 95% to 100% seroconversion following a second injection in all adult age groups (18 to 95 years old) across all doses. In the Supplemental Booster Cohort 2 of the VAT00002 trial, the safety and immunogenicity of the B.1.351 monovalent booster vaccine has been evaluated in over 1300 individuals previously primed with mRNA or adenovirus-vectored COVID-19 vaccines. In a randomized, blinded clinical study sponsored by Assistance Publique – Hôpitaux de Paris, evaluating the safety and immunogenicity of heterologous boosting with the Sanofi-GSK monovalent CoV2 preS dTM (Beta) and monovalent (D614) vaccines following a 2-dose primary series of BNT162b2 compared to a homologous BNT162b2 third dose (NCT05124171), the Sanofi-GSK Beta vaccine elicited a higher neutralizing antibody response against the SARS-CoV-2 D614G, Beta, Delta, and Omicron BA.1 variants compared with boosting with the BNT162b2 vaccine or the Sanofi-GSK D614 vaccine. This study, which included 223 participants in the per-protocol population, also found that all 3 boosters were well tolerated and not associated with any safety concerns.

Supplemental cohorts are currently being studied by Sanofi and GSK to address the safety and efficacy of various prime-boost options. Individuals who were initially vaccinated with other vaccine platforms are being given different formulations of the of the CoV2 preS dTM-AS03 vaccine, including monovalent (D614 or B.1.351) and bivalent (D614 + B.1.351) forms, for use as a universal late booster. ACV01 will evaluate the safety and immunogenicity of a boost with the Beta (B.1.351) variant-containing vaccine formulation (CoV2 preS dTM-AS03 [B.1.351]) in individuals with autoimmune diseases on IS medications who have had an inadequate response to previous COVID-19 vaccines.

2. Study Hypotheses/Objectives

- We hypothesize that adult and pediatric participants with autoimmune diseases requiring IS medications who have had a suboptimal response (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL) 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 pediatric participants with autoimmune diseases requiring IS medications who have a low immune response (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result >200 U/ml and ≤2500 U/mL) after an initial COVID-19 vaccine regimen may demonstrate enhanced immune response after receiving an additional dose of an additional homologous COVID-19 vaccine.
- We hypothesize that adult and pediatric participants with transient cessation of MMF/MPA or MTX before and after vaccination will have an enhanced immune response.
- We hypothesize that adult and pediatric participants with autoimmune diseases requiring IS medications who continue to have a suboptimal response after an initial COVID-19 vaccine regimen plus additional vaccine doses may demonstrate enhanced immune response after receiving an additional dose of an alternative COVID-19 vaccine.

- We hypothesize that adult and pediatric participants with autoimmune diseases requiring IS medications who have a low immune response after an initial COVID-19 vaccine regimen plus additional vaccine doses may demonstrate enhanced immune response after receiving an additional dose of an alternative COVID-19 vaccine.

2.1 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.

2.2 Secondary Objectives

2.2.1 Stage 1 Secondary Objectives

These secondary objectives are applicable to both the adult and pediatric populations.

- 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 assess the immune response following an additional homologous COVID-19 vaccine dose in the subgroup of participants that had a low immune response following a previous COVID-19 vaccine dose.
- To determine the incidence of AEs, including medically attended adverse events (MAAEs), new onset chronic medical conditions (NOCMCs), and 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.

2.2.2 Stage 2 Secondary Objectives

These secondary objectives are applicable to both the adult and pediatric populations.

- To determine the proportions of participants with a negative serologic or suboptimal response to a previous COVID-19 vaccine administration 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 assess the immune response following a subsequent alternative vaccine dose in the subgroup of participants that had a low immune response following a previous COVID-19 vaccine dose.
- 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 a previous 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.

2.3 Exploratory Objectives

The exploratory objectives are applicable to both the adult and pediatric populations.

- 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 BCDT.
- 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 (IP-10) serum levels that associate with an effective vaccine immune 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.

3. Study Design

3.1 Description of 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 suboptimal responses (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL) or a low immune response (defined as a Roche Elecsys® Anti-SARS-CoV-2 S result >200 U/ml and ≤2500 U/mL) to their previous doses of COVID-19 vaccine.

3.1.1 Adult Population

3.1.1.1 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: SLE, RA, MS, SSc, and pemphigus.

Participants will be assigned to 1 of 3 cohorts based on their IS regimens:

- Cohort A: Receipt of MMF or MPA (± other rheumatic disease medications, including biologics)
    - Participants who are taking MMF or MPA (without additional B cell depleting medications or MTX) will be placed in this cohort.
- Cohort B: Receipt of MTX (± other rheumatic disease medications, including biologics)
    - Participants who are taking MTX (without additional B cell depleting medications or MMF/ MPA) will be placed in this cohort.
- Cohort C: Receipt of BCDT within the past 18 months (± other rheumatic disease medications)
    - Participants taking B cell depletion medications, regardless of whether they are also taking MMF or MTX, will be placed in this cohort.

Treatment Arms: Participants in Cohorts A, B, and C will be assigned to receive an additional dose of the same COVID-19 vaccine as their original vaccine series.

Participants in Cohorts A and B will be randomized into 2 IS medication treatment plans as follows:

- Participants continue to take their 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 (see Section 7.1.1 Protocol-mandated Medications).

All potential treatment arms for Adult Stage 1 are detailed in Table 2.

***Update*:** Arms to receive an additional homologous vaccine dose after an initial Janssen COVID 19 Vaccine were closed to enrollment after the CDC updated its recommendations to express a clinical preference for individuals to receive an mRNA COVID-19 vaccine over the Janssen COVID-19 vaccine. All Adult Stage 1 treatment arms were closed to enrollment on 15 August 2022.

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. Participant and study flow diagrams are provided in Figure 1 and Figure 2, respectively.

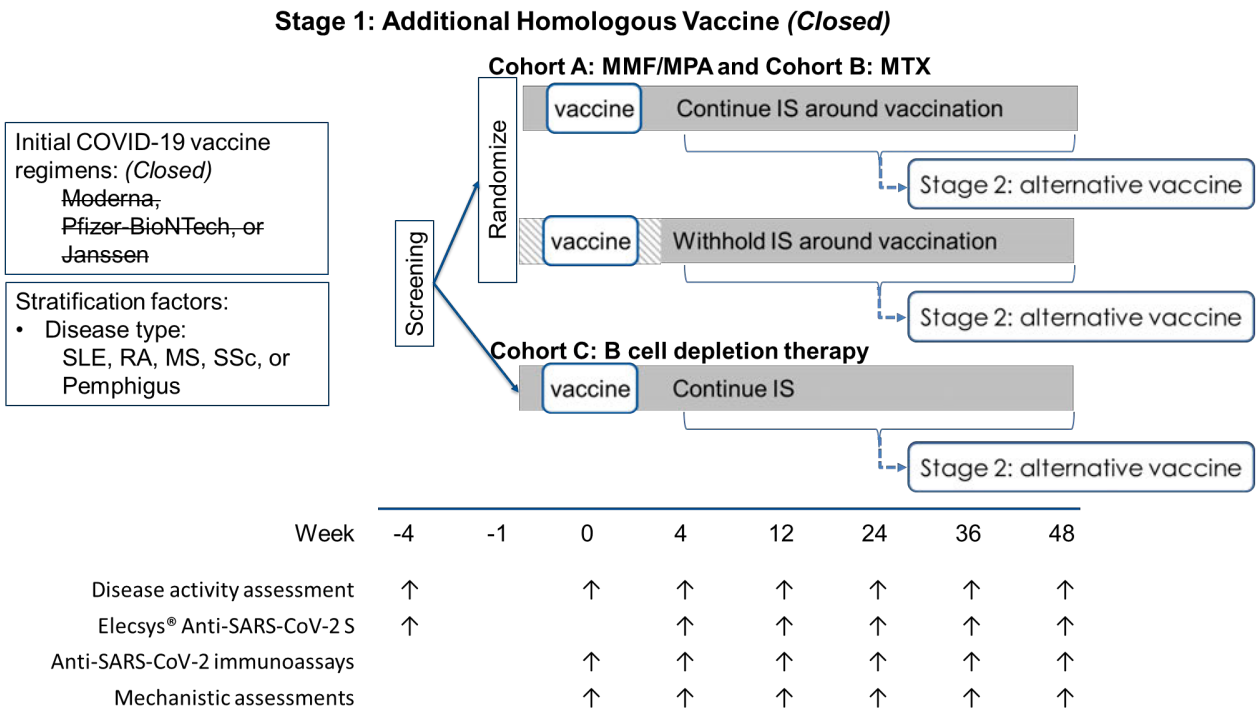
An Adult Stage 1 participant will be enrolled in the study for a maximum of approximately 13 months.

Table 2. Treatment Arm Assignments in Adult Stage 1

		Additional Homologous Vaccine Dose	Randomized Treatment Plan
Cohort A: MMF or MPA	ARM A1 (closed)	Moderna COVID-19 Vaccine	Continue MMF or MPA
	ARM A2 (closed)	Pfizer-BioNTech COVID-19 Vaccine	Continue MMF or MPA
	ARM A3 (closed)	Janssen COVID-19 Vaccine*	Continue MMF or MPA
	ARM A4 (closed)	Moderna COVID-19 Vaccine	Withhold MMF or MPA
	ARM A5 (closed)	Pfizer-BioNTech COVID-19 Vaccine	Withhold MMF or MPA
	ARM A6 (closed)	Janssen COVID-19 Vaccine*	Withhold MMF or MPA
Cohort B: Methotrexate	ARM B1 (closed)	Moderna COVID-19 Vaccine	Continue MTX
	ARM B2 (closed)	Pfizer-BioNTech COVID-19 Vaccine	Continue MTX
	ARM B3 (closed)	Janssen COVID-19 Vaccine*	Continue MTX
	ARM B4 (closed)	Moderna COVID-19 Vaccine	Withhold MTX
	ARM B5 (closed)	Pfizer-BioNTech COVID-19 Vaccine	Withhold MTX
	ARM B6 (closed)	Janssen COVID-19 Vaccine*	Withhold MTX
Cohort C: B cell depletion therapy	ARM C1 (closed)	Moderna COVID-19 Vaccine	N/A
	ARM C2 (closed)	Pfizer-BioNTech COVID-19 Vaccine	N/A
	ARM C3 (closed)	Janssen COVID-19 Vaccine*	N/A

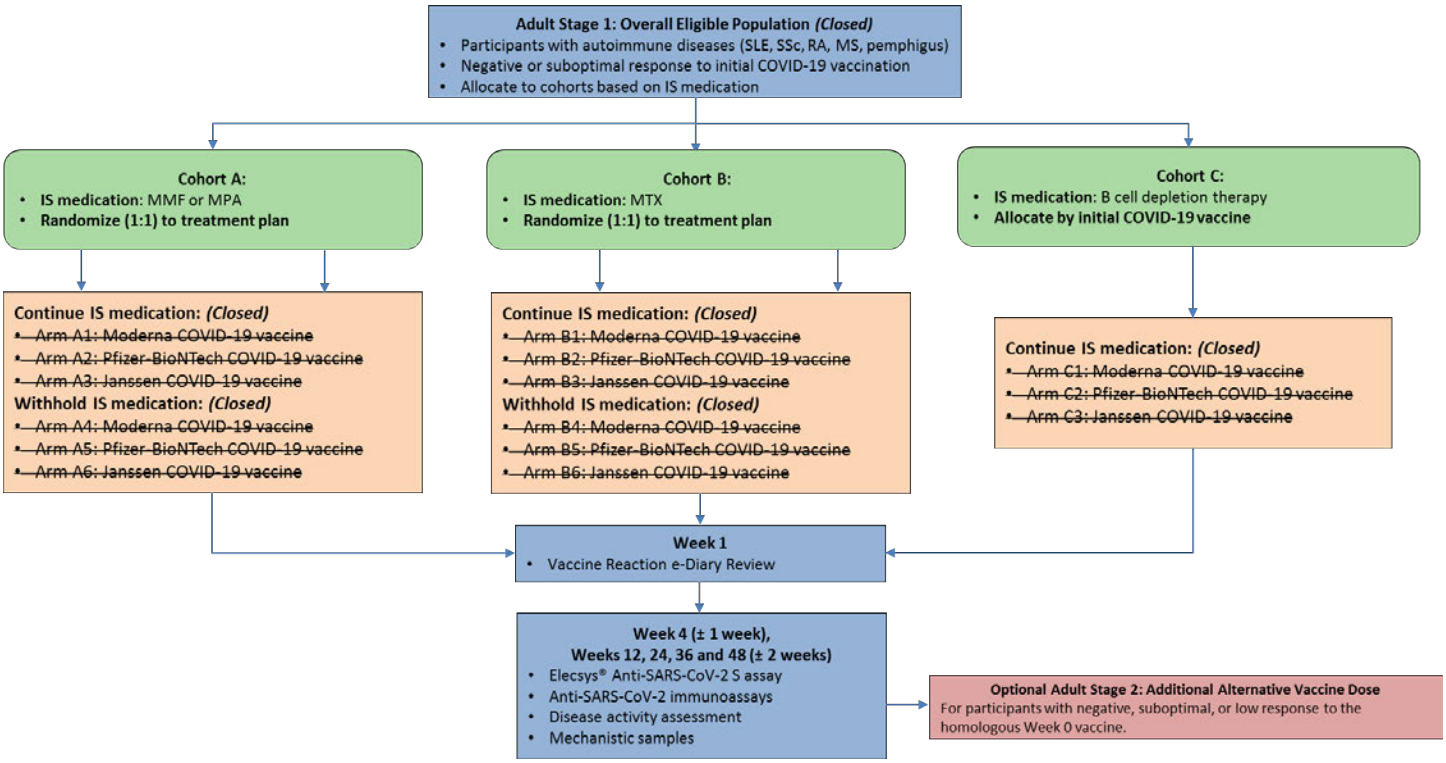
IS = immunosuppressive; MMF = mycophenolate mofetil; MPA = mycophenolic acid
*The Janssen COVID-19 Vaccine treatment arms are currently closed to enrollment.

Figure 1. Participant Flow Diagram for Adult Stage 1 (Closed)



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 (Closed)



IS = immunosuppressive medication

3.1.1.2 Adult Stage 2

Stage 2 of this trial will include up to a maximum of 960 adult study participants (up to 80 per arm) with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL after previous COVID-19 vaccine administration (at least 3 doses of mRNA vaccine(s) or 2 doses of the Janssen COVID-19 Vaccine). Participants will be eligible to receive a dose of an alternative COVID-19 vaccine.

Participants may have received their previous COVID-19 vaccine prior to enrollment in the study ("newly recruited participant"), or they may have received their previous COVID-19 vaccine as a study participant and then (re-) enter into Stage 2 ("rollover participant").

Newly recruited Stage 2 participants will be evaluated for eligibility per Section 4.2.1.2.1 Inclusion and Exclusion Criteria for Adult Stage 2 Newly Recruited Participants.

Participants can also roll over into Stage 2 via two pathways:

- Stage 1 participant rolls over to Stage 2
    - A Stage 1 participant who has a Roche Elecsys result ≤2500 U/mL at a post-Baseline visit may elect to roll over into Stage 2, starting the Stage 2 schedule of events for rollovers.
- Stage 2 participant rolls over to a different Stage 2 treatment arm
    - A Stage 2 participant who received an alternative mRNA vaccine dose and has a Roche Elecsys result ≤2500 U/mL at a post-Baseline visit may elect to re-enter Stage 2, restarting the Stage 2 schedule of events for rollovers.

Rollover participants will be evaluated for Stage 2 eligibility per Section 4.2.1.2.2 Inclusion and Exclusion Criteria for Adult Stage 2 Rollover Participants.

Participants will be allocated to 1 of 3 cohorts based on their IS regimens:

- Cohort D: Receipt of MMF or MPA (± other rheumatic disease medications, including biologics)
    - Participants who are taking MMF or MPA (without additional B cell depleting medications or MTX) will be placed in this cohort.
- Cohort E: Receipt of MTX (± other rheumatic disease medications, including biologics)
    - Participants who are taking MTX (without additional B cell depleting medications or MMF/ MPA) will be placed in this cohort.
- Cohort F: Receipt of BCDT within the past 18 months (± other rheumatic disease medications)
    - Participants taking B cell depletion medications, regardless of whether they are also taking MMF or MTX, will be placed in this cohort.

Treatment Arms: Table 3 describes the vaccines available to newly recruited participants and Table 4 describes the vaccines available to rollover participants depending on the previous COVID-19 vaccines they received. 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. Originally, participants who previously received 3 total doses of a single mRNA vaccine (Moderna COVID-19 Vaccine OR Pfizer-BioNTech COVID-19 Vaccine) received 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 received the Moderna COVID-19 Vaccine.

Update: Beginning with v4.0 of the protocol, this trial will not utilize the Janssen vector-based COVID-19 vaccine. Participants who previously received 3 total doses of a single mRNA vaccine will receive their choice of an alternative mRNA COVID-19 vaccine or the Sanofi-GSK protein-based COVID-19 vaccine. Participants who previously received 4 or more doses of a single mRNA vaccine or 3 or more doses of a mixture mRNA vaccines (Moderna COVID-19 Vaccine AND Pfizer-BioNTech COVID-19 Vaccine, in any order or combination) will receive the Sanofi-GSK protein-based COVID-19

vaccine. Beginning with v6.0 of the protocol, bivalent versions of the mRNA vaccines, Moderna and Pfizer-BioNTech COVID-19 vaccines, replaced original monovalent versions.

Participants in Cohorts D and E will withhold their cohort-defining IS medications before and after the alternative vaccine dose per protocol instructions (see Section 7.1.1 Protocol-mandated Medications).

Participants in Cohort F who are taking MMF, MPA, or MTX in addition to BCDTs will withhold these medications before and after the alternative vaccine dose per protocol instructions (see Section 7.1.1 Protocol-mandated Medications).

All potential treatment arms for Adult Stage 2 are detailed in Table 5.

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. Participant and study flow diagrams for Stage 2 are provided in Figure 3 and Figure 4, respectively.

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. A participant who enters Stage 2 after a serologic negative, suboptimal, or low immune response to their Stage 1 vaccine dose may be on study for up to a maximum of 26 months. Rollover participants will discontinue follow-up as part of Stage 1 upon rollover into Stage 2. A participant who rolls over to a different Stage 2 treatment arm after a serologic negative, suboptimal, or low immune response to another Stage 2 vaccine dose may be on study for up to a maximum of 38 months.

Table 3. Vaccines Available to Adult Stage 2 Newly Recruited Participants

Previous Vaccines Received	**Vaccine Option for Study Treatment Stage Two: First Dose**
3 doses of the same mRNA COVID-19 vaccine	A choice of an alternative mRNA COVID-19 bivalent vaccine ***OR*** Sanofi-GSK COVID-19 Vaccine
4 or more doses of the same mRNA COVID-19 vaccine	Sanofi-GSK COVID-19 Vaccine
3 or more doses of a mixture of Moderna mRNA and Pfizer mRNA COVID-19 vaccines	Sanofi-GSK COVID-19 Vaccine
2 doses of Janssen COVID-19	Moderna COVID-19 Vaccine, bivalent

Table 4. Vaccines Available to Adult Stage 2 Rollover Participants

Previous Vaccines Received	**Vaccine Option for Study Treatment Stage Two: First Dose**
3 doses of the same mRNA COVID-19 vaccine	A choice of an alternative mRNA COVID-19 bivalent vaccine ***OR*** Sanofi-GSK COVID-19 Vaccine
2 doses of Janssen COVID-19 vaccine	Moderna COVID-19 Vaccine, bivalent

Previous Vaccines Received	**Vaccine Option for Study Treatment Stage Two: Second Dose**
3 doses of Moderna mRNA COVID-19 vaccine followed by 1 dose of Pfizer mRNA COVID-19 vaccine	Sanofi-GSK COVID-19 Vaccine
3 doses of Pfizer mRNA COVID-19 vaccine followed by 1 dose of the Moderna mRNA COVID-19 vaccine	Sanofi-GSK COVID-19 Vaccine

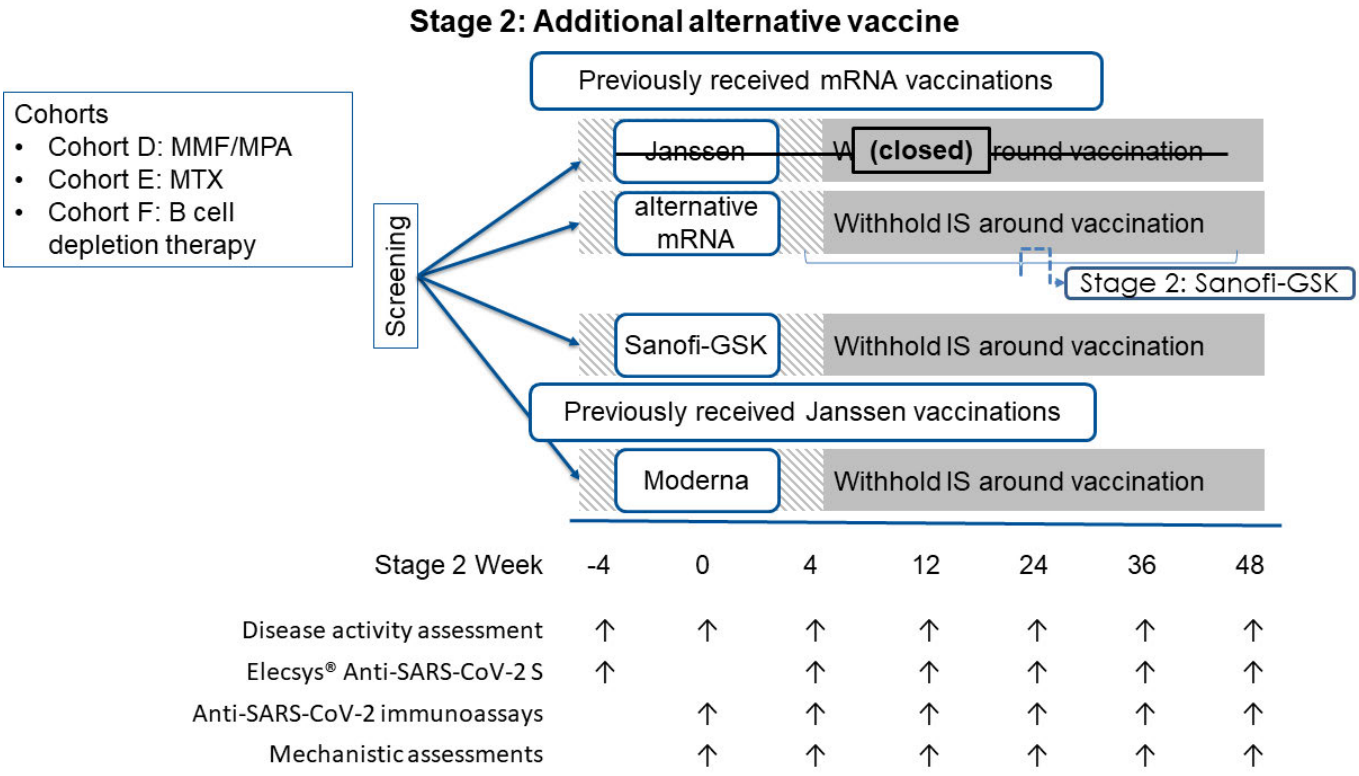
Table 5. Treatment Arms in Adult Stage 2

	Previous Vaccine Doses	Stage 2 Arm	Stage 2 Alternative Vaccine Dose
Cohort D: MMF or MPA	**mRNA COVID-19 vaccine** • 3 doses of a single mRNA vaccine (from Arms A1, A2, A4, or A5, or newly recruited)	ARM D1 (closed)	Janssen COVID-19 Vaccine*
		ARM D2	Alternative mRNA COVID-19 vaccine
		ARM D4	Sanofi-GSK COVID-19 Vaccine
	mRNA COVID-19 vaccine(s) • 4 or more doses of a single mRNA vaccine • 3 or more doses of a mixture of mRNA vaccines (from Arm D2 or newly recruited)	ARM D4	Sanofi-GSK COVID-19 Vaccine
	vector-based COVID-19 vaccine • 2 doses of Janssen COVID-19 vaccine (from Arms A3 or A6, or newly recruited)	ARM D3	Moderna COVID-19 Vaccine
Cohort E: Methotrexate	**mRNA COVID-19 vaccine** • 3 doses of a single mRNA vaccine (from Arms B1, B2, B4, or B5, or newly recruited)	ARM E1 (closed)	Janssen COVID-19 Vaccine*
		ARM E2	Alternative mRNA COVID-19 vaccine
		ARM E4	Sanofi-GSK COVID-19 Vaccine
	mRNA COVID-19 vaccine(s) • 4 or more doses of a single mRNA vaccine • 3 or more doses of a mixture of mRNA vaccines (from Arm E2 or newly recruited)	ARM E4	Sanofi-GSK COVID-19 Vaccine
	vector-based COVID-19 vaccine • 2 doses of Janssen COVID-19 vaccine (from Arms B3 or B6, or newly recruited)	ARM E3	Moderna COVID-19 Vaccine
Cohort F: B cell depletion therapy	**mRNA COVID-19 vaccine** • 3 doses of a single mRNA vaccine (from Arms C1 or C2, or newly recruited)	ARM F1 (closed)	Janssen COVID-19 Vaccine*
		ARM F2	Alternative mRNA COVID-19 vaccine
		ARM F4	Sanofi-GSK COVID-19 Vaccine
	mRNA COVID-19 vaccine(s) • 4 or more doses of a single mRNA vaccine • 3 or more doses of a mixture of mRNA vaccines (from Arm F2 or newly recruited)	ARM F4	Sanofi-GSK COVID-19 Vaccine
	vector-based COVID-19 vaccine • 2 doses of Janssen COVID-19 vaccine (from Arm C3 or newly recruited)	ARM F3	Moderna COVID-19 Vaccine

IS = immunosuppressive; MMF = mycophenolate mofetil; MPA = mycophenolic acid

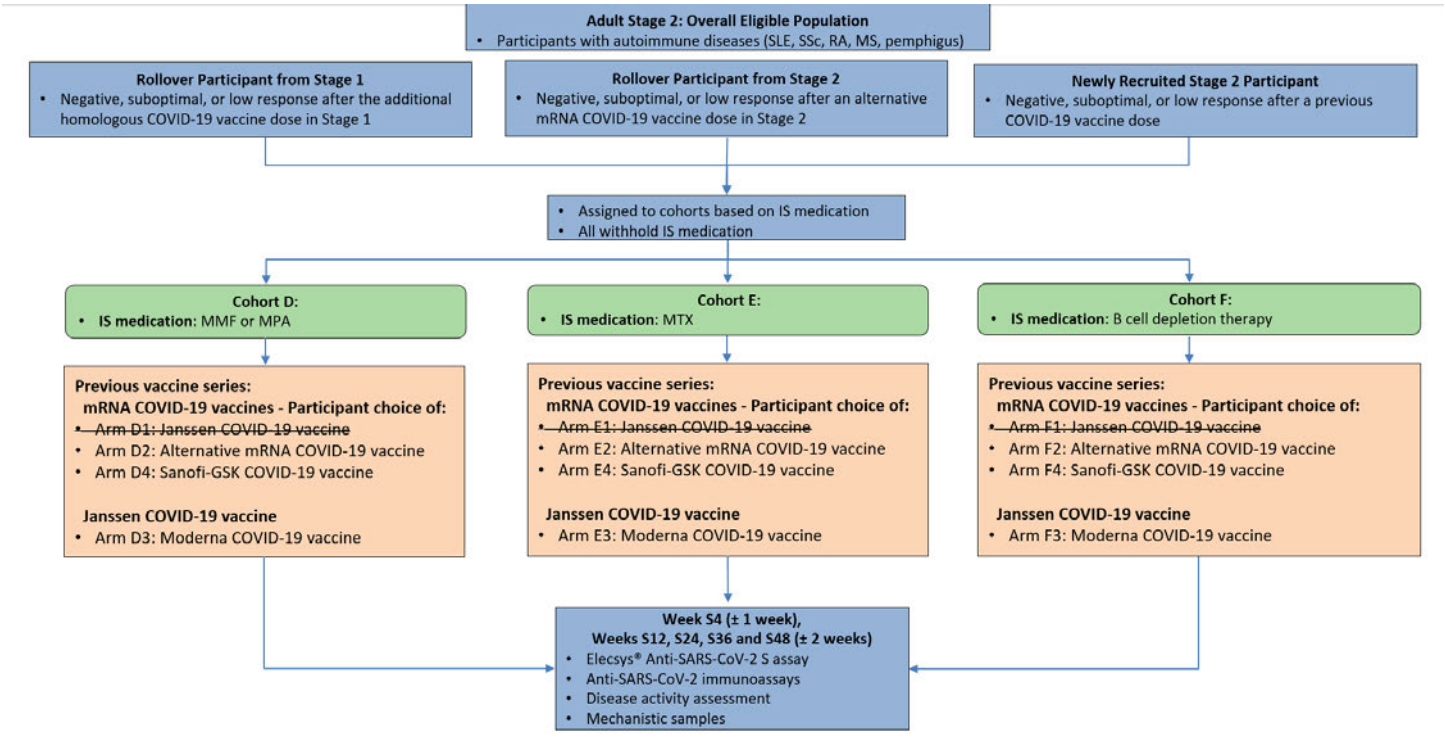
* The Janssen COVID-19 Vaccine treatment arms are currently closed to enrollment.

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

3.1.2 Pediatric Population

3.1.2.1 Pediatric Stage 1

The pediatric portion of this trial will enroll up to a maximum of 800 participants (2 through 17 years of age) with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL after receiving an age-appropriate EUA-authorized initial COVID-19 vaccine regimen as shown in Table 6 (up to 80 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, JIA, JDM, or POMS.

Participants will be assigned to 1 of 3 cohorts based on their IS regimens:

- Cohort A: Receipt of MMF or MPA (± other rheumatic disease medications, including biologics)
    - Participants who are taking MMF or MPA (without additional B cell depleting medications or MTX) will be placed in this cohort.
- Cohort B: Receipt of MTX (± other rheumatic disease medications, including biologics)
    - Participants who are taking MTX (without additional B cell depleting medications or MMF/ MPA) will be placed in this cohort.
- Cohort C: Receipt of BCDT within the past 18 months (± other rheumatic disease medications)
    - Participants taking B cell depletion medications, regardless of whether they are also taking MMF or MTX, will be placed in this cohort.

Treatment Arms: Participants in Cohorts A, B, and C will be assigned to receive an additional dose of the same COVID-19 vaccine as their original vaccine series. Table 6 describes the age-appropriate qualifying initial COVID-19 vaccine regimen for participation in Pediatric Stage 1.

Update: Beginning with v6.0 of the protocol, bivalent versions of the mRNA vaccines, Moderna and Pfizer-BioNTech COVID-19 vaccines, replaced original monovalent versions.

Participants in Cohorts A and B will be randomized into 2 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 (see Section 7.1.1 Protocol-mandated Medications).

All potential treatment arms for the pediatric population are detailed in Table 7. As of the date of Protocol Version 5.0, the Pfizer-BioNTech and Moderna COVID-19 vaccines have been authorized for use in children (ages 6 months through 17 years) in addition to adults.

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. Participant and study flow diagrams are provided in Figure 5 and Figure 6, respectively.

A pediatric participant will be enrolled in the study for a maximum of approximately 13 months.

Table 6. Initial COVID-19 Vaccine Regimens Qualifying Participants for Pediatric Stage 1 and ACV01 Stage 1 Study Doses

Pfizer-BioNTech COVID-19 Vaccine		
Age of Participant	**Qualifying Regimen**	**ACV01 Stage 1 Study Dose**
2 years through 4 years	3 doses of 3 mcg	3 mcg bivalent
5 years through 11 years *	2 doses of 10 mcg	10 mcg bivalent
12 years through 17 years **	2 doses of 30 mcg	30 mcg bivalent

* Individuals who turned from 4 years to 5 years of age between any doses in the primary series may also have received one or two doses of 3 mcg as part of the qualifying regimen. Individuals who turned from 4 years to 5 years of age after completion of the primary series may also have received three doses of 3 mcg as the qualifying regimen.

**Individuals who turned from 11 years to 12 years of age between doses in the primary regimen may also have received one or two doses of 10 mcg as part of the qualifying regimen. Individuals who turned from 11 years to 12 years of age after completion of the primary series may also have received two doses of 10 mcg as the qualifying regimen.

Moderna COVID-19 Vaccine		
Age of Participant	**Qualifying Regimen**	**ACV01 Stage 1 Study Dose**
2 years through 5 years	2 doses of 25 mcg	25 mcg bivalent
6 years through 11 years *	2 doses of 50 mcg	50 mcg bivalent
12 years through 17 years **	2 doses of 100 mcg	100 mcg bivalent

* Individuals who turned from 5 years to 6 years of age between any doses in the primary series may also have received one or two doses of 25 mcg as part of the qualifying regimen. Individuals who turned from 5 years to 6 years of age after completion of the primary series may also have received two doses of 25 mcg as the qualifying regimen.

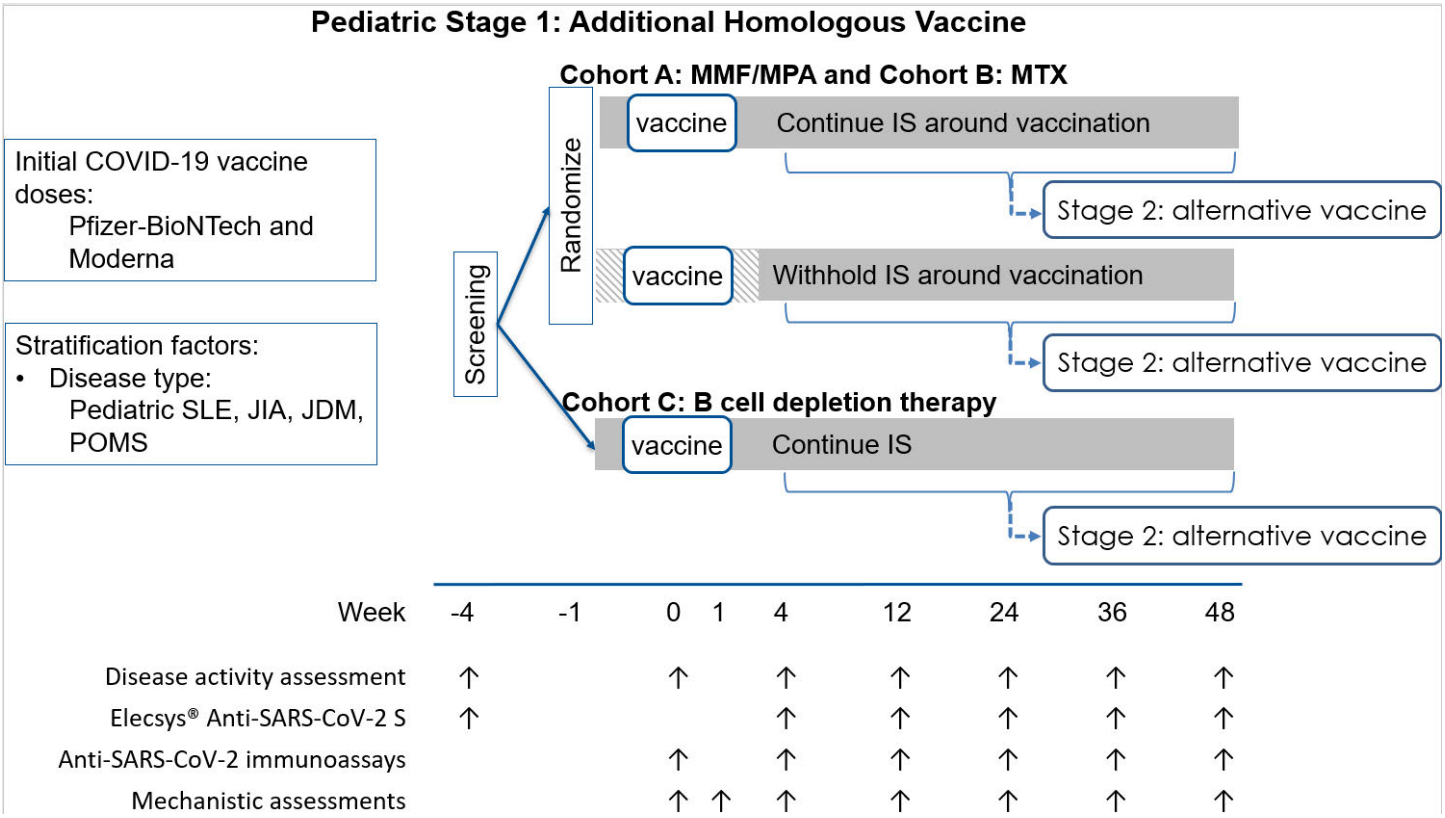
**Individuals who turned from 11 years to 12 years of age between doses in the primary regimen may also have received one or two doses of 50 mcg as part of the qualifying regimen. Individuals who turned from 11 years to 12 years of age after completion of the primary series may have received two doses of 50 mcg as the qualifying regimen.

Table 7. Treatment Arm Assignments in Pediatric Stage 1

		Additional Homologous Vaccine Dose*	**Randomized Treatment Plan**
Cohort A: MMF or MPA	ARM A1P	Moderna COVID-19 Vaccine	Continue MMF/MPA
	ARM A2P	Pfizer-BioNTech COVID-19 Vaccine	Continue MMF/MPA
	ARM A4P	Moderna COVID-19 Vaccine	Withhold MMF/MPA
	ARM A5P	Pfizer-BioNTech COVID-19 Vaccine	Withhold MMF/MPA
Cohort B: Methotrexate	ARM B1P	Moderna COVID-19 Vaccine	Continue MTX
	ARM B2P	Pfizer-BioNTech COVID-19 Vaccine	Continue MTX
	ARM B4P	Moderna COVID-19 Vaccine	Withhold MTX
	ARM B5P	Pfizer-BioNTech COVID-19 Vaccine	Withhold MTX
Cohort C: B cell depletion therapy	ARM C1P	Moderna COVID-19 Vaccine	N/A
	ARM C2P	Pfizer-BioNTech COVID-19 Vaccine	N/A

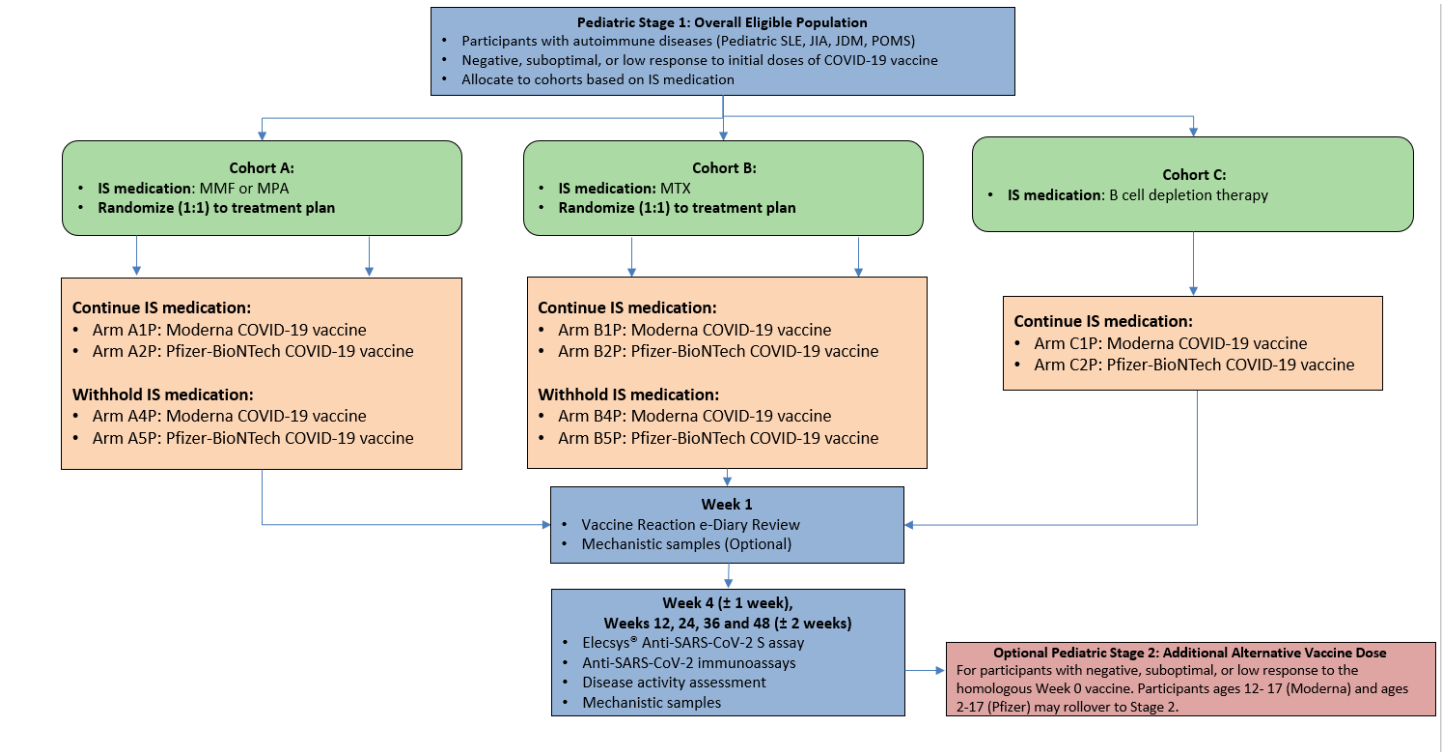
IS = immunosuppressive; MMF = mycophenolate mofetil; MPA = mycophenolic acid
*Bivalent vaccines will be administered per Section 6, Investigational Agents

Figure 5. Participant Flow Diagram for Pediatric Stage 1



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 Stage 1



IS = immunosuppressive medication

3.1.2.2 Pediatric Stage 2

Stage 2 of this trial will include up to a maximum of 480 pediatric study participants (up to 80 per arm) with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL after previous COVID-19 vaccine administration (an age-appropriate EUA-authorized or FDA-approved initial COVID-19 vaccine regimen plus 1 additional dose of the same vaccine as shown in Table 8). All participants (2-17 years of age) who previously received doses of the Pfizer-BioNTech COVID-19 Vaccine are eligible to receive an age-appropriate dose of the Moderna COVID-19 Vaccine. Participants 12 through 17 years of age who previously received doses of the Moderna COVID-19 vaccine are eligible to receive an age-appropriate dose of the Pfizer-BioNTech COVID-19 Vaccine.

Participants will be eligible to receive a dose of an alternative COVID-19 vaccine. Participants may have received their previous COVID-19 vaccine as a study participant and then enter into Stage 2 ("rollover participant"), or they may have received their previous COVID-19 vaccine 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 (± other rheumatic disease medications, including biologics)
    - Participants who are taking MMF or MPA (without additional B cell depleting medications or MTX) will be placed in this cohort.
- Cohort E: Receipt of MTX (± other rheumatic disease medications, including biologics)
    - Participants who are taking MTX (without additional B cell depleting medications or MMF/ MPA) will be placed in this cohort.
- Cohort F: Receipt of B cell depletion therapy within the past 18 months (± other rheumatic disease medications)
    - Participants taking B cell depletion medications, regardless of whether they are also taking MMF or MTX, will be placed in this cohort.

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 age-appropriate doses of a single mRNA vaccine (Moderna COVID-19 Vaccine OR Pfizer-BioNTech COVID-19 Vaccine, as noted above) will receive the other mRNA COVID-19 vaccine. Table 8 describes the age-appropriate qualifying COVID-19 vaccine regimen for participation in Pediatric Stage 2.

Update: Beginning with v6.0 of the protocol, bivalent versions of the mRNA vaccines, Moderna and Pfizer-BioNTech COVID-19 vaccines, replaced original monovalent versions.

Participants in Cohorts D and E will withhold their cohort-defining IS medications before and after the alternative vaccine dose per protocol instructions (see Section 7.1.1 Protocol-mandated Medications).

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 instruction (see Section 7.1.1 Protocol-mandated Medications).

All potential treatment arms for Pediatric Stage 2 are detailed in Table 9.

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. Participant and study flow diagrams for Stage 2 are provided in Figure 7 and Figure 8, respectively.

A participant who enters Stage 2 after a serologic negative, suboptimal, or low immune response to their Stage 1 vaccine dose may be on study for up to a maximum of 26 months. Rollover participants will discontinue follow-up as part of Stage 1 upon rollover into Stage 2. 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.

Table 8. Qualifying COVID-19 Vaccine Regimens and Study Doses for Pediatric Stage 2 Participants

Pfizer-BioNTech COVID-19 Vaccine		
Age of Participant	**Qualifying Regimen**	**ACV01 Stage 2 Study Dose of Moderna**
2 years through 4 years	4 doses of 3 mcg	25 mcg bivalent
5 years *	4 doses of 3 mcg ***OR*** 3 doses of 10 mcg	25 mcg bivalent
6 years through 11 years	3 doses of 10 mcg	50 mcg bivalent
12 years through 17 years **	3 doses of 30 mcg	100 mcg bivalent

* Individuals who turned from 4 years to 5 years of age between any doses in the previous vaccine series may also have received one, two or three doses of 3 mcg as part of the qualifying regimen. Individuals who turned from 4 years to 5 years of age after completion of the previous vaccine series may also have received four doses of 3 mcg as the qualifying regimen.

**Individuals who turned from 11 years to 12 years of age between doses in the primary regimen may also have received one or two doses of 10 mcg as part of the qualifying regimen. Individuals who turned from 11 years to 12 years of age after completion of the primary series may also have received three doses of 10 mcg as the qualifying regimen.

Moderna COVID-19 Vaccine		
Age of Participant	**Qualifying Regimen**	**ACV01 Stage 2 Study Dose of Pfizer-BioNTech**
12 years through 17 years *	3 doses of 100 mcg	30 mcg bivalent

**Individuals who turned from 11 years to 12 years of age between doses in their primary vaccine series may also have received one or two doses of 50 mcg as part of the qualifying regimen. Individuals who turned from 11 years to 12 years of age after completion of the previous vaccine series primary series may have also received three doses of 50 mcg as the qualifying regimen.

Table 9. Treatment Arm Assignments in Pediatric Stage 2

	Previous Vaccine Doses	**Stage 2 Arm**	**Stage 2 Alternative Vaccine Dose***
Cohort D: MMF or MPA	Moderna COVID-19 vaccine (from Arms A1P or A4P, or newly recruited) **Ages 12-17 only**	ARM D1P	Pfizer-BioNTech COVID-19 Vaccine
	Pfizer-BioNTech COVID-19 vaccine (from Arms A2P or A5P, or newly recruited) **Ages 2-17**	ARM D2P	Moderna COVID-19 Vaccine
Cohort E: Methotrexate	Moderna COVID-19 vaccine (from Arms B1P or B4P, or newly recruited) **Ages 12-17 only**	ARM E1P	Pfizer-BioNTech COVID-19 Vaccine
	Pfizer-BioNTech COVID-19 vaccine (from Arms B2P or B5P, or newly recruited) **Ages 2-17**	ARM E2P	Moderna COVID-19 Vaccine
Cohort F: B cell depletion therapy	Moderna COVID-19 vaccine (from Arms C1P, or newly recruited) **Ages 12-17 only**	ARM F1P	Pfizer-BioNTech COVID-19 Vaccine
	Pfizer-BioNTech COVID-19 vaccine (from Arms C2P or newly recruited) **Ages 2-17**	ARM F2P	Moderna COVID-19 Vaccine

*Bivalent vaccines will be administered per Section 6, Investigational Agents

Figure 7. Participant Flow Diagram for Pediatric Stage 2

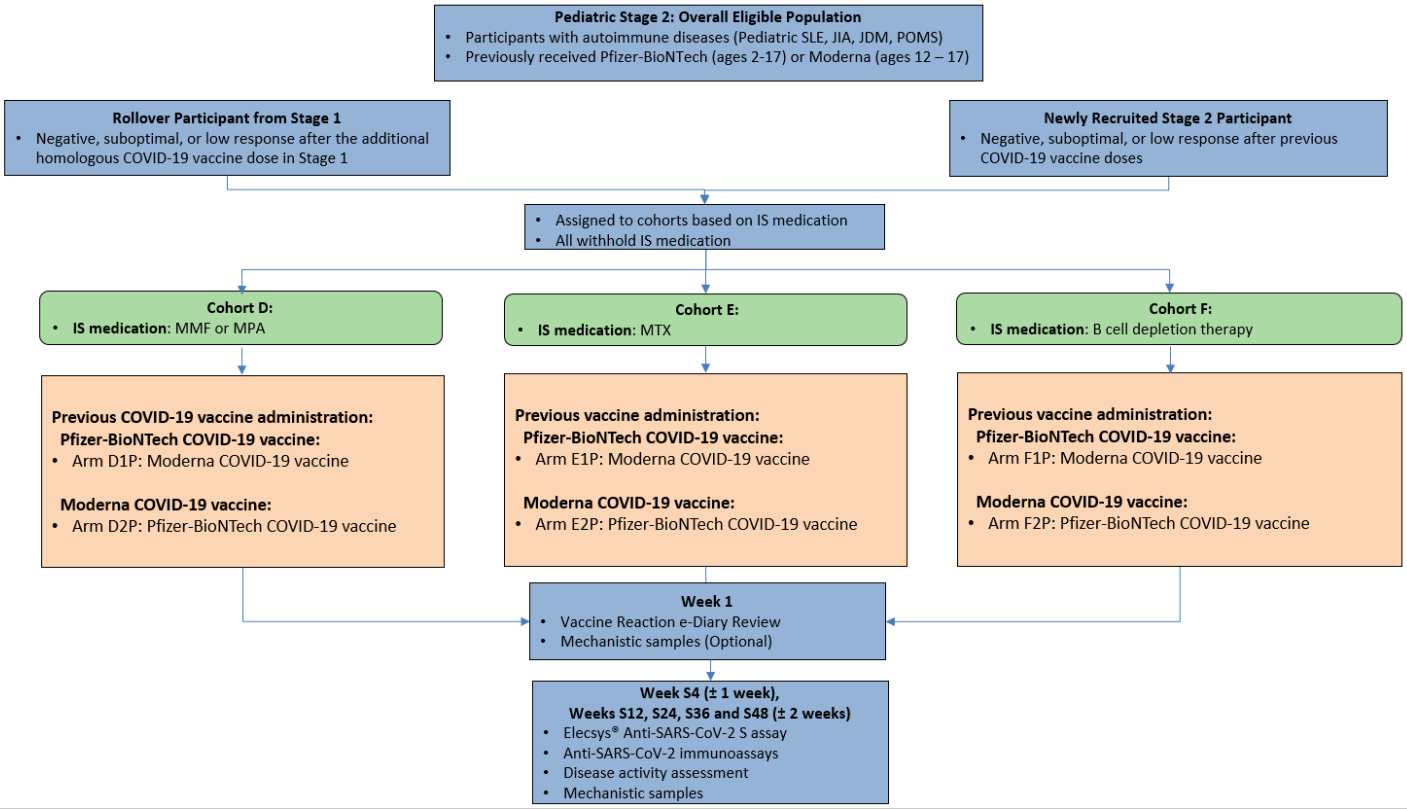
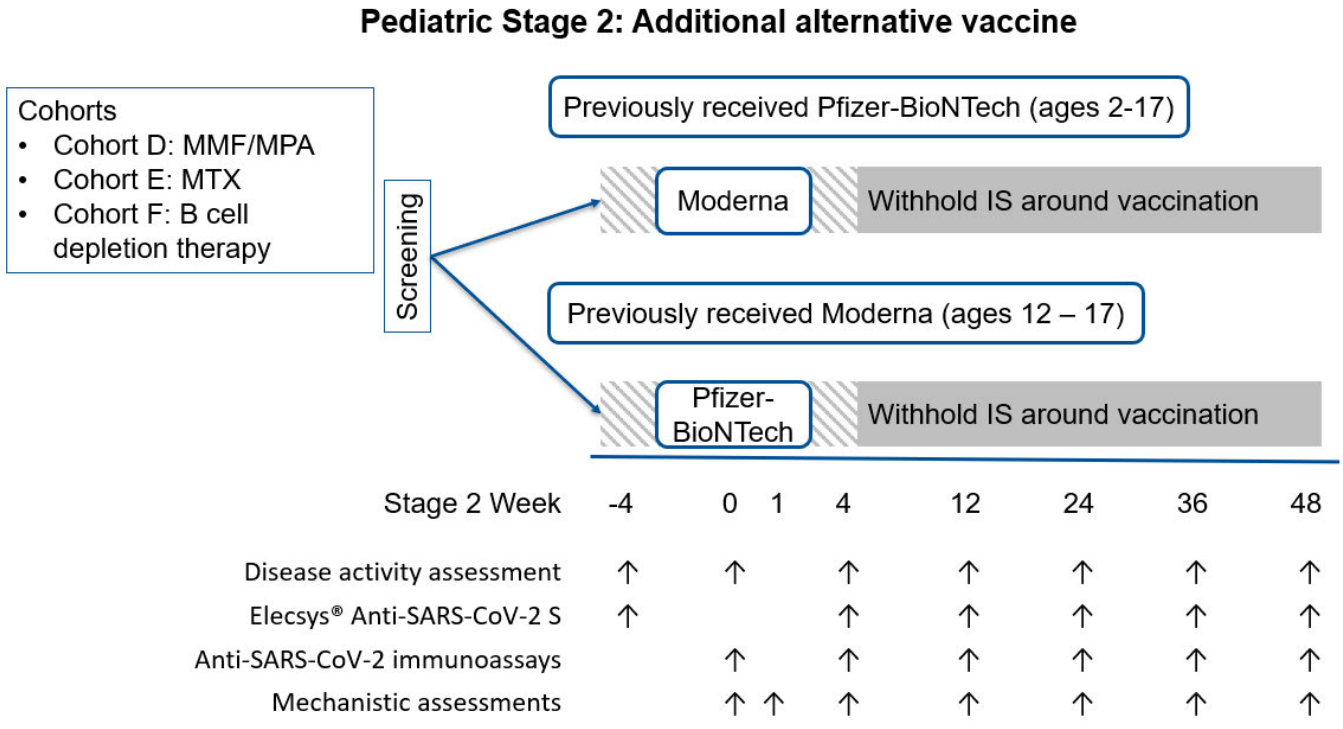


Figure 8. Study Flow Diagram for Pediatric Stage 2



3.1.3 Adaptive Design

An adaptive design will be employed in this trial 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 EUA authorizations 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 suboptimal or low immune 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 suboptimal or low immune response 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 COVID-19 vaccines 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.

3.2 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.

3.3 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:
    - Adult population disease assessments:

- 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
- Disease Activity Score 28 using C-reactive protein (DAS28-CRP) for RA
- Flare assessment for SSc (including patient reported flare assessment)
- Pemphigus Disease Area Index (PDAI) for pemphigus
- Physician-assessed relapse for MS

- Pediatric population disease assessments:
  - JIA:
    - JADAS10 for polyarthritis, enthesitis related to JIA, oligoarthritis, and psoriatic arthritis
    - Psoriasis Area and Severity Index (PASI) for psoriatic arthritis
  - SLEDAI-2K and Childhood-onset SLE Criteria for Global Flare [1] for pediatric SLE
  - Childhood Myositis Assessment Scale (CMAS) and Flare Assessment for JDM (Disease Activity Score [DAS]) for JDM
  - 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

3.4 Exploratory Endpoints

The exploratory endpoints are applicable to both the adult and pediatric populations.

- 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

3.5 Stratification, Randomization, and Blinding

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.

The same password-protected, web-based system will be used for allocation of participants to arms and associated tasks and tracking when randomization is not employed.

3.5.1 Adult Population

3.5.1.1 Adult Stage 1

Participants who sign the informed consent form and meet all eligibility criteria for Adult Stage 1 will be assigned to cohorts defined by IS medication (Cohort A: MMF/MPA; Cohort B: MTX; and Cohort C: BCDT) and by the initial COVID-19 vaccine regimen received (Moderna COVID-19 Vaccine, Pfizer-BioNTech COVID-19 Vaccine, or Janssen COVID-19 Vaccine).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.

3.5.1.2 Adult Stage 2

Participants who have signed the informed consent form and meet all eligibility criteria for Adult Stage 2 will be allocated to cohorts defined by IS medication (Cohort D: MMF/MPA; Cohort E: MTX; and Cohort F: BCDT) and by the previous COVID-19 vaccine regimen. See Section 3.1.1.2 Adult Stage 2 for treatment arm vaccine assignments.

Participants in Cohort D will withhold their MMF/MPA, participants in Cohort E will withhold their MTX, and any participants in Cohort F (BCDT) who are also taking MMF/MPA or MTX will withhold these medications. No randomization will be employed.

A total of 80 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL will be allocated to each arm. In each arm, the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results ≤200 U/mL will be capped at 40 participants; the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results > 200 U/mL and ≤2500 U/mL will be capped at 40 participants.

3.5.2 Pediatric Population

3.5.2.1 Pediatric Stage 1

Participants and their legal guardian(s) who sign the consent and assent forms, as appropriate to age, and meet all eligibility criteria for Pediatric Stage 1 will be assigned to cohorts defined by IS medication (Cohort A: MMF/MPA; Cohort B: MTX; and Cohort C: BCDT) 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 80 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 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 ≤200 U/mL will be

capped at 40 participants, and the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results >200 U/mL and ≤2500 U/mL will be capped at 40 participants.

3.5.2.1 Pediatric Stage 2

Participants who have signed the informed consent and assent forms, as appropriate to age, and meet all eligibility criteria for Pediatric Stage 2 will be allocated to cohorts defined by IS medication (Cohort D: MMF/MPA; Cohort E: MTX; and Cohort F: B cell depletion therapy) and by the previous COVID-19 vaccine regimen (Pfizer-BioNTech COVID-19 Vaccine in ages 2 through 17 years or Moderna COVID-19 Vaccine in ages 12 through 17 years). 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 80 participants with a Roche Elecsys® Anti-SARS-CoV-2 S result ≤2500 U/mL will be allocated to each arm. In each arm, the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results ≤200 U/mL will be capped at 40 participants, and the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results > 200 U/mL and ≤2500 U/mL will be capped at 40 participants.

4. Selection of Participants and Clinical Sites

4.1 Rationale for Study Population

Patients with autoimmune disease are at higher risk for SARS-CoV-2 infection and inadequate response to initial COVID-19 vaccine regimen, both of which may be due in part to IS medication use. The 5 autoimmune diseases in adults and 4 autoimmune diseases in children included in this clinical trial were chosen for several reasons:

1. They represent a broad spectrum of autoimmune disease. Three diseases (MS, RA, and SLE) are among the more common autoimmune diseases in adults in the US, and 3 diseases (JIA, pediatric SLE, and JDM) are among the most common autoimmune disease in pediatric populations.
2. The medications of interest (MMF/MPA, MTX, and BCDTs) are used commonly for treatment of these autoimmune diseases.
3. They comprise a population with significant ethnic and racial diversity that was underrepresented in the original clinical trials that were used to determine EUA eligibility and that have been more severely afflicted by COVID-19.
4. Each of these diseases is studied at one or more of the NIAID-funded ACE Network institutions. This is important, as access to existing patient cohorts will be critical to rapid implementation of this clinical trial.

Due to disease-associated immune abnormalities and IS medication use, the proposed patient population is at increased risk for AEs compared to a non-autoimmune disease population. The inclusion/exclusion criteria are designed to limit these risks and ensure the safety of those participating in the study. Specifically, participants with active disease at Screening or who have initiated new IS therapy within 8 weeks of Screening for active disease or with active infection will be excluded. Only autoimmune disease patients with a negative or suboptimal serologic response to the initial COVID-19 vaccine regimen will be included in Adult Stage 1. A suboptimal response to primary vaccine is defined as an Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL at the Screening visit. In Pediatric Stage 1 and in Adult and Pediatric Stage 2, patients with a negative or suboptimal serologic response will be included along with patients with a low immune response, defined as an Elecsys® Anti-SARS-CoV-2 S result >200 U/mL and ≤2500 U/mL. Other antibody and cellular measures of response will be tested in the trial.

In order to maximize participant response to Stage 2 vaccination, all participants will withhold MTX or MMF/MPA around vaccination. In addition, enrollment into Pediatric Stage 2 of participants who have previously received doses of the Moderna COVID-19 Vaccine and are to receive the Pfizer COVID-19 Vaccine is limited to individuals aged 12 through 17.

The CDC recommends bivalent COVID-19 vaccines for moderately or severely immunocompromised individuals who are eligible to receive one under FDA EUA [55]. If a bivalent version of a COVID-19 vaccine is not available for a participant via the ACV01 study design but is available through the community, the participant will be directed to obtain the bivalent COVID-19 vaccine in the community.

Due to the rapid nature of the evaluation of the COVID pandemic, the speed with which COVID vaccinations are coming into use, and ongoing data generated in the observational studies and in autoimmune disease cohorts, an adaptive clinical trial design will be used in this study. The initial IS medications, MMF/MPA, MTX, and BCDTs were originally selected as those that have a deleterious impact on vaccination response. However, as the trial evolves, and other autoimmune disease therapies emerge as negatively impacting COVID-19 vaccination effects then they may be added to the trial. Second, as data emerges, it may become evident through the ACV02 observational study, cohort studies, published literature, or real-world exposures that other autoimmune diseases treated with the therapies included in this trial are more severely impaired in their vaccination responses. If so, and if additional resources are available, then other autoimmune diseases, such as psoriasis, psoriatic arthritis, vasculitis, inflammatory bowel disease, or others may be added to the protocol through the adaptive design.

4.2 Inclusion and Exclusion Criteria

Prior to evaluation of the entry criteria for a potential participant, the participant's cohort placement and qualifying disease will be determined according to the description in Section 8.1.2.2 Determination of Participant Cohort and Identification of Qualifying Disease.

4.2.1 Inclusion and Exclusion Criteria for Adult Participants

4.2.1.1 Inclusion and Exclusion Criteria for Adult Stage 1

4.2.1.1.1 Inclusion Criteria for Adult Stage 1

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 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [2] or 2012 Systemic Lupus International Collaborating Clinics (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 (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, 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 BCDT cohort, the participant must have received an anti-CD20 or an anti-CD19 BCDT in the past 18 months.

7. No changes in background IS medications, including MMF/MPA or MTX, in the 4 weeks prior to Screening, excluding the following:

a. Hydroxycholoroquine (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 chronic obstructive pulmonary disease (COPD), are permitted.

4.2.1.1.2 Exclusion Criteria for Adult Stage 1

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 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 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 BCDT 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.

4.2.1.2 Inclusion and Exclusion Criteria for Adult Stage 2

4.2.1.2.1 Inclusion and Exclusion Criteria for Adult Stage 2 Newly Recruited Participants

4.2.1.2.1.1 *Inclusion Criteria for Adult Stage 2 Newly Recruited Participants*

Individuals who meet all of the following criteria are eligible for enrollment as participants in Adult 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 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 a previous COVID-19 vaccine administration 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, or a low immune response, defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 U/mL, within 4 weeks of the Stage 2 Baseline/Week 0 visit.

6. The regimens of COVID-19 vaccination that qualify are as follows:
    a. 3 doses of the Pfizer-BioNTech COVID-19 Vaccine
    b. 3 doses of the Moderna COVID-19 Vaccine
    c. 2 doses of the Janssen COVID-19 Vaccine
    d. 4 or more doses of a single mRNA vaccine (Pfizer-BioNTech COVID-19 Vaccine OR Moderna COVID-19 Vaccine)
    e. 3 or more doses of a mixture of mRNA vaccines (Pfizer-BioNTech COVID-19 Vaccine OR Moderna COVID-19 Vaccine)
7. 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 BCDT cohort, the participant must have received an anti-CD20 or an anti-CD19 BCDT in the past 18 months.
8. 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.

4.2.1.2.1.2 *Exclusion Criteria for Adult Stage 2 Newly Recruited Participants*

Individuals who meet any of these criteria are not eligible for enrollment as participants in Adult 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 the COVID-19 vaccine, or to any component of the COVID-19 vaccine, that is to be administered in Stage 2, including polysorbate for participants receiving the Sanofi-GSK COVID-19 Vaccine, 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 a mixture of Janssen COVID-19 vaccines and mRNA COVID-19 vaccines (in any order or combination) prior to Stage 2 Screening.
8. Inflammatory myocarditis/pericarditis within 6 weeks of 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 BCDT as part of a clinical trial within 18 months of Stage 2 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.

4.2.1.2.2 Inclusion and Exclusion Criteria for Adult Stage 2 Rollover Participants

Individuals who were previously enrolled in Adult Stage 1 or Adult Stage 2 will have met some inclusion and exclusion criteria at that time. Only a subset of the criteria for (re-)entering Adult Stage 2 will be assessed in rollover participants at the time of screening for Stage 2. The criteria below are numbered to match the criteria for newly recruited participants. The criteria that are not noted below do not need to be reassessed for rollover participants.

4.2.1.2.2.1 *Inclusion Criteria for Adult Stage 2 Rollover Participants*

Individuals who meet all of the following criteria are eligible to (re-)enter Adult Stage 2*:*

4. Received an additional COVID-19 vaccine dose that was completed at least 4 weeks prior and no more than 48 weeks prior to the Stage 2 vaccination.
5. Negative or suboptimal serologic response to a previous COVID-19 vaccine administration 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, or a low immune response, defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 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 doses of the Pfizer-BioNTech COVID-19 Vaccine
   b. 3 doses of the Moderna COVID-19 Vaccine
   c. 2 doses of the Janssen COVID-19 Vaccine
   d. 4 doses of a combination of mRNA vaccines (i.e., Pfizer-BioNTech COVID-19 Vaccine, 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 7.5 mg 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 BCDT cohort, the participant must have received an anti-CD20 or an anti-CD19 BCDT 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.

4.2.1.2.2.2 *Exclusion Criteria for Adult Stage 2 Rollover Participants*

Individuals who meet any of these criteria are not eligible to (re-)enter Adult Stage 2*:*

2. History of severe allergic reaction to the COVID-19 vaccine, or to any component of the COVID-19 vaccine, that is to be administered in Stage 2, including polysorbate for participants receiving the Sanofi-GSK COVID-19 Vaccine, 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 or Stage 2 Baseline/Week 0.
8. Inflammatory myocarditis/pericarditis within 6 weeks of 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.

4.2.2 Inclusion and Exclusion Criteria for Pediatric Participants

4.2.2.1 Inclusion and Exclusion Criteria for Pediatric Stage 1

4.2.2.1.1 Inclusion Criteria for Pediatric Stage 1

Individuals who meet all of the following criteria are eligible for enrollment randomization/allocation as participants in Pediatric Stage 1:

1. Individuals 2-17 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 all pediatric participants and participants ages 14 – 17 must be willing and able to sign informed consent. Participants ages 7-13 must be willing and able to sign assent.
3. Documented EUA-authorized or FDA-approved COVID-19 vaccine doses (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 EUA-authorized or FDA-approved COVID-19 vaccine doses, defined as an Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL, or a low immune response, defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 U/mL, within 4 weeks of the Stage 1 Baseline/Week 0 visit.
    a. Initial COVID-19 vaccine regimen is defined as:
        i. Pfizer-BioNTech COVID-19 Vaccine (2 through 4 years of age): 3 age-appropriate doses.
        ii. Pfizer-BioNTech COVID-19 Vaccine (5 through 17 years of age): 2 age-appropriate doses.
        iii. Moderna COVID-19 Vaccine (2 through 17 years of age): 2 age-appropriate doses.
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 BCDT cohort, participant must have received an anti-CD20 or an anti-CD19 BCDT 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 <0.15mg/kg/dose 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.

4.2.2.1.2 Exclusion Criteria for Pediatric Stage 1

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

1. Inability or unwillingness of a participant to give assent or consent; 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 within 6 weeks of any COVID-19 vaccine doses.
9. Participants with active, ongoing chronic infections.

    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.

    Note: Participants on IVIG therapeutically may enter the study provided they have sufficiently quiet disease that they can withhold their IVIG from 8 weeks prior to the Screening visit through 4 weeks after vaccination.
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 BCDT 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.

4.2.2.2 Inclusion and Exclusion Criteria for Pediatric Stage 2

4.2.2.2.1 Inclusion and Exclusion Criteria for Pediatric Stage 2 Newly Recruited Participants

4.2.2.2.1.1 *Inclusion Criteria for Pediatric Stage 2 Newly Recruited Participants*

Individuals who meet all of the following criteria are eligible for enrollment as participants in Pediatric Stage 2:

1. Individuals 2-17 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 all pediatric participants and participants ages 14 – 17 must be willing and able to sign informed consent. Participants ages 7-13 must be willing and able to sign assent.
3. Documented full COVID-19 vaccination (CDC card or documentation in medical records).
4. Received an additional 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 homologous doses of 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, or a low immune response, defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 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. Pfizer-BioNTech COVID-19 Vaccine (2 through 5 years of age): 4 full, age-appropriate doses of the Pfizer-BioNTech COVID-19 Vaccine
    b. Pfizer-BioNTech COVID-19 Vaccine (5 through 17 years old): 3 full, age-appropriate doses of the Pfizer-BioNTech COVID-19 Vaccine

        Note: Participants who are 5 years old and previously received the Pfizer-BioNTech COVID-19 Vaccine may have received either age-appropriate regimen. See Section 3.1.2.2, Pediatric Stage 2 *for additional details.*

    c. Moderna COVID-19 Vaccine (12 through 17 years of age): 3 full, age-appropriate 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 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 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, 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 Screening, excluding the following:

   a. HCQ,

   b. Intraarticular steroids,

   c. The addition of prednisone at <0.15mg/kg/dose 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.

4.2.2.2.1.2 *Exclusion Criteria for Pediatric Stage 2 Newly Recruited Participants*

Individuals who meet any of these criteria are not eligible for enrollment as participants in Pediatric Stage 2*:*

1. Inability or unwillingness of a participant to give assent or consent; 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 vaccine, that is to be administered in Stage 2, 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 an additional heterologous COVID-19 vaccine dose prior to Stage 2 Screening, i.e., a participant cannot have received a mixture of mRNA vaccines.
8. Inflammatory myocarditis/pericarditis within 6 weeks of any COVID-19 vaccine doses.
9. Participants with active, ongoing chronic infections.

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.

    Note: Participants on IVIG therapeutically may enter the study provided they have sufficiently quiet disease that they can withhold their IVIG from 8 weeks prior to the Screening visit through 4 weeks after vaccination.

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.

4.2.2.2.2 Inclusion and Exclusion Criteria for Pediatric Stage 2 Rollover Participants

Individuals who were previously enrolled in Pediatric Stage 1 will have met some inclusion and exclusion criteria at that time. Only a subset of the criteria for entering Pediatric Stage 2 will be assessed in rollover participants at the time of screening for Stage 2. The criteria below are numbered to match the criteria for newly recruited participants. The criteria that are not noted below do not need to be reassessed for rollover participants.

4.2.2.2.2.1 *Inclusion Criteria for Pediatric Stage 2 Rollover Participants*

Individuals who meet all of the following criteria are eligible to continue as participants in Pediatric Stage 2:

4. Received an additional COVID-19 vaccine dose that was completed at least 4 weeks prior and no more than 48 weeks prior to the Stage 2 vaccination.
5. Negative or suboptimal serologic response to a previous COVID-19 vaccine administration 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, or a low immune response, defined as an Elecsys® Anti-SARS-CoV-2 S (RBD) result of ≤2500 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. Pfizer-BioNTech COVID-19 Vaccine (2 through 5 years of age): 4 full, age-appropriate doses of the Pfizer-BioNTech COVID-19 Vaccine

b. Pfizer-BioNTech COVID-19 Vaccine (5 through 17 years old): 3 full, age-appropriate doses of the Pfizer-BioNTech COVID-19 Vaccine

Note: Participants who are 5 years old and previously received the Pfizer-BioNTech COVID-19 Vaccine may have received either age-appropriate regimen. See Section 3.1.2.2, Pediatric Stage 2 *for additional details.*

c. Moderna COVID-19 Vaccine (12 through 17 years of age): 3 full, age-appropriate 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 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 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, 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, excluding the following:

a. HCQ,

b. Intraarticular steroids,

c. The addition of prednisone at <0.15mg/kg/dose 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.

4.2.2.2.2.2 *Exclusion Criteria for Pediatric Stage 2 Rollover Participants*

Individuals who meet any of these criteria are not eligible to enter Pediatric Stage 2*:*

2. History of severe allergic reaction to the initial COVID-19 vaccine regimen, or any component of any of the COVID-19 vaccine, that is to be administered in Stage 2, 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 or Stage 2 Baseline/Week 0.

8. Inflammatory myocarditis/pericarditis within 6 weeks of 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 (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 Stage 2 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.

22. Participants with active systemic infections who have received systemic antimicrobials within the 14 days prior to Stage 2 Baseline/Week 0.

5. Known and Potential Risks and Benefits to Participants

5.1 Risks of Investigational Products

5.1.1 Risks of COVID vaccine based on the mRNA vaccines (Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine)

Adverse reactions reported in a clinical trial following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, erythema at the injection site, swelling at the injection site, fever, and rash [48]. Groin swelling/tenderness was observed in individuals aged 17 months – 5 years. In addition, irritability/crying, swelling/tenderness in the groin, and loss of appetite adverse reactions were reported in individuals aged 6 – 36 months [61]. Severe allergic reactions have been reported following the Moderna COVID-19 Vaccine during mass vaccination outside of clinical trials, most commonly in participants with allergic history and usually within the first 15-20 minutes of vaccination [48]. Other side effects reported during post-authorization use include urticaria, myocarditis, pericarditis, and fainting associated with injection of the vaccine.

Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, injection site swelling, fever, injection site redness, lymphadenopathy, nausea, malaise, pain in extremity, rash, decreased appetite, diarrhea, vomiting, arm pain, fainting in association with injection of the vaccine, and dizziness [58]. Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials, most commonly in participants with allergic history and usually within the first 15-20 minutes of vaccination [58].

Myocarditis and pericarditis adverse reactions have been noted following administration of both mRNA vaccines (Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine). These adverse reactions have been reported mainly in male adolescents and young adults after receipt of the second dose of vaccine [62]. Short-term follow-up data suggests most individuals have had complete resolution with conservative management, although some have required intensive care support. Long-term data are not available.

Symptoms of myocarditis or pericarditis include chest pain, shortness of breath, or feelings of having a fast-beating, fluttering, or pounding heart, with onset of symptoms most commonly reported within a few days following vaccination. Symptoms may differ in younger pediatric populations, particularly in the 6 month to <5 year age group, and may include respiratory distress, fainting, irritability, lethargy, unusual and persistent cool, pale skin, or nonspecific gastrointestinal symptoms (poor feeding, abdominal pain, and vomiting). If any of these symptoms occur following vaccination, study participants should seek immediate medical attention and notify study site staff. Participants reporting acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis within 6 weeks after vaccination must be referred to a cardiologist for evaluation and management.

Syncope may occur with the administration of vaccines, particularly in adolescents.

Two SAEs of facial swelling in individuals with a history of injection of dermatological fillers were reported following administration of the Moderna vaccine and were deemed as likely related to vaccine administration.

SPIKEVAX (COVID-19 Vaccine, mRNA) and Moderna COVID-19 Vaccine can be used interchangeably. Moderna COVID-19 Vaccine, Bivalent is made in the same way as SPIKEVAX and Moderna COVID-19 Vaccine, but it also contains an Omicron component to help prevent COVID-19 caused by the Omicron variant of SARS-CoV-2. Safety data with Moderna COVID-19 Vaccine are relevant to Moderna COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process.

COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine, when prepared according to their respective instructions for use, can be used interchangeably. The Pfizer-BioNTech COVID-19 Vaccine, Bivalent is made in the same way as COMIRNATY and Pfizer-BioNTech COVID-19 Vaccine but it also contains an Omicron component to help prevent COVID-19 caused by the Omicron variant of SARS-CoV-2. Safety data with Pfizer-BioNTech COVID-19 Vaccine are relevant to Pfizer-BioNTech COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process.

5.1.1.1 Allergic Reactions and Anaphylaxis

Allergic reactions have been reported to occur after vaccination with both the Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine. Allergic reactions range from mild to severe and include life-threatening anaphylactic reactions, although no deaths have been reported with either vaccine [48, 58].

If a participant has an allergic reaction, he/she may need oral, intramuscular, or intravenous medications and will be treated per institutional standard (see Section 7.4 Rescue Medications). Emergency medications, oxygen, and equipment will be available to treat any allergic reactions.

5.1.2 Risks of COVID vaccine based on the Janssen COVID-19 Vaccine

Adverse reactions following administration of the Janssen COVID-19 Vaccine include injection site pain, erythema and swelling. Systemic reactions include headache, fatigue, myalgia, nausea, chills, and fever. Most solicited adverse reactions are mild to moderate, occur within 1-2 days of vaccine administration and have a median duration of 1-2 days [63]. Severe allergic reactions, including 1 case of anaphylaxis, have been reported following the Janssen COVID-19 Vaccine administered in clinical studies [59].

Data from clinical studies showed numerical imbalance with more events in the vaccine arm in the following events [59]:

1. Thromboembolic events including deep vein thrombosis, pulmonary embolism, transverse sinus thrombosis
2. Seizures
3. Tinnitus

5.1.2.1 Thrombosis with Thrombocytopenia after Janssen COVID-19 Vaccination

Reports to the Vaccine Adverse Events Reporting System (VAERS) have provided evidence for an increased risk of thrombosis with thrombocytopenia syndrome (TTS) with onset of symptoms occurring one to two weeks following administration of the Janssen COVID-19 vaccine. Cases of TTS have been reported in males and females over a wide range of ages. The highest reporting rate (approximately 1 case per 100,000 doses) is in females aged 30-49. Overall, approximately 15% of cases have been fatal. The clinical course of TTS shares features with heparin-induced thrombocytopenia [59].

The following case definition of TTS were used:

1. A thrombosis in an unusual location for a thrombus and new onset thrombocytopenia (platelet count <150,000/uL) any time after vaccination. OR
2. New onset thrombocytopenia, thrombosis in an extremity vein, or the pulmonary artery in the absence of thrombosis at an unusual location and a positive anti-PF-4 antibody or functional heparin-induced thrombocytopenia.

Providers should maintain a high index of suspicion for symptoms consistent with TTS within several weeks of receipt of the Janssen COVID-19 Vaccine.

Recipients of the Janssen COVID-19 vaccine should seek immediate medical attention if they develop shortness of breath, chest pain, leg swelling, persistent abdominal pain, neurological symptoms, or petechiae beyond the site of vaccination.

5.1.2.2 Booster Doses in Immunologically Competent Individuals

Additional safety concerns have not been identified with homologous booster doses of any of the 3 SARS-CoV-2 vaccines discussed above.

An independent Phase 1/2 open-label clinical trial (NCT04889209) was conducted in the US that evaluated heterologous dosing of individuals who had completed a primary series of one of the 3 vaccine discussed above and had no evidence of infection with SARS-CoV-2. Adverse events were assessed through 28 days following the booster dose, and the data revealed no safety concerns for any of the 3 vaccines given as a heterologous dose compared with adverse reactions following the primary series dosing or an homologous booster dose.

5.1.2.3 Guillain Barré Syndrome after Janssen COVID-19 Vaccination

After approximately 12.5 million doses of the Janssen vaccine were administered, a review of data from VAERS identified 100 occurrences of Guillain Barré Syndrome (GBS) following administration of the Janssen COVID-19 Vaccine[64]. Of the 100 cases of GBS following Janssen vaccine administration, 95 were categorized as serious and resulted in hospitalization, and 1 death was reported[64]. These events suggest an increased risk of GBS during the 42 days following Janssen COVID-19 Vaccine administration[59].

5.1.2.4 Syncope

Syncope may occur in association with administration of injectable vaccines.

5.1.3 Risks of COVID vaccine based on the Sanofi-GSK COVID-19 Vaccine

Expected risks of the Sanofi-GSK COVID-19 Vaccine and AS03 adjuvant, based on the Sanofi Pasteur CoV2 preS dTM-AS03 adjuvanted vaccine Investigator's Brochure (v11; 25MAR2022) and the AS03 Adjuvant System Investigational Brochure (Edition 2, Version 2; 10MAR2022), include solicited injection site and systemic events. Injection site reactions may include injection site pain, injection site erythema, injection site swelling, injection site pruritus, upper limb edema, and, possibly, the extensive swelling of the vaccinated limb extending beyond the closest joint. Systemic reactions may include fatigue, nausea, diarrhea, fever, headache, malaise, myalgia, arthralgia, and chills as separate events or a combination of events.

Potential (not observed in clinical trials) class effect for all vaccines include anaphylactic reactions, vaccine-associated enhanced disease, exacerbation of pre-existing or development of new immune-mediated disease, and vasovagal reactions or psychogenic reactions.

5.2 Risks of Other Protocol-specified Medications

There are no other protocol-mandated medications. All other medications used by participants are prescribed for their underlying conditions and will be recorded on the appropriate electronic case report form (eCRF). Depending on assignment, participants may be instructed to hold their MTX or MMF/MPA during the period around their vaccination.

5.3 Risks of Study Procedures

5.3.1 Risks Associated with Withdrawal of IS Medications

Participants in Cohorts A and B may be randomized to withdraw their cohort-defining IS medications around the time of the additional homologous vaccine dose. Withdrawal of IS medications could lead to disease exacerbation and flare. Participants will be evaluated for increases in disease activity during the Baseline/Week 0 visit prior to administration of the additional homologous vaccine dose.

5.3.2 Risks Associated with Blood Collection

Risks associated with drawing blood include possible pain when the needle is inserted, as well as bleeding, bruising and/or infection at the puncture site. Some people may experience lightheadedness, nausea, or fainting. National Institutes of Health (NIH) guidelines for blood collection (amount and frequency) will be followed [65].

5.3.3 Risks Associated with Physical Exam

There are no known risks associated with the physical exam.

5.3.4 Risks Associated with Medical History or Participant Diary

There is a possibility that participants may find questions about their medical history or questions asked on the participant diary to be too personal. Participants may refuse to answer any questions that make them feel uncomfortable. There is also a possibility that a participant's answers may be read by others; however, participants' records are carefully protected so this is very unlikely. See Section 17.3 Privacy and Confidentiality for more information.

5.3.5 Risks Associated with Urine Collection

There are no risks associated with urine sample collection.

5.3.6 Risks Associated with Nasal Swab Collection

Nasal swab collection may cause localized discomfort. The participant may experience moderate discomfort, and in rare instances, nosebleeds can occur as a result of nasopharyngeal, nasal swab and/or other mechanistic oronasal samples. The participant may also experience watery eyes and/or coughing, but only for the short duration of the swab.

5.4 Potential Benefits

There is no guaranteed benefit to participants. Recent preliminary reports have suggested that individuals with autoimmune disease on IS medications may not develop a protective immune response to vaccination against SARS-CoV-2. Information gained from this study may identify reasons for the lack of response, enhance understanding of the immunologic mechanism for protective response other than antibody titers and/or identify clinical methods of improving the vaccine response by inducing higher levels of antibodies or cell mediated immunity in individuals with suboptimal antibody responses to primary vaccination [19].

6. Investigational Agents

The investigational agents provided in the study include: the Moderna COVID-19 vaccines, the Pfizer-BioNTech vaccines, the Janssen COVID-19 vaccine, and the Sanofi-GSK CoV2 preS dTM-AS03 adjuvanted vaccine. The vaccines no longer offered in the study are indicated in the sections below.

Additional details regarding vaccine storage, dosage, preparation, and administration can be found in the ACV01 Pharmacy Manual. Vaccine administration details will be recorded on the Vaccine Administration eCRF.

6.1 Investigational Agent #1: Moderna COVID-19 Vaccine

The Moderna COVID-19 vaccines are being used in the study to provide additional booster doses to eligible study participants.

The table below describes the Moderna COVID-19 Vaccine dosing used in ACV01 protocol v7.0:

Table 10. Moderna COVID-19 Vaccine Dosing

Age of Participant	Stage 1 Dose	Stage 2 Dose
2 years through 5 years	25 mcg (Bivalent)	25 mcg (Bivalent)
6 years through 11 years	50 mcg (Bivalent)	50 mcg (Bivalent)
12 years through 17 years	100 mcg (Bivalent)	100 mcg (Bivalent)
18 years and older	N/A (*Closed*)	100 mcg (Bivalent)

The table below describes details on the Moderna COVID-19 Vaccine products provided in ACV01 Protocol v7.0:

Table 11. Moderna COVID-19 Vaccine Products

COVID-19 Vaccine Information & Vial cap color/Label Border	**Moderna Dark Blue Cap/Gray Label Border BIVALENT Vaccine; Currently Provided in ACV01**	**Moderna Dark Blue Cap/Magenta Border MONOVALENT Vaccine; NO LONGER PROVIDED in ACV01: (DATE DISCONTINUED IN ACV01: 08 December 2022)**	**Moderna Red cap/Light Blue Border MONOVALENT Vaccine; NO LONGER PROVIDED in ACV01 (DATE DISCONTINUED IN ACV01: 31 August 2022)**
EUA APPROVED AGE	6 years and older	6 months through 5 years	12 years and older
AGE of ACV01 Study Participants	2 years through 17 years 18 years and older (Stage 2 only)	2 years through 5 years Stage 1 only	12 years and older
Pharmaceutical Formulation	➤ Each 0.5 mL dose of vaccine contains: ✓ mRNA-1273.222*: 50 mcg ✓ Tromethamine: 0.25 mg ✓ Tromethamine hydrochloride: 1.2 mg ✓ Acetic acid: 0.021 mg ✓ Sodium acetate trihydrate: 0.10 mg ✓ Sucrose: 43.5 mg ✓ Total lipid content: 1.01 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]). ➤ Each 0.25 mL dose of vaccine contains half of these ingredients ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.5 mL of vaccine contains 25 mcg nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Wuhan-Hu-1 strain (Original) and 25 mcg mRNA encoding the pre-fusion stabilized S-protein of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.	➤ Each 0.25 mL dose of vaccine contains: ✓ mRNA-1273*: 25 mcg ✓ Tromethamine: 0.13 mg ✓ Tromethamine hydrochloride: 0.62 mg ✓ Acetic acid: 0.011 mg ✓ Sodium acetate trihydrate: 0.049 mg ✓ Sucrose: 21.8 mg ✓ Total lipid content: 0.5 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]). ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.25 mL dose of vaccine contains 25 mcg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Wuhan-Hu-1 strain.	➤ Each 0.5 mL dose of vaccine contains: ✓ mRNA-1273*: 100 mcg ✓ Tromethamine: 0.31 mg ✓ Tromethamine hydrochloride: 1.18 mg ✓ Acetic acid: 0.043 mg ✓ Sodium acetate trihydrate: 0.20 mg ✓ Sucrose: 43.5 mg ✓ Total lipid content: 1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]) ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.5 mL dose of vaccine contains 100 mcg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Wuhan-Hu-1 strain.
Dosage Form	Suspension for IM injection	Suspension for IM injection	Suspension for IM injection
Final Concentration	100 mcg/mL	100 mcg/mL	200 mcg/mL
Total Dose and Volume Per Vial	250 mcg/ 2.5 mL	250 mcg/ 2.5 mL	1100 mcg/ 5.5 mL
No. of Doses Per Vial	10 doses of 25 mcg 5 doses of 50 mcg	10 doses of 25 mcg	10-11 doses of 100mcg
Dilution Required?	NO	NO	NO
ACV01 mRNA Dose and Volume	25 mcg/0.25mL (2 through 5 years) 50 mcg/0.5 mL (6 through 11 years) 100 mcg/ 1 mL (12 years and older)	25 mcg/ 0.25 mL	100 mcg/ 0.5 mL
ACV01 Number of Doses Per Vial	Multiple Dose Vial: 10 doses of 25 mcg, 5 doses of 50 mcg, or 2 doses of 100 mcg	Multiple Dose Vial: 10 doses of 25 mcg	Multiple Dose Vial: 10 to 11 doses

6.2 Investigational Agent #2: Pfizer-BioNTech COVID-19 Vaccine

The Pfizer-BioNTech COVID-19 vaccines are being used in the study to provide additional booster doses of vaccine to eligible participants.

The table below describes the Pfizer-BioNTech COVID-19 Vaccine dosing provided in the ACV01 protocol v7.0:

Table 12. Pfizer-BioNTech COVID-19 Vaccine Dosing

Age of Participant	**Stage 1 Dose**	**Stage 2 Dose (Alternative Dose)**
2 years through 4 years	3 mcg (Bivalent)	N/A
5 years through 11 years	10 mcg (Bivalent)	N/A
12 years through 17 years	30 mcg (Bivalent)	30 mcg (Bivalent)
18 years and older	N/A *(Closed)*	30 mcg (Bivalent)

The table below describes details on the Pfizer-BioNTech COVID-19 Vaccine products provided in ACV01 Protocol v7.0:

Table 13. Pfizer-BioNTech COVID-19 Vaccine Products

COVID-19 Vaccine Information & Vial cap color/Label Border	**Pfizer Maroon Cap/Maroon Label Border BIVALENT Vaccine; Currently Provided in ACV01**	**Pfizer Orange Cap/Orange Label Border BIVALENT Vaccine; Currently Provided in ACV01**	**Pfizer Gray Cap/Gray Label Border BIVALENT Vaccine; Vaccine Currently Provided in ACV01**
EUA Approved Age	6 months through 4 years	5 years through 11 years	12 years and older
Age of ACV01 Study Participants	2 years through 4 years (Stage 1 only)	5 years through 11 years (Stage 1 only)	12 years through 17 years 18 years and older (Stage 2 only)
Pharmaceutical Formulation	➤ Each 0.2 mL dose of vaccine contains: ✓ modRNA*: 3 mcg ✓ Tromethamine: 0.006 mg ✓ Tromethamine hydrochloride: 0.04 mg ✓ Sucrose: 3.2 mg ✓ Total lipid content: 0.075 mg (0.04 mg ((4hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.005 mg 2[(polyethylene glycol)-2000]N,N-ditetradecylacetamide, 0.01 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.02 mg cholesterol) ✓ The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes 1.52 mg sodium chloride per dose ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.2 mL dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is formulated to contain 1.5 mcg of modRNA encoding the (S)-glycoprotein of SARS-CoV-2 Wuhan-Hu-1 strain (Original) and 1.5 mcg of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.	➤ Each 0.2 mL dose of vaccine contains: ✓ modRNA*: 10 mcg ✓ Tromethamine: 0.02 mg ✓ Tromethamine hydrochloride: 0.13 mg ✓ Sucrose: 10.3 mg ✓ Total lipid content: 0.25 mg (0.14 mg ((4hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.02 mg 2[(polyethylene glycol)-2000]N,N-ditetradecylacetamide, 0.03 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.06 mg cholesterol) ✓ The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes 0.9 mg sodium chloride per dose. ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.2 mL dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is formulated to contain 5 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 Wuhan-Hu-1 strain (Original) and 5 mcg of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.	➤ Each 0.3 mL dose of vaccine contains: ✓ modRNA*: 30 mcg ✓ Tromethamine: 0.06 mg ✓ Tromethamine hydrochloride: 0.4 mg ✓ Sucrose: 31 mg ✓ Total lipid content: 0.76 mg (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2distearoyl-sn-glycero-3-phosphocholine, and 0.19 mg cholesterol) ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is formulated to contain 15 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 Wuhan-Hu-1 strain (Original) and 15 mcg of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.
Dosage Form	Suspension for IM injection	Suspension for IM injection	Suspension for IM injection
Final Concentration	15 mcg/mL (After Dilution)	50 mcg/mL (After Dilution)	100 mcg/mL
Total Dose and Volume Per Vial	40 mcg/ 2.6 mL (After Dilution)	130 mcg/2.6 mL (After Dilution)	225 mcg/ 2.25 mL
No. of Doses Per Vial	10 doses (After Dilution)	10 doses (After Dilution)	6 doses of 30 mcg
Dilution Required?	YES; 2.2 mL of 0.9% NS	YES; 1.3 mL of 0.9% NS	NO
ACV01 mRNA Dose and Volume	3 mcg/ 0.2 mL	10 mcg/ 0.2 mL	30 mcg/ 0.3 mL
ACV01 Number of Doses Per Vial	Multiple Dose Vial: 10 doses of 3 mcg (After Dilution)	Multiple Dose Vial: 10 doses of 10mcg (After Dilution)	Multiple Dose Vial: 6 doses of 30 mcg

The table below describes details on the Pfizer-BioNTech COVID-19 Vaccine products **no longer being provided** in ACV01 Protocol v7.0:

Table 14a. Discontinued Pfizer-BioNTech COVID-19 Vaccine Products

COVID-19 Vaccine Information & Vial cap color/Label Border	**Pfizer Maroon Cap/Maroon Label Border MONOVALENT Vaccine**	**Pfizer Orange Cap/Orange Label Border MONOVALENT Vaccine**
DATE DISCONTINUED IN ACV01	08 December 2022	12 October 2022
EUA APPROVED AGE	6 months through 4 years	5 years through 11 years
AGE of ACV01 Study Participants	2 years through 4 years	5 years through 11 years
Pharmaceutical Formulation	➤ Each 0.2 mL dose of vaccine contains: ✓ modRNA*: 3 mcg ✓ Tromethamine: 0.006 mg ✓ Tromethamine hydrochloride: 0.04 mg ✓ Sucrose: 3.2 mg ✓ Total lipid content: 0.075 mg (0.04 mg ((4hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.005 mg 2[(polyethylene glycol)-2000]N,N-ditetradecylacetamide, 0.01 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.02 mg cholesterol) ✓ The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes 1.52 mg sodium chloride per dose ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.2 mL dose of vaccine contains 3 mcg of nucleoside-modified messenger RNA (mRNA) encoding the viral Spike (S) glycoprotein of the SARS-CoV-2 Wuhan-Hu-1 strain.	➤ Each 0.2 mL dose of vaccine contains: ✓ modRNA*: 10 mcg ✓ Tromethamine: 0.02 mg ✓ Tromethamine hydrochloride: 0.13 mg ✓ Sucrose: 10.3 mg ✓ Total lipid content: 0.25 mg (0.14 mg ((4hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.02 mg 2[(polyethylene glycol)-2000]N,N-ditetradecylacetamide, 0.03 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.06 mg cholesterol) ✓ The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes 0.9 mg sodium chloride per dose ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.2 mL dose of the prepared vaccine contains 10 mcg of modRNA encoding the viral spike (S) glycoprotein of the SARS-CoV-2 Wuhan-Hu-1 strain.
Dosage Form	Suspension for IM injection	Suspension for IM injection
Final Concentration	15 mcg/mL (After Dilution)	50 mcg/mL (After Dilution)
Total Dose and Volume Per Vial	40 mcg/ 2.6 mL (After Dilution)	130 mcg/2.6 mL (After Dilution)
No. of Doses Per Vial	10 doses (After Dilution)	10 doses (After Dilution)
Dilution Required?	YES; 2.2 mL of 0.9% NS	YES; 1.3 mL of 0.9% NS
ACV01 mRNA Dose and Volume	3 mcg/ 0.2 mL	10 mcg/ 0.2 mL
ACV01 Number of Doses Per Vial	Multiple Dose Vial: 10 doses of 3 mcg (After Dilution)	Multiple Dose Vial: 10 doses (After Dilution)

Table 14b. Discontinued Pfizer-BioNTech COVID-19 Vaccine Products

COVID-19 Vaccine Information & Vial cap color/Label Border	Pfizer Gray Cap/Gray Label Border MONOVALENT, Vaccine	Pfizer Purple Cap/Purple Label Border MONOVALENT Vaccine
DATE DISCONTINUED IN ACV01	31 August 2022	31 August 2022
EUA APPROVED AGE	12 years of age and older	12 years of age and older
AGE of ACV01 Study Participants	12 years of age and older	12 years of age and older
Pharmaceutical Formulation	➤ Each 0.3 mL dose of vaccine contains: ✓ modRNA*: 30 mcg ✓ Tromethamine: 0.06 mg ✓ Tromethamine hydrochloride: 0.4 mg ✓ Sucrose: 31 mg ✓ Total lipid content: 0.76 mg (0.43 mg ((4hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.19 mg cholesterol) ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.3 mL dose of the prepared vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of the SARS-CoV-2 Wuhan-Hu-1 strain.	➤ Each 0.3 mL dose of vaccine contains: ✓ modRNA*: 30 mcg ✓ Potassium chloride: 0.01 mg ✓ Monobasic potassium phosphate: 0.01 mg ✓ Sodium chloride: 0.36 mg ✓ Dibasic sodium phosphate dihydrate: 0.07 mg ✓ Sucrose: 6 mg ✓ Total lipid content: 0.77 mg (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol) ✓ The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose ➤ Contains no preservative and the vial stoppers are not made with natural rubber latex *Each 0.3 mL dose of the prepared vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of the SARS-CoV-2 Wuhan-Hu-1 strain.
Dosage Form	Suspension for IM injection	Suspension for IM injection
Final Concentration	100 mcg/mL	100 mcg/mL (After Dilution)
Total Dose and Volume Per Vial	225 mcg/2.25 mL	225 mcg/2.25 mL (After Dilution)
No. of Doses Per Vial	6 doses	6 doses (After Dilution)
Dilution Required?	NO	YES; 1.8 mL 0.9% NS
ACV01 mRNA Dose and Volume	30 mcg/ 0.3 mL	30 mcg/ 0.3 mL
ACV01 Number of Doses Per Vial	Multiple Dose Vial: 6 doses	Multiple Dose Vial: 6 doses (After Dilution)

6.3 Investigational Agent #3: Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine (AD26.COV2.S) has not been a study-provided vaccine since 01/06/2022.

6.4 Investigational Agent #4: Sanofi-GSK COVID-19 Vaccine

The Sanofi Pasteur Monovalent (B.1.351) CoV2 preS dTM-AS03 adjuvanted vaccine, referred to as the Sanofi-GSK COVID-19 Vaccine in this protocol, is under investigational use to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Eligible study participants will receive one dose of vaccine.

The table below describes details on the Sanofi-GSK CoV2 preS dTM-AS03 Adjuvanted Vaccine product provided in ACV01 Protocol v7.0:

Table 15. Sanofi-GSK COVID-19 Vaccine Product

AGE of ACV01 Study Participants	Adult participants only (18 years and older)	
Sanofi GSK COVID-19 Vaccine Components **Pharmaceutical Formulation** **(CoV2 preS dTM antigen and AS03 are mixed together to form the prepared vaccine)**	**CoV2 preS dTM antigen** is a sterile, clear, colorless solution (with possible presence of endogenous particles) of SARS-CoV-2 prefusion S proteins for intramuscular injection. The CoV2 preS dTM antigen contains phosphate-buffered saline (PBS) buffer, residual amounts of baculovirus and Spodoptera frugiperda cell proteins (≤2 to 3 µg), baculovirus and cellular deoxyribonucleic acid (DNA, ≤10 ng).	**AS03** is an adjuvant system containing α-tocopherol and squalene in an oil/water, whitish to yellowish, homogenous, milky liquid emulsion. AS03 also contains the following excipients: Sodium chloride, Sodium dihydrogen phosphate, Potassium dihydrogen phosphate, Potassium chloride, Water for injection
Sanofi Pasteur and GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 Prepared Vaccine	➤ Each 0.5 mL dose contains the following: ✓ preS-delta TM B.1.351, prefusion S delta TM B.1.351 COVID-19 antigen: 5 mcg • Sodium phosphate monobasic monohydrate • Sodium phosphate dibasic dodecahydrate • Sodium chloride • Polysorbate 20 • Water for injection ✓ AS03 adjuvant (full dose) is an oil-in-water emulsion containing squalene: 10.69 mg • DL-α- tocopherol: 11.86 mg • Polysorbate 80: 4.86 mg	
Dosage Form	Liquid emulsion for IM injection	
Concentration of Prepared Vaccine	10 mcg/mL (After mixing antigen and AS03 adjuvant)	
Total Dose and Volume per Vial	CoV2 preS dTM antigen: 3 mL and AS03: 3mL; Total of 6 mL after mixing	
No. of doses Per Vial	10 doses (After Mixing)	
Dilution Required?	NO, but need to mix antigen and AS03 adjuvant together	
ACV01 Dose and Volume	5 mcg/ 0.5mL	
ACV01 Number of Doses Per Vial	Multiple Dose Vial: 10 doses (After Mixing)	

6.5 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62), the investigator bears the responsibility to maintain adequate investigational product (IP) disposition records (receipt, storage, dispense, return, and destruction). DAIT/ NIAID requires the principal investigator(s) to delegate the IP disposition responsibility to a licensed/registered pharmacist at a registered investigational pharmacy at a clinical research site. Detailed information on investigational pharmacy requirements is provided in the DAIT Pharmacy Guidelines. All IP inventory and dispensing will be documented using a DAIT/ NIAID main accountability as well as participant-specific dispensing fillable PDF forms or

electronic logs that are 21 CFR 11 compliant and approved by DAIT/NIAID. The participant dispensing log(s) will be kept current and will contain the identification of each participant as well as the date and quantity of each IP prepared and dispensed. Detailed IP shipment records to each clinical site's investigational pharmacy will be maintained by the DAIT/ NIAID's Clinical Product Center (EMINENT Services Corporation). All records regarding IP disposition will be available for inspection. All remaining unused IP will be returned to the IND Sponsor (DAIT/ NIAID) or sponsor's representative after study termination or destroyed with the prior approval from the sponsor in accordance with applicable federal and state laws as well as the study site procedures.

6.6 Assessment of Participant Compliance with Investigational Agent

Participants in this study will receive the assigned vaccine under direct observation.

6.7 Toxicity Prevention and Management

Participants will receive investigational agents in facilities where the investigative team is familiar and practiced in the treatment and care of participants with systemic autoimmune diseases and complications associated with those disorders and the associated treatments. Vaccinations will also only be given by personnel trained in recognizing and managing treatment of systemic allergic reactions and in areas equipped with the necessary medications and supplies to treat systemic allergic reactions. Participants who are experiencing a disease flare at Baseline/Week 0, or who meet any of the conditions listed in Section 8.1.3 Baseline (Week 0/Day 1) Visit will not proceed with vaccination. Refer to Section 5.1.1.1 Allergic Reactions and Anaphylaxis and Section 7.4 Rescue Medications.

7. Other Medications

7.1 Concomitant Medications

7.1.1 Protocol-mandated Medications

There are no protocol-mandated medications in this clinical trial. However, there is protocol-mandated temporary cessation as follows:

- Adult and Pediatric Stage 1 participants:
    - There will be a protocol-mandated temporary cessation of cohort-defining IS in **some** participants in Cohort A (MMF/MPA) and Cohort B (MTX).
- Adult and Pediatric Stage 2 participants:
    - There is a protocol-mandated temporary cessation of cohort-defining IS in **all** Cohort D (MMF/MPA) and Cohort E (MTX) participants.
    - Any participants in Cohort F (BCDT) who are also taking MMF/MPA or MTX will have a protocol-mandated temporary cessation of their MMF/MPA or MTX dose.

Adult and Pediatric Stage 1 in Cohort A: MMF/MPA and Cohort B: MTX that are randomized to hold these medications at the time of the additional homologous vaccine dose (per Section 3.1 Description of Study Design) and all Adult and Pediatric Stage 2 participants will be required to hold these medications as follows:

- Participants taking MMF/MPA (any dose) will hold the doses for 3 days before and 10 days after their vaccine dose.
    - Participants taking additional IS medications (such as tumor necrosis factor [TNF] inhibitors, JAK inhibitors, abatacept, belimumab, etc.) will be required to continue them during the time of the additional vaccine dose.
- Participants taking MTX (at any dose) will be required to hold their weekly dose for **at least 7 days before** their vaccine dose and for **at least 7 days after** administration of the vaccine. In total, the participant should not hold their MTX for more than 21 days.

- Participants taking additional IS medications (such as TNF inhibitors, JAK inhibitors, abatacept, belimumab, etc.) will be required to continue them during the time of their vaccine dose.

Participants that are randomized to continue medications (per Section 3.1 Description of Study Design) are required to maintain a stable dose of medication during the same period (Cohort A: MMF/MPA from 3 days before to 10 days after the additional homologous vaccine dose; Cohort B: MTX from 7 days before to 7 days after the additional homologous vaccine dose) unless they experience a change in disease activity requiring medication changes.

All participants in Cohort C: B-cell depleting therapy will continue to take their prescribed medications throughout the trial, unless they experience a change in disease activity requiring medication changes. It is preferred that these medications be stabilized before entry and continued wherever practical without variation of dose or regimen during the study.

7.1.2 Other permitted concomitant medications

Other than the prohibited medications listed in Section 7.3 Prohibited Medications, treatment with concomitant medications for treatment of SLE, RA, MS, pemphigus, and SSc in adult participants and JIA, JDM, pediatric SLE, and POMS in pediatric participants is permitted throughout study participation. Permitted concomitant medications include B cell modulating therapies such as epratuzumab (anti-CD22, modulates B cell signaling) or agents that target B-lymphocyte stimulator (BlyS; belimumab, atacicept), but these agents are not considered to be BCDT for defining assignment to Cohort C.

Concomitant therapies taken for the long-term treatment of pre-existing conditions other than SLE, RA, MS, pemphigus, and SSc should be continued during the study, provided that they are in accordance with the exclusion criteria. Other permitted concomitant medications may not change between Randomization/Allocation and the Baseline/Week 0 visit. This includes the addition of new medications, or changes in dose and/or frequency of existing medications.

7.2 Prophylactic Medications

Female participants of childbearing potential will be counseled to use an effective method of contraception (e.g., total abstinence, oral contraceptives, intrauterine devices, barrier method with spermicide, surgical sterilization or surgically sterilized partner, medroxyprogesterone acetate, levonorgestrel implant, etonogestrel/ethinyl estradiol vaginal ring, or hormonal implants) for the duration of study participation.

7.3 Prohibited Medications

All participants are to have access to any care deemed medically necessary, but administering the following medications, for the purposes of this study, are prohibited and will be considered protocol deviations unless otherwise noted.

- Any SARS-CoV-2 vaccine administered outside of the study is prohibited.
- All other vaccines administered outside of the study are prohibited between Screening and Week 4 during Stage 1 participation and between Screening and Week 4 during Stage 2 participation.
- Other vaccines, including the flu vaccine, administered within 4 weeks prior to a study visit, starting with the Baseline visit.
- Intravenous or subcutaneously administered immune globulin within 4 weeks prior to a study visit
- Monoclonal antibodies for pre-exposure prophylaxis are prohibited between Screening and Week 4 during Stage 1 participation and between Screening and Week 4 during Stage 2 participation.

If a participant takes a prohibited medication during the study, it should be recorded as a protocol deviation in the eCRF. Participants who received a SARS-CoV-2 vaccine outside of the study will be withdrawn. All other participants will continue to be followed for safety.

7.4 Rescue Medications

The following medications may be used to treat an allergic reaction:

- Epinephrine 1 mg/mL; 0.3 – 0.5 mg intramuscularly

- β-adrenergic agonist inhaler or nebulizer (e.g., albuterol)
- Antihistamines
- Steroids
- Intravenous fluids
- Oxygen

Guidelines for the treatment of systemic allergic reactions are detailed in the Manual of Procedures (MOP). Rescue medications should be recorded on the Concomitant Medications eCRF.

8. Study Procedures

8.1 Adult Stage 1 Study Procedures

8.1.1 Visit Windows

Appendix 20.1, Table 17 presents the Schedule of Events for participants in Adult Stage 1. The visit windows are defined below:

- Screening until Randomization/Allocation: up to 21 days from time of obtaining informed consent until the participant is determined to meet study entry criteria (allocation for Cohort C) or randomization (for Cohorts A and B).
- Randomization: phone visit that must occur at least 7 days prior to administration of the additional homologous vaccine dose at the Baseline/Week 0 visit for Cohorts A and B.
    - See Section 8.1.2.4 Randomization/Allocation for more details on Randomization visit activities.
- Baseline (Week 0/Day 1)
    - See Section 8.1.3 Baseline (Week 0/Day 1) Visit for more details on Baseline visit activities.
- Week 1: Vaccine Diary Review Phone Visit (Day 8 – Day 12)
- Week 4: (+/- 1 week)
- Week 12: (+/- 2 weeks)
- Week 24: (+/- 2 weeks)
- Week 36: (+/- 2 weeks)
- Week 48 (End of Study): (+/- 2 weeks)

8.1.2 Screening and Randomization/Allocation

8.1.2.1 Pre-Screening

An optional Pre-Screening visit may be conducted to confirm that a participant has had a negative or suboptimal response to initial COVID-19 vaccine regimen prior to Screening. This study will be explained in lay language to each potential participant. Each participant will sign an informed consent form before committing to study Pre-Screening procedures. Pre-Screening procedures at the study site will vary by method of recruitment as outlined below:

Study site personnel are responsible for the following:

1. Consent the participant for an ACV01 Pre-Screening Evaluation.
2. Conduct the rapid result or other antibody testing.
3. Invite the participant to an ACV01 Screening Visit if the result is negative or weakly positive per the site preferred antibody test method.

8.1.2.2 Determination of Participant Cohort and Identification of Qualifying Disease

Prior to screening a potential participant, the site needs to determine which IS Cohort the participant will be assigned to and identify the participant's qualifying autoimmune disease.

Cohorts: The ACV01 study will be accepting participants who are taking 3 types of IS medications: MMF or MPA, MTX, and BCDTs. The criteria for assignment to each cohort are listed below:

- Cohort A: Receipt of MMF or MPA (± other rheumatic disease medications, including biologics)
    - Participants who are taking MMF or MPA will be placed in this cohort.
        - Participants may not also be taking MTX.
        - Participants may not have taken anti-CD20 and anti-CD19 BCDT in the past 18 months.
- Cohort B: Receipt of MTX (± other rheumatic disease medications, including biologics)
    - Participants who are taking MTX will be placed in this cohort.
        - Participants may not also be taking MMF/MPA.
        - Participants may not have taken anti-CD20 and anti-CD19 BCDT in the past 18 months.
- Cohort C: Receipt of anti-CD20 or anti-CD19 BCDT within the past 18 months (± other rheumatic disease medications)
    - Participants who have taken B cell depletion medications in the past 18 months will be placed in this cohort.
        - Participants may also be taking MMF/MPA or MTX.

Qualifying Autoimmune Diseases: The ACV01 Adult Stage 1 study will be accepting adult participants diagnosed with SLE, RA, MS, SSc, or pemphigus. In the event that a participant has more than one of these 5 diseases, disease activity assessments will be collected throughout the trial for only the disease associated with IS medication cohort assignment at entry into the trial.

8.1.2.3 Screening

The research study will be explained in lay terms to each potential Stage 1 participant. The potential participant will sign an Institutional Review Board (IRB)-approved informed consent form before undergoing any study procedures. Once the informed consent has been signed, the participant will be assigned a unique participant number. At this time, study-specific procedures may be performed.

The purpose of the screening period, which begins at the time of signed consent, is to confirm eligibility to enter the study. All screening procedures, assessments, and laboratory measures to determine participant eligibility will be conducted within a 21-day screening window with shorter time periods expected for most participants.

The assessment of eligibility may take a series of visits that occur on separate days. The Screening visit biomarkers should reflect, as much as possible, the biometrics of the participant prior to any study procedures.

The following procedures, assessments, and laboratory measures will be conducted:

1. Informed Consent
2. Demographics
3. Medical History
4. Concomitant Medications (including contraceptives)
5. Comprehensive Physical Exam
6. Vital Signs

7. Confirmation of Disease Classification Criteria Assessment
    a. 2019 ACR/EULAR or 2012 SLICC classification criteria for SLE
    b. 2010 ACR/EULAR classification criteria for RA
    c. 2013 EULAR/ACR classification criteria for SSc
    d. 2017 McDonald diagnostic criteria for MS
    e. International consensus criteria for pemphigus
8. Complete assessments of disease activity: H-SLEDAI and PGA for SLE; DAS28-CRP and PtGA for RA; patient self-reported disease flare and Modified Rodnan Skin Score for SSc; physician-assessed relapse for MS; PDAI for pemphigus
9. Review of initial COVID-19 vaccination record and antibody response
10. Central laboratory assessments for all participants
    a. Infectious Disease Testing: HIV, Hepatitis B surface antigen, Hepatitis C antibody with viral load if indicated
    b. Elecsys® Anti-SARS-CoV-2 S assay to assess response to initial COVID-19 vaccine regimen
    c. Complete blood count (CBC) with differential
    d. Comprehensive metabolic panel (CMP), estimated glomerular filtration rate (eGFR)
11. Local laboratory assessments for all participants
    a. Molecular COVID-19 Testing:
    b. Urine pregnancy test (women of child-bearing potential only)
12. Disease-specific laboratory assessments:
    a. RA participants only
        i. C-Reactive Protein (CRP)
    b. SLE participants only
        i. Anti-dsDNA, C3, C4
        ii. Random urine protein-creatinine ratio
        iii. Urinalysis (microscopic)
    c. B-cell depleting therapy participants only
        i. If on CD20 depleting agent, CD19+ B cells
    d. Pemphigus participants only
        i. Anti-desmoglein 1/3 IgG autoantibodies by enzyme-linked immunosorbent assay (ELISA)
13. Inclusion/Exclusion criteria assessment

Participants with abnormal laboratory values that prohibit entry may be re-tested once during the screening period, which may last up to 21 days. Participants who screen fail may be rescreened one time and must repeat all screening assessments. Any further rescreening activity requires approval by the medical monitor.

During the Screening visit, the site will review vaccine eligibility criteria, per Section 8.1.3 Baseline Visit with the participant.

8.1.2.3.1 Evaluation of Eligibility and Randomization/Allocation

Cohorts A (MMF/MPA) or B (MTX): If the participant meets all eligibility criteria, then proceed as follows:

- Schedule Baseline/Week 0 Visit (within 28 days of first Screening assessment).
- Randomize the participant (within 21 days of screening and at least 7 days prior to the scheduled Baseline/Week 0 visit).

Cohort C (BCDT): If the participant meets all eligibility criteria, then proceed as follows:

- Schedule Baseline/Week 0 Visit (within 28 days of first Screening assessment).

8.1.2.4 Randomization/Allocation

Randomization is a phone visit that will occur up to 21 days after Screening and at least 7 days prior to the Baseline/Week 0 visit for participants in Cohorts A (MMF/MPA) and B (MTX). During Randomization, sites will call participants to confirm that concomitant medication and medical history data continue to meet eligibility criteria. After eligibility is confirmed, the site will randomize the participant to an IS medication treatment plan per Section 3.1 Description of Study Design. If the participant is randomized to withhold cohort-defining IS medication treatment, the site will communicate the details of the medication hold to the participant per Section 7.1.1 Protocol-mandated Medications. The site will inform the participant that there should be no changes to his/her other existing medications between Randomization and the Baseline/Week 0 visit.

For Stage 1, allocation is the confirmation that participants in Cohort C have met all study entry criteria and may proceed to the Baseline/Week 0 visit. The site will inform the participant that there should be no changes to his/her other existing medications between Allocation and the Baseline/Week 0 visit.

8.1.3 Baseline (Week 0/Day 1) Visit

Eligible participants who meet all inclusion criteria and none of the exclusion criteria will proceed with visits and assessments according to Section 20.1 Schedule of Events. Eligible participants will be assessed for disease activity and SARS-CoV-2 infection at the Baseline/Week 0 visit, prior to receipt of an additional homologous vaccine dose. Prior to administering the additional homologous vaccine dose at the Baseline visit, the site will confirm the participant meets vaccine eligibility per the criteria below:

- No increase to the permitted concomitant medications in participants in Cohorts A and B between Randomization and Baseline/Week 0.
- No B-cell depletion infusions or changes in permitted concomitant medications in participants in Cohort C between allocation and Baseline/Week 0.
- No clinically active disease (including myocarditis or pericarditis) at Baseline/Week 0 resulting in an increase/addition of IS medications. For participants with MS, no suggestion of a MS relapse per the investigator.
- No active myocarditis or pericarditis based on review of clinical symptoms.
- No positive molecular COVID-19 test at Baseline/Week 0.
- No increase in oral, intramuscular, or intravenous steroids within 14 days of Baseline/Week 0.

If the vaccine cannot be administered at the Baseline/Week 0 visit, it must be administered during the following 2-3 days. Vaccine eligibility will be confirmed prior to administration of the vaccine. **Administration of the additional homologous vaccine dose must occur within 28 days of the Screening visit.**

If a participant is not eligible to receive the additional homologous vaccine dose at Baseline/Week 0, he/she will be terminated from the study. The participant may rescreen under a new participant ID after 30 days from the determination of vaccine ineligibility. Participants who were randomized to withhold cohort-defining IS medications before the Baseline visit and who are not eligible to receive an additional homologous vaccine dose at that visit, may restart their IS medications immediately. The participant will be replaced.

See Section 8.1.4 Study Procedures and Assessments for more information on individual clinical and research assessments.

If the participant is randomized to the withhold cohort-defining IS medication treatment plan, the site will call the participant after the Baseline visit to provide instructions on resuming IS medication per Section 7.1.1 Protocol-mandated Medications.

8.1.4 Study Procedures and Assessments

8.1.4.1 General Assessments

- **Informed Consent Process**
- **Demographics.** Participants should provide demographic information. In particular, race and ethnicity should be self-identified.
- **Medical History.** Medical history will be performed as part of screening activities and standard medical care. The medical history assessment will include current illnesses/conditions and past medical history.
- **Concomitant Medications (including contraceptives).** A current list of prescription and over-the-counter medications, supplements, and treatments will be obtained. Assessment of eligibility should include a review of permitted and prohibited medications. The medication, dose, frequency, route, start date, stop date, and indication should be captured.
- **Comprehensive Physical Examination (Screening Only).** Physical examinations are to include, at least, the following systems: general appearance, skin, head/eyes/ears/nose/neck/throat, respiratory/chest, cardiovascular, abdominal, neurological, & musculoskeletal/extremities.
- **Targeted physical examination:** to be guided by participant complaints and prior abnormalities.
- **Neurological Exam:** for all MS participants and for participants with other diagnoses who have a neurological complaint after Screening.
- **Vital Signs.** Height will only be collected at Screening. Weight, temperature, pulse, and blood pressure will be collected at each visit. Vital signs should be obtained with the participant in a seated position, and prior to taking samples for laboratory testing at applicable study visits.
- **Adverse Events**
- **Vaccine Reaction Diary Overview, Training, & Distribution:** Participants will be 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 will include 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. As some solicited adverse events and grading scales are age-dependent and apply only to the pediatric population, separate age-specific Pediatric Vaccine Reaction Diaries will be provided to pediatric participants.

8.1.4.2 Disease-Specific Assessments

- **SLE Disease Assessments**
    - H-SLEDAI
    - Thanou modified SELENA-SLEDAI Flare Index
- **SSc Disease Assessments**
    - Flare assessment for SSc (including patient reported flare assessment)

- Modified Rodnan Skin Score

- **MS Disease Assessments**
  - Physician-assessed relapse for MS
  - Expanded Disability Status Scale (EDSS [at Baseline/Week 0])
    - If an MS relapse is suspected, the EDSS will be assessed at the following time points:
      - Time of suspected relapse
      - Time of relapse recovery (to occur 8-12 weeks after the suspected relapse EDSS assessment)

- **RA Disease Assessments**
  - DAS28-CRP

- **Pemphigus Disease Assessments**
  - PDAI
  - Flare assessment for pemphigus

8.1.4.3 Participant- and Clinician-reported Outcomes

- **Participant Reported Outcomes**
  - PROMIS-29
  - PtGA
  - PGI-C

- **Clinician Reported Outcomes**
  - PGA
  - CGI-C

8.1.4.4 Clinical Laboratory Assessments

Blood and urine for the clinical laboratory assessments listed below will be collected per Section 20.1 Schedule of Events. The results will be evaluated for safety by the site investigator. Abnormal tests that meet grading and reporting criteria will be reported as adverse events (See Section 12.3 Grading and Attribution of Adverse Events).

- **Local Laboratory Assessments**
  - **Pregnancy Testing (Women of Childbearing Potential Only).** Urine pregnancy test at Screening and Baseline/Week 0 visit.
  - **Molecular COVID-19 Testing** Baseline/Week 0/Day 1 molecular COVID-19 Testing can be collected and run and the results reported by a community-based laboratory (national chain pharmacy, Local MD office, State or Local Government run testing center, Urgent Care Center) not listed on the 1572. This test must be performed within the 48 hours prior to the Baseline/Week 0/Day 1 visit. For additional details, please see the ACV01 Manual of Procedures.

- **Central Laboratory Assessments**
  - **Hematology**, including complete blood count (CBC) with differential.
  - **Blood Chemistry** including CMP, eGFR.

- **Detection of antibodies against SARS-CoV-2 Spike protein (IgG)** using the Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay intended for qualitative and semi-quantitative detection of antibodies to SARS-CoV-2 spike protein (RBD) in human serum.
- **Disease-specific laboratory assessments:**
  - RA participants only
    - C-Reactive Protein (CRP)
  - SLE participants only
    - Anti-dsDNA, C3, C4
    - Random urine protein-creatinine ratio
    - Urinalysis: microscopic
  - B-cell depleting therapy participants only
    - If on CD20 depleting agent, CD19+ B cells
  - Pemphigus participants only
    - Anti-desmoglein 1/3 IgG autoantibodies by ELISA

8.1.4.5 Mechanistic Specimens

- Serum
  - Antibody levels will be tested at each time point to test for IgG and immunoglobulin M (IgM) responses against SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins.
- Whole blood/peripheral blood mononuclear cell (PBMC)/plasma/DNA
- RNA assays

8.1.5 Unscheduled Visits

If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an “unscheduled” visit.

8.1.6 Early Termination

An Early Termination Visit should be requested for participants who withdraw from the study prior to study completion. Assessments to be conducted at an early termination visit can be found in Section 20.1 Schedules of Events.

8.2 Adult Stage 2 Study Procedures

8.2.1 Visit Windows

8.2.1.1 Visit Windows for Adult Stage 2 Newly Recruited Participants

Appendix 20.1, Table 18 presents the Schedule of Events for participants who are newly recruited to Adult Stage 2. The visit windows are defined below:

- Screening and Allocation: 28 to 7 days prior to the S2 Baseline/Week 0 visit.
- Baseline (Week 0/Day 1)
  - See Section 8.2.4 Baseline (Week 0/Day 1) Visit for more details on Baseline/Week 0 visit activities.
- Week 1: Vaccine Diary Review Phone Visit (Day 8 – Day 12)
- Week 4: (+/- 1 week)

- Week 12: (+/- 2 weeks)
- Week 24: (+/- 2 weeks)
- Week 36: (+/- 2 weeks)
- Week 48 (End of Study): (+/- 2 weeks)

8.2.1.2 Visit Windows for Adult Stage 2 Rollover Participants

Participants can roll over into Stage 2 via two pathways:

- Stage 1 participant rolls over to Stage 2
    - A Stage 1 participant who has a Roche Elecsys result ≤2500 U/mL at a post-Baseline visit may elect to roll over into Stage 2, starting the Stage 2 schedule of events for rollovers.
- Stage 2 participant rolls over to a different Stage 2 treatment arm
    - A Stage 2 participant who received an alternative mRNA vaccine dose and has a Roche Elecsys result ≤2500 U/mL at a post-Baseline visit may elect to re-enter Stage 2, restarting the Stage 2 schedule of events for rollovers.

For participants rolling into Adult Stage 2, the visit windows are defined below.

- Total Screening Period:
    - Up to 28 days from the Stage 1 or Stage 2 Visit at which negative, suboptimal or low immune response to the previous COVID-19 vaccine was obtained until the S2 Baseline/Week 0 visit.
        - If the S2 Baseline/Week 0 visit cannot be conducted within 28 days of the qualifying Follow-up Visit noted above, the participant will return to the site for a full S2 Screening visit, as described in Section 8.2.2.3.2 Screening for Adult Stage 2 Rollover Participants.
    - S2 Screening Phone Visit: at least 7 days prior to administration of the alternative vaccine at S2 Baseline/Week 0.
        - See Section 8.2.2.3.2 Screening for Adult Stage 2 Rollover Participants for more details on the screening procedures for rollover participants.
- S2 Baseline (S2 Week 0/Day 1)
    - See Section 8.2.4 Baseline (Week 0/Day 1) Visit for more details on the S2 Baseline/Week 0 visit activities.
- S2 Week 1: Vaccine Diary Review Phone Visit (Day 8 – Day 12)
- S2 Week 4: (+/- 1 week)
- S2 Week 12: (+/- 2 weeks)
- S2 Week 24: (+/- 2 weeks)
- S2 Week 36: (+/- 2 weeks)
- S2 Week 48 (End of Study): (+/- 2 weeks)

8.2.2 Screening and Allocation

8.2.2.1 Pre-Screening

8.2.2.1.1 Pre-Screening for Adult Stage 2 Newly Recruited Participants

An optional Pre-Screening visit may be conducted to confirm that a participant has had a negative, suboptimal, or low immune response to initial COVID-19 vaccine regimen prior to Screening. This study will be explained in lay language to each potential participant. Each participant will sign an informed consent form before committing to study Pre-Screening procedures. Pre-Screening procedures at the study site will vary by method of recruitment as outlined below:

Study site personnel are responsible for the following:

1. Consent the participant for an ACV01 Pre-Screening Evaluation.
2. Conduct the rapid result or other antibody testing.
3. Invite the participant to an ACV01 Screening Visit if the result is negative or weakly positive per the site preferred antibody test method.

8.2.2.1.2 Pre-Screening for Adult Stage 2 Rollover Participants

Elecsys® Anti-SARS-CoV-2 S assay results for study participants from visits at Week 4 through Week 48 will be reviewed when received by study sites. Participants with a negative, suboptimal, or low immune response at any visit following receipt of the previous COVID-19 vaccine dose will have the data from their last study visit pre-screened to determine if they may qualify for Stage 2.

If a participant pre-screens successfully for Stage 2, the study site will contact the participant to offer them the opportunity to be fully screened for Stage 2.

8.2.2.2 Determination of Participant Cohort and Identification of Qualifying Disease

Prior to screening a potential newly recruited participant, the site needs to determine to which IS cohort the participant will be allocated and identify the participant's qualifying autoimmune disease.

Note that the qualifying disease for rollover participants will be the same as for their previous Stage.

Cohorts: Stage 2 will be accepting participants who are taking 3 types of IS medications: MMF or MPA, MTX, and BCDTs. The criteria for allocation to each cohort are listed below:

- Cohort D: Receipt of MMF or MPA (± other rheumatic disease medications, including biologics)
    - Participants who are taking MMF or MPA will be placed in this cohort.
        - Participants may not also be taking MTX.
        - Participants may not have taken anti-CD20 and anti-CD19 BCDT in the past 18 months.
- Cohort E: Receipt of MTX (± other rheumatic disease medications, including biologics)
    - Participants who are taking MTX will be placed in this cohort.
        - Participants may not also be taking MMF/MPA.
        - Participants may not have taken anti-CD20 and anti-CD19 BCDT in the past 18 months.
- Cohort F: Receipt of anti-CD20 or anti-CD19 BCDT within the past 18 months (± other rheumatic disease medications)
    - Participants who have taken B cell depletion medications in the past 18 months will be placed in this cohort.
        - Participants may also be taking MMF/MPA or MTX.

Qualifying Autoimmune Diseases: The ACV01 study will be accepting participants diagnosed with SLE, RA, MS, SSc, or pemphigus. In the event that a participant has more than one of these 5 diseases, disease activity assessments will be collected throughout the trial for only the disease associated with IS medication cohort assignment at entry into the trial.

8.2.2.3 Screening

8.2.2.3.1 Screening for Adult Stage 2 Newly Recruited Participants

The research study will be explained in lay terms to each potential Stage 2 newly recruited participant. The potential participant will sign an IRB-approved informed consent form before undergoing any study procedures. Once the informed consent has been signed, the participant will be assigned a unique participant number. At this time, study-specific procedures may be performed.

The purpose of the screening period, which begins at the time of signed consent, is to confirm eligibility to enter the study. All screening procedures, assessments, and laboratory measures to determine participant eligibility will be conducted within a 21-day screening window with shorter time periods expected for most participants.

The assessment of eligibility may take a series of visits that occur on separate days. The Screening visit biomarkers should reflect, as much as possible, the biometrics of the participant prior to any study procedures.

The following procedures, assessments, and laboratory measures will be conducted:

1. Informed Consent
2. Demographics
3. Medical History
4. Concomitant Medications (including contraceptives)
5. Comprehensive Physical Exam
6. Vital Signs
7. Confirmation of Disease Classification Criteria Assessment
    a. 2019 ACR/EULAR or 2012 SLICC classification criteria for SLE
    b. 2010 ACR/EULAR classification criteria for RA
    c. 2013 EULAR/ACR classification criteria for SSc
    d. 2017 McDonald diagnostic criteria for MS
    e. International consensus criteria for pemphigus
8. Complete assessments of disease activity: H-SLEDAI, and PGA for SLE; DAS28-CRP, Tender/Swollen Joint Count, and PtGA for RA; patient self-reported disease flare and Modified Rodnan Skin Score for SSc; physician-assessed relapse for MS; PDAI for pemphigus
9. Review of COVID-19 vaccination record and antibody responses, infections and treatments.
10. Central laboratory assessments for all participants
    a. Infectious Disease Testing: HIV, Hepatitis B surface antigen, Hepatitis C antibody with viral load if indicated
    b. Elecsys® Anti-SARS-CoV-2 S assay to assess response to initial COVID-19 vaccine regimen
    c. CBC with differential
    d. CMP, eGFR
11. Local laboratory assessments for all participants
    a. Molecular COVID-19 Testing
    b. Urine pregnancy test (women of child-bearing potential only)
12. Disease-specific laboratory assessments:

a. RA participants only
    i. CRP
b. SLE participants only
    i. Anti-dsDNA, C3, C4
    ii. Random urine protein-creatinine ratio
    iii. Urinalysis (microscopic)
c. B-cell depleting therapy participants only
    i. If on CD20 depleting agent, CD19+ B cells
d. Pemphigus participants only
    i. Anti-desmoglein 1/3 IgG autoantibodies by ELISA

13. Inclusion/Exclusion criteria assessment

Participants with abnormal laboratory values that prohibit entry may be re-tested once during the screening period, which may last up to 21 days. Participants who screen fail may be rescreened one time and must repeat all screening assessments. Any further rescreening activity requires approval by the medical monitor.

During the Screening visit, the site will review vaccine eligibility criteria, per Section 8.2.4 Baseline (Week 0/Day 1) Visit with the participant.

8.2.2.3.2 Screening for Adult Stage 2 Rollover Participants

The study site will contact potential Stage 2 rollover participants to offer them the opportunity to be fully screened for Stage 2. There are two options for the conduct of Screening for Adult Stage 2 for rollover participants:

- The screening process for Stage 2 may be able to be completed with only a telephone visit if the necessary information is available from the last study visit from Stage 1, informed consent can be appropriately completed, etc.
    - *Notes:*
        - *Information that may be available from the last study visit from Stage 1 includes lab tests for eligibility and disease-specific laboratory tests noted below.*
        - *The pregnancy test and molecular COVID-19 tests do not need to be completed during the Stage 2 Screening period if the Screening visit is conducted by phone. In such cases, these assessments will be conducted at the beginning of the Stage 2 Baseline visit before the vaccine is administered.*
- If the needed data are not available from the previous Stage 1 visit or 28 days will have passed when the S2 Baseline/Week 0 visit is reached, then the Stage 2 Screening visit must be conducted at the clinical site.

The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility for Stage 2.

1. Confirm that participant agrees to proceed to Stage 2.
    a. If the participant has not yet signed an informed consent form that includes a description of Stage 2, the participant must provide signed informed consent for Stage 2 screening to proceed.
2. Updated Medical History
3. Updated Concomitant Medications (including contraceptives)
4. Updated Physical Exam

a. Results of the Targeted Physical Exam and the Neurological Exam from the most recent Stage 1 visit may be used to fulfill this assessment in place of a new Comprehensive Physical Exam

5. Vital Signs
6. AE assessment following vaccination in Stage 1
7. Complete assessments of disease activity: H-SLEDAI and PGA, for SLE; DAS28-CRP and PtGA for RA; patient self-reported disease flare and Modified Rodnan Skin Score for SSc; physician-assessed relapse for MS; PDAI for pemphigus
8. Central laboratory assessments for all participants
    a. Response to previous COVID-19 vaccine dose assessed by Elecsys® Anti-SARS-CoV-2 S assay
    b. CBC with differential
    c. CMP, eGFR
9. Local laboratory assessments for all participants
    a. Molecular COVID-19 Testing (only if the Stage 2 Screening visit is conducted at the clinical site)
    b. Urine pregnancy test (only if Stage the 2 Screening visit is conducted at the clinical site for women of child-bearing potential only)
10. Disease-specific laboratory assessments:
    a. RA participants only
        i. CRP
    b. SLE participants only
        ii. Anti-dsDNA, C3, C4
        iii. Random urine protein-creatinine ratio
        iv. Urinalysis (microscopic)
    c. B-cell depleting therapy participants only
        v. If on CD20 depleting agent, CD19+ B cells
    d. Pemphigus participants only
        vi. Anti-desmoglein 1/3 IgG autoantibodies by ELISA
11. Inclusion/Exclusion criteria assessment

8.2.3 Evaluation of Eligibility and Allocation

If the participant meets all eligibility criteria for Stage 2, then proceed as follows during the Screening phone call:

- Allocate the participant to the appropriate cohort based on IS medication
- If the participant previously received 3 doses of an mRNA vaccine, determine which alternative COVID-19 vaccine the participant will receive.
- Schedule S2 Baseline/Week 0 visit (within 28 days of the Stage 2 Screening assessments and no sooner than 7 days from the Screening visit).
- Communicate to the participant the details of the medication hold to the participant per Section 7.1.1 Protocol-mandated Medications.
- Inform the participant that there should be no changes to his/her other existing medications between Screening and the S2 Baseline/Week 0 visit.

8.2.4 Baseline (Week 0/Day 1) Visit

Eligible participants who meet all inclusion criteria and none of the exclusion criteria for Stage 2 will proceed with visits and assessments according to Section 20.1 Schedule of Events, Table 18 (newly recruited participant) or Table 19 (rollover participant). Eligible participants will be assessed for disease activity and SARS-CoV-2 infection at the S2 Baseline/Week\ 0 visit, prior to receipt of an alternative vaccine dose. Prior to administering the alternative vaccine dose at the Baseline visit, the site will confirm the participant meets vaccine eligibility per the criteria below:

- No increase to the permitted concomitant medications in participants in Cohorts D and E between S2 Screening and S2 Baseline/Week 0.
- No B-cell depletion infusions or changes in permitted concomitant medications in participants in Cohort F between allocation and S2 Baseline/Week 0.
- No clinically active disease (including myocarditis or pericarditis) at S2 Baseline/Week 0 resulting in an increase/addition of IS medications. For participants with MS, no suggestion of a MS relapse per the investigator.
- No active myocarditis or pericarditis based on review of clinical symptoms.
- No positive molecular COVID-19 test at S2 Baseline/Week 0.
- No increase in oral, intramuscular, or intravenous steroids within 14 days of S2 Baseline/Week 0.

If the vaccine cannot be administered at the S2 Baseline Week 0 visit, it must be administered during the following 2-3 days. Vaccine eligibility will be confirmed prior to administration of the vaccine. **Administration of the alternative vaccine dose must occur within 28 days of the S2 Screening visit (newly recruited participant) or 28 days of when the data used for screening were obtained (rollover participant).**

If a **newly recruited participant** is not eligible to receive the alternative vaccine dose at S2 Baseline Week 0, he/she will be terminated from the study (see Section 11.2 Participant Stopping Rules and Withdrawal Criteria), and the participant will be replaced. If a **rollover participant** is not eligible to receive the alternative vaccine dose at S2 Baseline Week 0, he/she will continue on the previous Schedule of Events.

The participant may rescreen after 30 days from determination of vaccine ineligibility. New recruit participants who fail to receive the vaccine must be rescreened under a new participant ID. Participants who are not eligible to receive an alternative vaccine dose at that visit may restart their IS medications immediately.

See Section 8.1.4 Study Procedures and Assessments for more information on individual clinical and research assessments.

Sites will call all Stage 2 participants who withheld an IS medication after the S2 Baseline visit to provide instructions on resuming IS medication per Section 7.1.1 Protocol-mandated Medications.

8.2.5 Study Procedures and Assessments

Study procedures and assessments are as described in Section 8.1.4 Study Procedures and Assessments

8.2.6 Unscheduled Visits

Unscheduled visits are described in Section 8.1.5 Unscheduled Visits.

8.2.7 Early Termination

Early termination is described in Section 8.1.6 Early Termination.

8.3 Pediatric Stage 1 Study Procedures

8.3.1 Visit Windows

Appendix 20.1, Table 20 presents the Schedule of Events for Stage 1 pediatric participants. The visit windows are defined below:

- Screening until Randomization/Allocation: up to 21 days from time of obtaining informed consent until the participant is determined to meet study entry criteria (allocation for Cohort C) or randomization (for Cohorts A and B).
- Randomization: phone visit that must occur at least 7 days prior to administration of the additional homologous vaccine dose at the Baseline/Week 0 visit for Cohorts A and B.
    - See Section 8.1.2.4 Randomization/Allocation for more details on Randomization visit activities.
- Baseline (Week 0/Day 1)
    - See Section 8.1.3 Baseline (Week 0/Day 1) Visit for more details on Baseline visit activities.
- Week 1: Vaccine Diary Review Phone Visit (Day 8 – Day 12)
    - Pediatric participants may consent to an optional mechanistic specimen collection at Week 1. If the participant has consented to this mechanistic specimen collection, the Vaccine Diary Review will occur on site per the assessments outlined in Section 20.1 Schedules of Events, Table 20.
- Week 4: (+/- 1 week)
- Week 12: (+/- 2 weeks)
- Week 24: (+/- 2 weeks)
- Week 36: (+/- 2 weeks)
- Week 48 (End of Study): (+/- 2 weeks)

8.3.2 Screening and Randomization/Allocation

8.3.2.1 Pre-Screening

An optional Pre-Screening visit may be conducted to confirm that a participant has had a negative or suboptimal, or low immune response to initial COVID-19 vaccine regimen prior to Screening. This study will be explained in lay language to each potential participant and his or her parent. Each participant and their parent/guardian will sign informed consent and assent forms, as appropriate to age of the participant, before committing to study Pre-Screening procedures. Pre-Screening procedures at the study site will vary by method of recruitment as outlined below:

Study site personnel are responsible for the following:

1. Consent the participant for an ACV01 Pre-Screening Evaluation.
2. Conduct the rapid result or other antibody testing.
3. Invite the participant to an ACV01 Screening Visit if the result is negative or weakly positive per the site preferred antibody test method.

8.3.2.2 Determination of Participant Cohort and Identification of Qualifying Disease

Prior to screening a potential participant, the site needs to determine which IS Cohort the participant will be assigned to and identify the participant's qualifying autoimmune disease.

Cohorts: Determination of participant cohort is described in Section 8.1.2.2 Determination of Participant Cohort and Identification of Qualifying Disease.

Qualifying Autoimmune Diseases: The ACV01 study will be accepting pediatric participants diagnosed with pediatric SLE, JIA, JDM, or POMS. In the event that a participant has more than one of these 4 diseases, disease activity

assessments will be collected throughout the trial for only the disease associated with IS medication cohort assignment at entry into the trial.

8.3.2.3 Screening

The research study will be explained in lay terms to each potential pediatric participant and his or her parent/guardian. The potential participant and their parent/guardian will sign IRB-approved informed consent and assent forms, as appropriate to the age of the participant, before undergoing any study procedures. Once the informed consent/assent forms have been signed, the participant will be assigned a unique participant number. At this time, study-specific procedures may be performed.

The purpose of the screening period, which begins at the time of signed consent, is to confirm eligibility to enter the study. All screening procedures, assessments, and laboratory measures to determine participant eligibility will be conducted within a 21-day screening window with shorter time periods expected for most participants.

The assessment of eligibility may take a series of visits that occur on separate days. The Screening visit biomarkers should reflect, as much as possible, the biometrics of the participant prior to any study procedures.

The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility:

1. Informed Consent/Assent
2. Demographics
3. Medical History
4. Concomitant Medications (including contraceptives)
5. Comprehensive Physical Exam
6. Vital Signs
7. Confirmation of Disease Classification Criteria Assessment
    a. 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups for pediatric SLE
    b. 2010 ILAR classification criteria for JIA
    c. 2017 McDonald diagnostic criteria for MS
    d. Bohan and Peter criteria or the 2017 EULAR/ACR classification criteria for JDM.
8. Complete assessments of disease activity: SLEDAI-2K for pediatric SLE; Tender/Swollen Joint Count for JIA; Physician-assessed relapse for POMS; Flare Assessment for JDM (Disease Activity Score [DAS]) and CMAS for JDM
9. Review of initial COVID-19 vaccination record and antibody responses, infections and treatments.
10. Central laboratory assessments for all participants
    a. Elecsys® Anti-SARS-CoV-2 S assay to assess response to initial COVID-19 vaccine regimen
    b. CBC with differential
    c. CMP, eGFR
11. Local laboratory assessments for all participants
    a. Molecular COVID-19 Testing
    b. Urine pregnancy test (postmenarchal females must have a negative urine pregnancy test at Screening)
12. Disease-specific laboratory assessments:
    a. Pediatric SLE participants only

i. Anti-dsDNA, C3, C4
ii. Random urine protein-creatinine ratio
iii. Urinalysis (microscopic)
iv. Erythrocyte sedimentation rate (ESR) – local assessment

b. JIA participants only
i. CRP

c. B-cell depleting therapy participants only
i. If on CD20 depleting agent, CD19+ B cells

d. JDM participants only
i. Disease-specific tests assessed as part of the CMP:
1. Creatine kinase (CK) only
2. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST)
ii. Aldolase

13. Inclusion/Exclusion criteria assessment

Participants with abnormal laboratory values that prohibit entry may be re-tested once during the screening period, which may last up to 21 days. Participants who screen fail may be rescreened one time and must repeat all screening assessments. Any further rescreening activity requires approval by the medical monitor.

During the Screening visit, the site will review vaccine eligibility criteria, per Section 8.1.3 Baseline Visit with the participant.

8.3.2.3.1 Evaluation of Eligibility and Randomization/Allocation

Evaluation of eligibility and randomization/allocation are described in Section 8.1.2.3.1 Evaluation of Eligibility and Randomization/Allocation.

8.3.2.4 Randomization/Allocation

Randomization/allocation are described in Section 8.1.2.4 Randomization/Allocation.

8.3.3 Baseline (Week 0/Day 1) Visit

The Baseline visit is described in Section 8.1.3 Baseline (Week 0/Day 1) Visit.

8.3.4 Study Procedures and Assessments

8.3.4.1 General Assessments

General assessments are described in Section 8.1.4.1 General Assessments.

8.3.4.2 Disease-Specific Assessments

- **Pediatric SLE Disease Assessments**
  - SLEDAI-2K
  - ACR Provisional Criteria for Global Flare in Childhood-onset SLE (for SLEDAI)
- **JIA Disease Assessments**

- Tender/Swollen Joint Count
- PASI
  - Assessed for JIA participants with psoriatic arthritis only.
  - This assessment will be conducted at Baseline/Week 0 and any time a flare is suspected.

- **POMS Disease Assessments**
  - Physician-assessed relapse for MS
  - EDSS (at Baseline/Week 0)
    - If a POMS relapse is suspected, the EDSS will be assessed at the following time points:
      - Time of suspected relapse
      - Time of relapse recovery (to occur 8-12 weeks after the suspected relapse EDSS assessment)

- **JDM Disease Assessments**
  - Flare Assessment for JDM (Disease Activity Score [DAS])
  - CMAS for JDM
    - The CMAS is required for JDM participants ages 6-17.
    - The CMAS is optional for JDM participants who are 2-5 years old.

8.3.4.3 Participant- and Clinician-reported Outcomes

- **Participant-reported Outcomes**
  - PedsQL
  - PtGA
  - PGI-C
- **Clinician-reported Outcomes**
  - PGA
  - CGI-C

8.3.4.4 Clinical Laboratory Assessments

Blood and urine for the clinical laboratory assessments listed below will be collected per Section 20.1 Schedule of Events. The results will be evaluated for safety by the site investigator. Abnormal tests that meet grading and reporting criteria will be reported as adverse events (See Section 12.3 Grading and Attribution of Adverse Events).

- **Local Laboratory Assessments**
  - **Pregnancy Testing** Urine pregnancy test at Screening and Baseline/Week 0 visit will be conducted only on postmenarchal females.
  - **Molecular COVID-19 Testing** Baseline/Week 0/Day 1 molecular COVID-19 Testing can be collected and run and the results reported by a community-based laboratory (national chain pharmacy, Local MD office, State or Local Government run testing center, Urgent Care Center) not listed on the 1572. This test must be performed within the 48 hours prior to the Baseline/Week 0/Day 1 visit. For additional details, please see the ACV01 Manual of Procedures.
  - **ESR** (pediatric SLE participants only)

- **Central Laboratory Assessments**
    - **Hematology**, including CBC with differential.
    - **Blood Chemistry** including CMP, eGFR.
    - **Detection of antibodies against SARS-CoV-2 Spike protein (IgG)** using the Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay intended for qualitative and semi-quantitative detection of antibodies to SARS-CoV-2 spike protein (RBD) in human serum.
    - **Disease-specific laboratory assessments:**
        - Pediatric SLE participants only
            - Anti-dsDNA, C3, C4
            - Random urine protein-creatinine ratio
            - Urinalysis (microscopic)
        - JIA participants only
            - CRP
        - B-cell depleting therapy participants only
            - If on CD20 depleting agent, CD19+ B cells
        - JDM participants only
            - CK only
            - ALT/AST
            - Aldolase

8.3.4.5 Mechanistic Assessments

- Mechanistic assessments are described in Section 8.1.4.5 Mechanistic Specimens.

8.3.5 Unscheduled Visits

Unscheduled visits are described in Section 8.1.5 Unscheduled Visits.

8.3.6 Early Termination

Early termination is described in Section 8.1.6 Early Termination.

8.4 Pediatric Stage 2 Study Procedures

8.4.1 Visit Windows

8.4.1.1 Visit Windows for Pediatric Stage 2 Newly Recruited Participants

Appendix 20.1, Table 21 presents the Schedule of Events for participants who are newly recruited to Pediatric Stage 2. The visit windows are defined below:

- Screening and Allocation: 28 to 7 days prior to the S2 Baseline/Week 0 visit.
- Baseline (Week 0/Day 1)
    - See Section 8.4.4 Baseline (Week 0/Day 1) Visit for more details on Baseline/Week 0 visit activities.
- Week 1: Vaccine Diary Review Phone Visit (Day 8 – Day 12)
    - Pediatric participants may consent to an optional mechanistic specimen collection at Week 1. If the participants have consented to this mechanistic specimen collection, the Vaccine Diary Review will occur on site per the assessments outlined in Section 20.1 Schedules of Events, Table 21.

- Week 4: (+/- 1 week)
- Week 12: (+/- 2 weeks)
- Week 24: (+/- 2 weeks)
- Week 36: (+/- 2 weeks)
- Week 48 (End of Study): (+/- 2 weeks)

8.4.1.2 Visit Windows for Pediatric Stage 2 Rollover Participants

For participants rolling from Pediatric Stage 1 into Pediatric Stage 2, the visit windows are defined below:

- Total Screening Period:
    - Up to 28 days from the Stage 1 Study Follow-up Visit at which negative, suboptimal or low immune response to the previous COVID-19 vaccine was obtained until the S2 Baseline/Week 0 visit.
        - If the S2 Baseline/Week 0 visit cannot be conducted within 28 days of the qualifying Stage 1 Follow-up Visit noted above, the participant will return to the site for a full S2 Screening visit, as described in Section 8.4.2.3.2 Screening for Pediatric Stage 2 Rollover Participants.
    - S2 Screening Phone Visit: at least 7 days prior to administration of the alternative vaccine at S2 Baseline/Week 0.
        - See Section 8.4.2.3.2 Screening for Pediatric Stage 2 Rollover Participants for more details on the screening procedures for rollover participants
- S2 Baseline (S2 Week 0/Day 1)
    - See Section 8.2.4 Baseline (Week 0/Day 1) Visit for more details on the S2 Baseline/Week 0 visit activities.
- S2 Week 1: Vaccine Diary Review Phone Visit (Day 8 – Day 12)
- S2 Week 4: (+/- 1 week)
- S2 Week 12: (+/- 2 weeks)
- S2 Week 24: (+/- 2 weeks)
- S2 Week 36: (+/- 2 weeks)
- S2 Week 48 (End of Study): (+/- 2 weeks)

8.4.2 Screening and Allocation

8.4.2.1 Pre-Screening

8.4.2.1.1 Pre-Screening for Pediatric Stage 2 Newly Recruited Participants

An optional Pre-Screening visit may be conducted to confirm that a participant has had a negative, suboptimal, or low immune response to initial COVID-19 vaccine regimen prior to Screening. This study will be explained in lay language to each potential participant. Each participant will sign an informed consent form before committing to study Pre-Screening procedures. Pre-Screening procedures at the study site will vary by method of recruitment as outlined below:

Study site personnel are responsible for the following:

1. Consent the participant for an ACV01 Pre-Screening Evaluation.
2. Conduct the rapid result or other antibody testing.
3. Invite the participant to an ACV01 Screening Visit if the result is negative or weakly positive per the site preferred antibody test method.

8.4.2.1.2 Pre-Screening for Pediatric Stage 2 Rollover Participants

Elecsys® Anti-SARS-CoV-2 S assay results for Stage 1 participants from visits at Week 4 through Week 48 will be reviewed when received by study sites. Participants with a negative, suboptimal, or low immune response at any visit following receipt of the previous COVID-19 vaccine dose will have the data from their last Stage 1 study visit pre-screened to determine if they may qualify for Stage 2.

If a participant pre-screens successfully for Stage 2, the study site will contact the participant to offer them the opportunity to be fully screened for Stage 2.

8.4.2.2 Determination of Participant Cohort and Identification of Qualifying Disease

Prior to screening a potential newly recruited participant, the site needs to determine to which IS cohort the participant will be allocated and identify the participant's qualifying autoimmune disease.

Note that the qualifying disease for rollover participants will be the same as for Stage 1.

Cohorts: Stage 2 will be accepting participants who are taking 3 types of IS medications: MMF or MPA, MTX, and B cell depletion therapies. The criteria for allocation to each cohort are listed below:

- Cohort D: Receipt of MMF or MPA (± other rheumatic disease medications, including biologics)
    - Participants who are taking MMF or MPA will be placed in this cohort.
        - Participants may not also be taking MTX.
        - Participants may not have taken anti-CD20 and anti-CD19 B cell depleting therapy in the past 18 months.
- Cohort E: Receipt of MTX (± other rheumatic disease medications, including biologics)
    - Participants who are taking MTX will be placed in this cohort.
        - Participants may not also be taking MMF/MPA.
        - Participants may not have taken anti-CD20 and anti-CD19 B cell depleting therapy in the past 18 months.
- Cohort F: Receipt of anti-CD20 or anti-CD19 B cell depletion therapy within the past 18 months (± other rheumatic disease medications)
    - Participants who have taken B cell depletion medications in the past 18 months will be placed in this cohort.
        - Participants may also be taking MMF/MPA or MTX.

Qualifying Autoimmune Diseases: The ACV01 study will be accepting participants diagnosed with SLE, JIA, JDM, or POMS. In the event that a participant has more than one of these 4 diseases, disease activity assessments will be collected throughout the trial for only the disease associated with IS medication cohort assignment at entry into the trial.

8.4.2.3 Screening

8.4.2.3.1 Screening for Pediatric Stage 2 Newly Recruited Participants

The research study will be explained in lay terms to each potential pediatric participant and his or her parent/guardian. The potential participant and their parent/guardian will sign IRB-approved informed consent and assent forms, as appropriate to the age of the participant, before undergoing any study procedures. Once the informed consent/assent forms have been signed, the participant will be assigned a unique participant number. At this time, study-specific procedures may be performed.

The purpose of the screening period, which begins at the time of signed consent, is to confirm eligibility to enter the study. All screening procedures, assessments, and laboratory measures to determine participant eligibility will be conducted within a 21-day screening window with shorter time periods expected for most participants.

The assessment of eligibility may take a series of visits that occur on separate days. The Screening visit biomarkers should reflect, as much as possible, the biometrics of the participant prior to any study procedures.

The following procedures, assessments, and laboratory measures will be conducted:

1. Informed Consent/Assent
2. Demographics
3. Medical History
4. Concomitant Medications (including contraceptives)
5. Comprehensive Physical Exam
6. Vital Signs
7. Confirmation of Disease Classification Criteria Assessment
    a. 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups for pediatric SLE
    b. 2010 ILAR classification criteria for JIA
    c. 2017 McDonald diagnostic criteria for MS
    d. Bohan and Peter criteria or the 2017 EULAR/ACR classification criteria for JDM.
8. Complete assessments of disease activity: SLEDAI-2K for pediatric SLE; Tender/Swollen Joint Count for JIA; Physician-assessed relapse for POMS; Flare Assessment for JDM and CMAS for JDM
9. Review of COVID-19 vaccination record and antibody responses, infections and treatments.
10. Central laboratory assessments for all participants
    a. Elecsys® Anti-SARS-CoV-2 S assay to assess response to initial COVID-19 vaccine regimen
    b. CBC with differential
    c. CMP, eGFR
11. Local laboratory assessments for all participants
    a. Molecular COVID-19 Testing
    b. Urine pregnancy test (postmenarchal females must have a negative urine pregnancy test at Screening)
12. Disease-specific laboratory assessments:
    a. Pediatric SLE participants only
        i. Anti-dsDNA, C3, C4
        ii. Random urine protein-creatinine ratio
        iii. Urinalysis (microscopic)
        iv. Erythrocyte sedimentation rate (ESR) – local assessment
    b. JIA participants only
        i. CRP
    c. B-cell depleting therapy participants only

i. If on CD20 depleting agent, CD19+ B cells

d. JDM participants only

i. Disease-specific tests assessed as part of the CMP:

1. Creatine kinase (CK) only

2. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST)

ii. Aldolase

13. Inclusion/Exclusion criteria assessment

Participants with abnormal laboratory values that prohibit entry may be re-tested once during the screening period, which may last up to 21 days. Participants who screen fail may be rescreened one time and must repeat all screening assessments. Any further rescreening activity requires approval by the medical monitor.

During the Screening visit, the site will review vaccine eligibility criteria, per Section 8.4.4 Baseline (Week 0/Day 1) Visit with the participant.

8.4.2.3.2 Screening for Pediatric Stage 2 Rollover Participants

The study site will contact potential Stage 2 rollover participants to offer them the opportunity to be fully screened for Stage 2. There are two options for the conduct of the full Screening for Pediatric Stage 2 for rollover participants:

- The screening process for Stage 2 may be able to be completed with only a telephone visit if the necessary information is available from the last study visit from Stage 1, informed consent can be appropriately completed, etc.
    - *Notes:*
        - *Information that may be available from the last study visit from Stage 1 includes lab tests for eligibility and disease-specific laboratory tests noted below.*
        - *The pregnancy test and molecular COVID-19 tests do not need to be completed during the Stage 2 Screening period if the Screening visit is conducted by phone. In such cases, these assessments will be conducted at the beginning of the Stage 2 Baseline visit before the vaccine is administered.*
- If the needed data are not available from the previous Stage 1 visit or 28 days will have passed when the S2 Baseline/Week 0 visit is reached, then the Stage 2 Screening visit must be conducted at the clinical site.

The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility for Stage 2.

1. Confirm that participant agrees to proceed to Stage 2.
    a. If the participant has not yet signed an informed consent/assent form that includes a description of Stage 2, the participant must provide signed informed consent for Stage 2 screening to proceed.
2. Updated Medical History
3. Updated Concomitant Medications (including contraceptives)
4. Updated Physical Exam
    a. Results of the Targeted Physical Exam and the Neurological Exam from the most recent Stage 1 visit may be used to fulfill this assessment in place of a new Comprehensive Physical Exam
5. Vital Signs
6. AE assessment following vaccination in Stage 1

7. Complete assessments of disease activity: SLEDAI-2K for pediatric SLE; Tender/Swollen Joint Count for JIA; Physician-assessed relapse for POMS; Flare Assessment for JDM and CMAS for JDM
8. Response to previous COVID-19 vaccine dose assessed by Elecsys® Anti-SARS-CoV-2 S assay
9. Central laboratory assessments for all participants
    a. Elecsys® Anti-SARS-CoV-2 S assay to assess response to previous COVID-19 vaccine dose
    b. CBC with differential
    c. CMP, eGFR
10. Local laboratory assessments for all participants
    a. Molecular COVID-19 Testing (if Stage 2 Screening visit is conducted at the clinical site only)
    b. Urine pregnancy test (if Stage 2 Screening visit is conducted at the clinical site for women of child-bearing potential only)
11. Disease-specific laboratory assessments:
    a. Pediatric SLE participants only
        i. Anti-dsDNA, C3, C4
        ii. Random urine protein-creatinine ratio
        iii. Urinalysis (microscopic)
        iv. Erythrocyte sedimentation rate (ESR) – local assessment
    b. JIA participants only
        i. CRP
    c. B-cell depleting therapy participants only
        i. If on CD20 depleting agent, CD19+ B cells
    d. JDM participants only
        i. Disease-specific tests assessed as part of the CMP:
            1. Creatine kinase (CK) only
            2. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST)
        ii. Aldolase
12. Inclusion/Exclusion criteria assessment

8.4.3 Evaluation of Eligibility and Allocation

If the participant meets all eligibility criteria for Stage 2, then proceed as follows during the Screening phone call:

- Allocate the participant to the appropriate cohort based on IS medication
- Schedule S2 Baseline/Week 0 visit (within 28 days of the Stage 2 Screening assessments and no sooner than 7 days from the Screening visit).
- Communicate to the participant the details of the medication hold to the participant per Section 7.1.1 Protocol-mandated Medications.
- Inform the participant that there should be no changes to his/her other existing medications between Screening and the S2 Baseline/Week 0 visit.

8.4.4 Baseline (Week 0/Day 1) Visit

Eligible participants who meet all inclusion criteria and none of the exclusion criteria for Stage 2 will proceed with visits and assessments according to Section 20.1 Schedule of Events, Table 21 (newly recruited participant) or Table 22 (rollover participant). Eligible participants will be assessed for disease activity and SARS-CoV-2 infection at the S2 Baseline/Week 0 visit, prior to receipt of an alternative vaccine dose. Prior to administering the alternative vaccine dose at the Baseline visit, the site will confirm the participant meets vaccine eligibility per the criteria below:

- No increase to the permitted concomitant medications in participants in Cohorts D and E between S2 Screening and S2 Baseline/Week 0.
- No B-cell depletion infusions or changes in permitted concomitant medications in participants in Cohort E between allocation and S2 Baseline/Week 0.
- No clinically active disease (including myocarditis or pericarditis) at S2 Baseline/Week 0 resulting in an increase/addition of IS medications. For participants with MS, no suggestion of a MS relapse per the investigator.
- No active myocarditis or pericarditis based on review of clinical symptoms.
- No positive molecular COVID-19 test at S2 Baseline/Week 0.
- No increase in oral, intramuscular, or intravenous steroids within 14 days of S2 Baseline/Week 0.

If the vaccine cannot be administered at the S2 Baseline Week 0 visit, it must be administered during the following 2-3 days. Vaccine eligibility will be confirmed prior to administration of the vaccine. **Administration of the alternative vaccine dose must occur within 28 days of the S2 Screening visit (newly recruited participant) or 28 days of when the data used for screening were obtained (rollover participant).**

If a **newly recruited participant** is not eligible to receive the alternative vaccine dose at S2 Baseline Week 0, he/she will be terminated from the study (see Section 11.2 Participant Stopping Rules and Withdrawal Criteria), and the participant will be replaced. If a **rollover participant** is not eligible to receive the alternative vaccine dose at S2 Baseline Week 0, he/she will continue on the previous Schedule of Events.

The participant may rescreen after 30 days from determination of vaccine ineligibility. New recruit participants who fail to receive the vaccine must be rescreened under a new participant ID. Participants who are not eligible to receive an alternative vaccine dose at that visit may restart their IS medications immediately.

See Section 8.3.4 Study Procedures and Assessments for more information on individual clinical and research assessments.

Sites will call all Stage 2 participants who withheld an IS medication after the S2 Baseline visit to provide instructions on resuming IS medication per Section 7.1.1 Protocol-mandated Medications.

8.4.5 Study Procedures and Assessments

Study procedures and assessments are as described in Section 8.3.4 Study Procedures and Assessments

8.4.6 Unscheduled Visits

Unscheduled visits are described in Section 8.1.5 Unscheduled Visits.

8.4.7 Early Termination

Early termination is described in Section 8.1.6 Early Termination.

9. Mechanistic Assays

Planned and potential mechanistic assays for this study are noted below. Blood drawn from participants for mechanistic and clinical blood draws may not exceed NIH blood draw limits (550mL over 8 weeks).

Antibody assays: Antibody levels will be tested at each time point to test for IgG and IgM responses against SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins using standardized ELISAs or comparable assays from the

NIAID-VRC, Seronet, or one of the ACE Centers. Additional assays testing for antibody responses against variants or providing epitope specificity, such as through on the University of Texas Southwestern or Stanford arrays [66], may be tested if resources are available. Assays to test for anti-cytokine, autoantibody, anti-adenoviral, and anti-RNA responses may also be tested by the aforementioned combination arrays, ELISAs or a combination of these. Finally, novel assays for antibodies may also be included, as possible. For example, the Ring laboratory (Yale) is using a novel Rapid Extracellular Antigen Profiling (REAP) assay to assess 2,770 extracellular and secreted proteins which have been informative in post-COVID infection [67]. Serum will be used for these assays.

Neutralizing assays: Assays will also be performed to see whether neutralizing antibodies are produced in autoimmune disease participants after additional vaccine administrations. Using the microneutralization assays by plaque reduction in use at the NIAID-VRC, Seronet or at an ACE Center, presence/absence and titer of neutralization will be recorded for each sample. Alternatively, pseudoneutralization assays, where the spike antigen is transfected into a lentiviral vector-based assay could be used as a surrogate. Another option would be the competition ELISA-based surrogate virus neutralization assay (sVNT) for rapid screening of all samples; however, this assay is not as useful for lower concentration neutralization and may not be ideal for autoimmune disease patient samples. Assays will follow the published literature [68]. Serum will be used for these assays.

Antigen-specific T cell responses and T cell repertoires: Autoimmune disease patients, especially those on BCDTs, may have undetectable SARS-CoV-2 antibodies but still mount effective T cell responses against the virus. Using T cell assays in place in the Bar-Or, Pillai, or NIAID labs, briefly PBMCs from each individual sample will be stimulated with SARS-CoV-2 spike protein, other SARS-CoV-2 antigens, positive (PMA) and negative controls, followed by readouts such as IFN gamma ELISPOT [69] or by CD4+ interferon gamma and/or Interleukin-2 (IL-2) and/or Tumor Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression by intracellular staining [70]. Please see the ACV01 Lab Manual for more information. T cell epitope mapping and TCR utilization assays may be performed in future use assays. Frozen PBMCs will be used for these assays.

Antigen-specific memory B cell responses and B cell repertoires: In addition to antibodies and T cell mediated immunity, memory B cell responses will also be assessed. Peripheral blood mononuclear cells (PBMCs) will be stimulated with SARS-CoV-2 spike or receptor binding domain and cells assessed for antibody production by ELISPOT. Alternatively, after discussion with the ACE Network investigators, whole blood stimulations with spike antigens may be performed with each blood draw with stabilization to allow the evaluation of B cell and T cell responses post-vaccination as has been performed for COVID-19 infection [71]. From an immunological standpoint, and in addition to overall profiling, detailed studies of antigen-specific B cell responses will be studied in order to understand: a) the cellular compartments in which SARS-CoV-2-specific B cell memory resides; b) its quality, magnitude and distribution within the population; c) its provenance (whether from early or late cellular precursors); and d) its concordance or conversely, uncoupling from serological responses. This approach would enable the group to differentiate between different types of long-term memory responses, including long-term serological memory (dependent on the generation of long-lived plasma cells (LLPC); and cellular memory (B cell memory with or without serological memory). Additional B cell repertoire sequencing may be performed in a subset of patients as well. Frozen PBMCs, or whole blood, will be used for these assays. Dr. Patrick Wilson has developed all the assays for SARS-CoV-2-specific B cell characterization and could be involved in performing these studies with ACV01 samples.

Immunophenotyping and Immune cell population profiling over time: In addition to the above assessments of antigen-specific B and T cell responses, additional immunophenotyping of samples will be performed, at least on a subset of individuals and time points, to determine cell populations that correlate with adequate vaccination responses after additional study vaccine dose administration, either with an mRNA vaccine, a vector-based COVID-19 vaccine, or a protein-based COVID-19 vaccine compared to inadequate responders. Deep immunophenotyping will be performed using the standard panels of the NIAID HIPCs by CyTOF or high dimensional flow cytometry as performed by one of the ACE Centers [72, 73]. Stabilized whole blood or PBMCs will be used for these assays. Please see the Lab Manual for additional details.

Gene expression profiling, soluble mediators, autoantibody assessments, and individual hypothesis testing: Several ACE Centers have specific hypotheses that they would like to test with this unique participant collection to determine whether specific immune cell types or pathways associate with neutralizing SARS-CoV-2 responses after vaccination. A

few examples are listed here and others will use the stored biospecimens outlined below. Through work in SLE with influenza and varicella (Zostavax) vaccination, ACE investigators have found that individuals with poor vaccine responses have a higher baseline IFN response [74, 75]. Other work has shown that individuals with increased numbers of CD86 positive naïve B cells, or activated CD11b+ monocytes (or both) are at higher risk of disease flare within the next 4-6 weeks [76]. Increased numbers of CD319+ T cells are found in systemic sclerosis patients compared to controls [77], and can be assessed across autoimmune diseases in this cohort and tested for association with impaired vaccine responses. RNA will be isolated from PAXgene tubes and transcript profiles determined by RNAseq. Module expression will be determined as per the Pascual group and modules assessed for association with impaired vaccination responses [78]. Soluble mediator levels of cytokines, chemokines, and soluble receptors will be tested in plasma as outlined by the James group [79]. Immunophenotyping data will be used from above to test other hypotheses [78]. Autoantibody profiling, related to the individual autoimmune diseases and with a broader coverage such as an autoantigen array, will be done at each visit to determine effects of an additional study vaccine dose on autoantibody production. Specific questions about changes in autoantibody concentration, isotypes, avidity, new specificities, and epitope expansion could be addressed, as funding allows.

scRNAseq, CITE-seq, scATAC-seq (TEA-Seq): Finally, in another subset analysis, smaller groups of participants on similar background meds who do and do not respond to an additional study vaccine dose will be tested by single cell technologies to generate additional hypotheses regarding the cell types, cell subsets, and immune cell pathways associated with impaired vaccination responses within and across autoimmune diseases. These assays will use frozen PBMCs (or stabilized whole blood) and will use the approaches in standard use within one of the ACE Network Centers.

Together, the data assembled through these mechanistic studies will inform the community about the mechanisms of vaccine response, and non-response, in autoimmune disease patients, as well as potentially in others taking similar medications. Information may also be uncovered regarding autoimmune disease pathogenesis, predictors of vaccine response, and autoimmune disease flare.

Background IS Medication Testing: A critical part of this study is to discover if withholding cohort-defining IS medications influences response to the additional vaccine dose. In order to determine if there is a correlation between IS medication level in the blood and vaccine response, a whole blood specimen will be collected at the Baseline/Week 0 visit for all participants in Cohorts A (MMF/MPA) and B (MTX). If the primary endpoint analysis yields no quantifiable difference between treatment arms withholding IS medication and those continuing their medication in Cohort A (MMF/MPA) and Cohort B (MTX), the Baseline whole blood and serum specimens will be tested to gain additional insight into a relationship between medication blood levels and vaccine response.

Optional Site-specific Sub-studies: The mechanistic assays noted above represent a small portion of the research that can be completed on autoimmune patients receiving an additional COVID-19 vaccine dose. This study presents a unique opportunity to collect data during a critical time in our vaccine response timeline. Individual site investigators may choose to collect additional optional specimens from Baseline/Week 0 to Week 4 to complete mechanistic analysis of their own. All optional mechanistic specimen sub-studies will be detailed in site-specific informed consent forms.

Optional Week 1 Pediatric Specimen Collection: Pediatric participants may choose to participate in an optional specimen collection during the Week 1 Vaccine Diary Review visit (window: Day 7-14). Procedures for this visit are outlined in Section 20.1 Schedules of Events.

10. Biospecimen Storage

The ACE Network investigators will also discuss and prioritize other assays to be performed on the longitudinal samples from this autoimmune disease COVID vaccination trial. To facilitate these future studies, the following biospecimens will be collected at participating sites, processed and stored at the Oklahoma Medical Research Foundation (OMRF) College of American Pathologists (CAP)-certified Biorepository. These biospecimens include: serum, plasma, peripheral blood mononuclear cells, RNA isolated from PAX gene tubes, and DNA isolated from buffy coats. Individuals will be asked to provide consent for genetic studies and to have data, including genetic and gene expression, stored in an NIH-approved public database. Individuals will be able to opt out of genetic testing based upon their preference. Samples will be used within the ACE Network or by outside investigators with compelling questions who collaborate with one of the ACE

Network investigators. Samples will be stored for up to 4 years after the completion of the trial (or for longer in an ACE Network Biorepository or other biorepository approved by NIAID DAIT and the ACE Network. If the NIAID ACE Network were to disband, then NIAID DAIT will work with the housing institution for the final dispensation of the samples.

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1 Participant Completion

Participation will be considered to be complete when the Week 48 visit of the participant's last stage of participation is complete.

11.2 Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant and/or legal guardian elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.
5. The participant does not receive the additional vaccine dose at Baseline/Week 0 or S2 Baseline/Week 0 (new recruits only) for any reason, including the criteria listed in Section 8.1.3 Baseline (Week 0/Day 1) Visit or at Section 8.2.4 Baseline (Week 0/Day 1) Visit, respectively.
6. The participant receives a SARS-CoV-2 vaccine outside of the study.

11.3 Participant Replacement

Participants who withdraw or are withdrawn will not be replaced if they have received a vaccine dose at a given stage of the study. If a Stage 1 or newly recruited Stage 2 participant is randomized or allocated to a study arm but does not receive the vaccine, the participant will be withdrawn and will not be counted toward the total accrual objective. If a Stage 2 rollover patient is allocated to a study arm but does not receive the vaccine, the participant will continue on their previous Schedule of Events and will not be counted toward the Stage 2 accrual objective. Additional participants will be consented and randomized/allocated to achieve the accrual objective(s).

11.4 Follow-up after Early Study Withdrawal

Participants who prematurely withdraw (without withdrawing consent) or who are withdrawn may be asked to complete a final phone visit to assess any AEs and concomitant medications as applicable depending on when they are withdrawn relative to the visit schedule. Participants who are withdrawn from the study prior to receipt of study treatment will not be followed after their last completed study visit. Monitoring of a pregnant participant will continue until the conclusion of the pregnancy.

11.5 Study Stopping Guidance

If any of the events listed, other than myocarditis/pericarditis, in Section 12.8.2.2 Ad hoc DSMB Reviews occur, the Data Safety Monitoring Board (DSMB) chair will be notified, and a review of safety data will be performed to determine if consent of potential participants, randomization/allocation, and/or administration of investigational study medication should be halted. If 2 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.

For any NCI-CTCAE Grade 2 or higher myocarditis or pericarditis that occurs within 6 weeks of vaccine administration, the DSMB chair be notified of the event within 3 business days from when the AESI was reported to DAIT/NIAID (see Section 12.5.2). The DSMB chair will adjudicate whether an expedited, ad hoc safety review by the full DSMB is required.

12. Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5 Reporting Adverse Events and Serious Adverse Events to Sponsor (DAIT/NIAID) to the Sponsor (DAIT/NIAID). Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and the FDA.

Information in this section complies with International Conference on Harmonisation (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R2), and 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related (see 21 CFR 312.32(a)).

An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use or in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

12.2.1.1 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the AE. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug (21 CFR 312.32(a)).

12.2.1.2 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or SAR is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

12.2.1.3 Solicited Adverse Events (Reactogenicity)

Solicited AEs are predefined local and systemic events for which the participants will be specifically questioned, and which will be noted by these participants. In this study, queried symptoms will include:

- Injection site reaction such as pain, erythema, induration/edema as well as development of papules, and ulceration.
- Axillary lymphadenopathy.
- Solicited systemic reactions including fever (assessed as daily oral temperature), chills, myalgia, arthralgia, fatigue*, headache*, nausea*, vomiting, hives, and diarrhea.

  *Participants that are 2-3 years old will have sleepiness, irritability/crying, and loss of appetite assessed rather than fatigue, headache, and nausea.

- Increased shortness of breath, chest pain**, swelling/pain in arm or leg**.

  **These symptoms will be assessed in participants age 5 years and above.

- Increase in symptoms of the participant's underlying autoimmune disease.

12.2.2 Unsolicited Adverse Event

For the purpose of this protocol, an AE is considered "unsolicited" when it is collected through an open-ended question and it is not specified as a solicited AE.

12.2.3 New-onset Chronic Medical Condition (NOCMC)

A NOCMC is defined as any new International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis 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.

12.2.4 Medically Attended Adverse Event

Medically attended adverse event (MAAE) is defined as a hospitalization, emergency room visit, or an otherwise unscheduled visit to or from medical personnel for any reason that is considered possibly related or related to study vaccine.

12.2.5 Adverse Events of Special Interest

Adverse events of special interest (AESIs) include the following:

- Myocarditis (probable and confirmed cases)
- Pericarditis
  See Appendix 20.8 for cases definitions of probable and confirmed myocarditis and pericarditis according to the Centers for Disease Control and Prevention (CDC) criteria

In addition, the following AESI will collected in the arms in which the Sanofi-GSK COVID-19 Vaccine is administered.

- New onset of potential immune-mediated diseases (pIMDs).

  See Appendix 20.7. Disease flares of the underlying autoimmune disease, including new manifestation of the disease will not be captured as an AESIs. Disease flares should be reported following Section 12.4.2 Increase in Autoimmune Disease Activity.

  pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs, including those listed in Appendix20.7.

  However, the Investigator will exercise their medical and scientific judgment in deciding whether other diseases have an autoimmune origin (that is pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD. When there is enough evidence to make any of the diagnoses mentioned in Appendix 20.7 the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

12.2.6 Serious Adverse Event (SAE)

An AE or SAR is considered "serious" if, in the view of either the investigator or Sponsor (DAIT/NIAID), it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.

2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor [add DAIT/NIAID or other Sponsor, *if applicable],* its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol-mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

12.3.1.1 Grading of Solicited Adverse Events

Participants will grade solicited AEs using a 0-3 participant symptom rating scale as outlined in the Vaccine Reaction Diary instructions (Appendix 20.3 Adult Vaccine Reaction Diary).

Participant Symptom Rating Scale

- 0 = No symptoms
- 1 = Mild: Present, but did not require over-the-counter or prescription medications; did not interfere with daily activities
- 2 = Moderate: Required over-the-counter or prescription medications; caused some interference with daily activities
- 3 = Severe: Required over-the-counter or prescription medications; significant, incapacitating discomfort preventing daily activities

12.3.1.1.1 Grading of Pediatric Gastrointestinal Solicited Adverse Events

Pediatric participants will grade nausea, vomiting, and diarrhea solicited adverse events using a 0-3 symptom-specific rating scale as noted below and in the Vaccine Reaction Diary for Pediatric Participants (Appendices20.4, 20.5, 20.6):

Nausea/Vomiting

- 0 = No symptoms
- 1 = Mild: 1 to 2 times in 24 hours
- 2 = Moderate: > 2 times in 24 hours
- 3 = Severe: Prevents daily activity

Diarrhea

- 0 = No symptoms
- 1 = Mild: 2 to 3 loose stools in 24 hours
- 2 = Moderate: 4 to 5 loose stools in 24 hours
- 3 = Severe: 6 or more loose stools in 24 hours

12.3.1.2 Grading of 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 Appendix 20.2 CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0).

12.3.1.3 Grading of 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 follows:

- Aspartate aminotransferase [AST] increased
  - Grade 1: >ULN – 3.0x ULN
  - Grade 2: >3.0x ULN - 5.0x ULN
  - Grade 3: >5.0x ULN - 20.0x ULN
  - Grade 4: >20.0x ULN
- Alanine aminotransferase [ALT] increased
  - Grade 1: >ULN – 3.0x ULN
  - Grade 2: >3.0x ULN - 5.0x ULN
  - Grade 3: >5.0x ULN - 20.0x ULN
  - Grade 4: >20.0x ULN
- Alkaline phosphatase [ALP] increased
  - Grade 1: >ULN – 2.5x ULN
  - Grade 2: >2.5x ULN - 5.0x ULN
  - Grade 3: >5.0x ULN - 20.0x ULN
  - Grade 4: >20.0x ULN
- Blood bilirubin increased
  - Grade 1: >ULN – 1.5x ULN
  - Grade 2: >1.5x ULN - 3.0x ULN
  - Grade 3: >3.0x ULN - 10.0x ULN
  - Grade 4: >10.0x ULN

12.3.1.4 Grading of 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. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event

Grade 2 = moderate adverse event

Grade 3 = severe or disabling adverse event

Grade 4 = life-threatening or urgent intervention

Grade 5 = death

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram, etc.), a treatment-emergent AE is defined as an increase in grade from Baseline or from the last post-Baseline value, that does not meet grading criteria. Changes in grade from Screening to Baseline will also be recorded as AEs if related to a study-mandated procedure, treatment, or change in treatment (but are not treatment-emergent). If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an AE if changes in therapy or monitoring are implemented as a result of the event/result.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.3.2 Attribution Definitions

Solicited AEs will be attributed as being related to the study-provided vaccine. The relationship, or attribution, of all other AEs to the study-provided vaccine or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE eCRF. Final determination of attribution for safety reporting will be determined by the DAIT/NIAID Medical Monitor. The relationship of an AE to vaccine, study therapy regimen, or study procedures will be determined using the descriptors and definitions provided in Table 16, Attribution of Adverse Events.

Table 16. Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

12.4 Collection and Recording of Adverse Events

12.4.1 Collection Period For All Cohorts

For this study, the timelines below apply after each study-administered vaccine:

- Solicited AEs (all grades) will be collected from Day 1 (vaccine administration) through 7 days post study vaccination.
- Unsolicited AEs will be collected as follows:
  - 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.

- AESIs will be collected as follows:
  - Pericarditis/myocarditis events will be collected in all treatment arms. NCI-CTCAE Grade 2 or higher myocarditis and pericarditis events from Day 1 through the end of the participant's study participation.
  - New onset of pIMDs will only be collected in arms where the Sanofi-GSK COVID-19 Vaccine is administered. All grades 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 NCI-CTCAE grade.
- 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.

12.4.2 Increase in Autoimmune Disease Activity

Any increase in autoimmune disease activity (flare/relapse) for the participant's qualifying autoimmune disease will not be reported as an AE. These events will be collected and reported on the disease-specific assessment eCRFs. (Section 8.1.4.2 Disease-Specific Assessments).

12.4.3 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the participant.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an AE, as defined in Section 12.3 Grading and Attribution of Adverse Events.

12.4.4 Recording Adverse Events

AEs will be recorded on the clinic's progress notes or other source documents in the participant's chart.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation. For AEs where an abnormal value or result of a clinical or laboratory evaluation is observed (see Section 12.3.1 Grading Criteria), resolution is defined as the first value post abnormality that is in the normal range (Grade 0).

12.5 Reporting Adverse Events and Serious Adverse Events to Sponsor (DAIT/NIAID)

12.5.1 Reporting Adverse Events

This section describes the responsibilities of site investigators to report AEs to the Sponsor (DAIT/NIAID) via the DAIT-SACCC.

Sites are responsible for ensuring the participant completion of the 7-day Vaccine Reaction Diary and assisting participants with entry of all Vaccine Reaction Diary data into the electronic e-Diary in the MyOwnMed portal, if required.

Investigators are responsible for reporting solicited AEs in electronic data capture (EDC) in the following special cases:

- If a solicited AE is also an SAE or MAAE, it 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 and graded according to the criteria defined in Section 12.3.1 Grading Criteria.

All grade ≥1 diagnoses of COVID-19 disease confirmed by molecular COVID-19 testing (or alternative test per institutional standards) will be reported to the Sponsor as AEs.

All MAAE, NOCMC, AESIs, and SAEs (listed in Section 12.4 Collection and Recording of Adverse Events) will be reported until the end of the study. Unless otherwise noted below in Section 12.5.2 Reporting Serious Adverse Events, SAEs and AESIs will be reported within 24 hours. Unsolicited AEs, MAAEs, and NOCMCs must be recorded on the appropriate eCRF within 5 days of discovery of the event. Whenever possible, a diagnosis should be provided rather than compilation of signs/symptoms, with grade of the event dictated by highest grade of the sign/symptom component.

12.5.2 Reporting Serious Adverse Events

This section describes the responsibilities of the site investigator to report SAEs and AESIs to the sponsor via the eCRF. Timely reporting of AEs is required by 21 CFR and ICH E6 R2 guidelines.

Site investigators will report all SAEs (see Section12.2.6 Serious Adverse Event (SAE)) and AESIs (see Section 12.2.5 Adverse Events of Special Interest), regardless of relationship or expectedness within 24 hours of discovering the event.

For SAEs and AESIs, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF will be updated and submitted.

When a site investigator identifies an SAE or AESI specified above, he or she must notify DAIT/NIAID via the DAIT-SACCC within 24 hours. Site investigators are to report these events on the SAE eCRF in EDC. Should EDC become unavailable/ inaccessible, the site investigator should notify DAIT/NIAID via the DAIT-SACCC email at Rho_productsafety@rhoworld.com. This email can serve as the initial notification; however, within the next business day, the SAE eCRF must be completed.

All requested information on the SAE eCRF should be provided. Unavailable details of the event at time of initial report should not delay submission of known information. The initial report should include at a minimum: AE term, relationship to vaccine, and reason why event is serious (per definitions). Supplementary CRF pages including medical history, concomitant medications, demographics, study drug administration, and death must be provided. As additional details become available, the SAE eCRF should be updated and submitted. Each SAE or AESI must be signed by the investigator in the EDC system at the time of initial submission and upon SAE or AESI closure. If an SAE or AESI is determined to require an expedited report to a Health Authority, then the SAE or AESI will be signed by the investigator on a more frequent basis. With each iteration of the form, the investigator (or designated sub-investigator) must sign the form electronically.

For additional information regarding SAE reporting, contact Rho Product Safety (DAIT-SACCC):

[redacted]

12.5.3 Reporting to Health Authority

After an AE requiring 24 hour reporting (per Section 12.5.2 Reporting Serious Adverse Events) is submitted by the site investigator and assessed by DAIT/NIAID, there are 2 options for DAIT/NIAID to report the AE to the appropriate health authorities (Annual Reporting and Expedited Reporting).

12.5.3.1 Annual Reporting

Per 21 CFR 312.33, DAIT/NIAID will include in the Investigational New Drug Application (IND) Annual Report to FDA all AEs classified as:

- Serious, expected, SARs (see Section 12.2.1.1 Suspected Adverse Reaction (SAR) and Section 12.5.2 Reporting Serious Adverse Events).
- Serious and not a SAR (see Section 12.2.1.3 Solicited Adverse Events (Reactogenicity)).
- Pregnancies.

Note that all AEs (not just those requiring 24-hour reporting) will be reported in the IND Annual Report.

12.5.3.2 Expedited Safety Reporting

This option, with 2 possible categories, applies if the AE is classified as one of the following:

Category 1: Serious and unexpected suspected adverse reaction [SUSAR] (see Section 12.2.1.1 Suspected Adverse Reaction (SAR) and Section 12.2.1.2 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction and 21 CFR 312.32(c)(1)i).

The sponsor shall report any SAR that is both serious and unexpected. The sponsor shall report an AE as a SAR only if there is evidence to suggest a causal relationship between the study drug and the AE, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Category 2: Any findings from studies that suggest a significant human risk

The sponsor shall report any findings from other epidemiological studies, analyses of AEs within the current study or pooled analysis across clinical studies or animal or in vitro testing (e.g., mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, and investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the FDA and all participating investigators of expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

12.5.4 Mandatory reporting to Vaccine Adverse Event Reporting System

Per the FDA EUA for the Pfizer-BioNTech COVID-19 Vaccine, FDA EUA for the Moderna COVID-19 Vaccine, the FDA EUA for the Janssen COVID-19 Vaccine, the site investigator or designee is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS) [48, 58, 59]:

- Vaccine administration errors, whether or not associated with an AE,
- SAEs (irrespective of attribution to vaccination),

- Cases of Multisystem Inflammatory Syndrome in adults and children, and
- Cases of COVID-19 that result in hospitalization or death.

Vaccination providers may report to VAERS other AEs that are not required to be reported.

The site investigator, or designee, is also responsible for recording vaccination information in the state/local jurisdiction's Immunization Surveillance System or other designated system.

12.5.5 Reporting of Adverse Events to Institutional Review Boards (IRBs)/Institutional Ethics Committees (IECs)

All investigators shall report AEs and SAEs, including expedited reports, in a timely fashion to their respective local IRBs and single IRB in accordance with applicable regulations and guidelines. All safety reports to the FDA shall be distributed by the Sponsor (DAIT/NIAID) or designee to the single IRB and all participating institutions for local IRB submission if required.

12.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study participant. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to the SACCC all participant pregnancies within 1 business day of becoming aware of the event using the Pregnancy eCRF. The SACCC will report all pregnancies to DAIT/NIAID. All pregnancies identified during the study shall be followed to conclusion, and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to the SACCC when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

Should pregnancy complications result in an event meeting the SAE definition outlined in Section 12.2.6, such as congenital abnormality, birth defect, miscarriage, or medically indicated abortion, an SAE must be submitted to the SACCC using the SAE reporting procedures described above.

12.7 Reporting of Other Safety Information

An investigator shall promptly notify their local and central IRB, in accordance with applicable regulations and guidelines, as well as the SACCC and DAIT/NIAID via email when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an AE.

12.8 Review of Safety Information

12.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the DAIT-SACCC compiling new and accumulating information on AEs, AESIs, SAEs, MAAEs, NOCMCs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received from the DAIT-SACCC.

12.8.2 DSMB Review

12.8.2.1 Planned DSMB Reviews

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, AESIs, 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.

12.8.2.2 *Ad hoc* DSMB Reviews

12.8.2.2.1 *Ad Hoc* DSMB Reviews for Adult Participants

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. Any of the following events 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 within 24 weeks of a Day 1 visit will be counted.*
- Occurrence of a Grade 2 or higher myocarditis or pericarditis within 6 weeks of vaccine administration. *Note: the DSMB chair will be notified within 3 business from when the AESI is reported to DAIT/NIAID.*
- 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 1 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.

Severe flare or relapse is defined as follows:

  - **RA**: DAS28-CRP score >5.1.
  - **SLE**: Severe score on the SELENA-SLEDAI flare index.
  - **SSc**: Onset of new or significant worsening of internal organ involvement requiring hospitalization or change in treatment or worsening of skin thickening on the modified Rodnan skin score of >4 units [absolute change from screening visit].
  - **MS**: Clinical relapse meeting either the criteria specified in (a) with investigator determination of relapse or the criteria in (a) **and** (b) below:

a. Occurrence of new, recurrent or worsening neurological symptoms attributable to MS, that meet all of the following criteria:

i. Appeared or evolved subacutely (over <3 months).

ii. Persisting for >24 hours.

iii. Cannot be attributed to confounding factors (e.g., fever, infection, injury, poor sleep, adverse reaction to medication).

iv. Occur ≥ 30 days after the onset of a prior confirmed relapse.

b. New, recurrent or worsening neurological symptoms accompanied by corresponding objective worsening on neurologic examination with an increase of any one of the following in MS participants compared to the immediate prior assessment:

i. ≥ 0.5 step(s) on the Expanded Disability Status Scale (EDSS), or

ii. ≥ 2 points on one Functional Systems Score (FSS), or

iii. ≥ 1 point on two or more FSS.

Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Sexual dysfunction and fatigue will not contribute to the EDSS or FSS for assessing MS relapse.

- **Pemphigus**: 3 or more new lesions a month that do not heal spontaneously within 1 week or by the extension of established lesions in a participant who has achieved disease control.

After review of the safety data, the DSMB will make recommendations regarding study conduct, including modifications and/or continuation. The DSMB will recommend and DAIT/NIAID, as Sponsor, will determine whether protocol changes should be implemented and/or whether and when consenting, allocation, randomization, and vaccinations can resume.

12.8.2.2.2 *Ad Hoc* DSMB Reviews for Pediatric Participants

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. Any of the following events 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 a Grade 2 or higher myocarditis or pericarditis within 6 weeks of vaccine administration. *Note: the DSMB chair will be notified within 3 business days from when the AESI is reported to DAIT/NIAID.*
- 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.

Severe flare or relapse is defined as follows:

- **JIA**:

a. JADAS10 >17 (polyarthritis, enthesitis-related JIA, and psoriatic arthritis), JADAS10 >13 (for oligoarthritis)

b. PASI ≥12 (for psoriatic arthritis)

- **Pediatric SLE**: ≥ 6.4 on the SLEDAI-based ACR provisional criteria for global flares in childhood-onset SLE
- **JDM**: Decline in CMAS to <30 or JDM DAS>5
- **POMS**: Clinical relapse meeting either the criteria specified in (a) with investigator determination of relapse or the criteria in (a) **and** (b) below:

a. Occurrence of new, recurrent or worsening neurological symptoms attributable to MS, that meet all of the following criteria:

v. Appeared or evolved subacutely (over <3 months)

vi. Persisting for >24 hours.

vii. Cannot be attributed to confounding factors (e.g., fever, infection, injury, poor sleep, adverse reaction to medication)

viii. Occur ≥ 30 days after the onset of a prior confirmed relapse.

b. New, recurrent or worsening neurological symptoms accompanied by corresponding objective worsening on neurologic examination with an increase of any one of the following compared to the immediate prior assessment:

i. ≥ 0.5 step(s) on the EDSS scale, or

ii. ≥ 2 points on one Functional Systems Score (FSS), or

iii. ≥ 1 point on two or more FSS.

Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Sexual dysfunction and fatigue will not contribute to the EDSS or FSS for assessing MS relapse.

After review of the safety data, the DSMB will make recommendations regarding study conduct, including modifications and/or continuation. The DSMB will recommend and DAIT/NIAID, as Sponsor, will determine whether protocol changes should be implemented and/or whether and when consenting, allocation, randomization, and vaccinations can resume.

12.8.2.2.3 Temporary Suspension of Randomization/Allocation and Vaccinations

Section 11.5 Study Stopping Guidance outlines the procedure for DSMB ad hoc review due to the events listed in Section 12.8.2.2 Ad hoc DSMB Reviews. If during the ad hoc review, the DSMB determines that a temporary halt in randomization/allocation is required, participants who received vaccination prior to the temporary halt will continue in the study as planned. During the halt in randomization/allocation, recruitment, screening and consenting may continue, but no additional study vaccine doses will be administered.

13. Statistical Considerations and Analytical Plan

13.1 Overview

This is a randomized, multi-site, adaptive, open-label clinical trial comparing the immune response of different additional doses of COVID-19 vaccine in participants with autoimmune disease requiring IS medications. All study participants will have negative serologic or suboptimal responses to an initial COVID-19 vaccine regimen (Adult and Pediatric Stage 1) or a negative, suboptimal, or low immune response to initial COVID-19 vaccine regimen plus additional COVID-19 vaccinations (Adult and Pediatric Stage 2). We will focus on 5 autoimmune diseases in adult participants (SLE, RA, MS, SSc, and pemphigus) and 4 autoimmune diseases in pediatric participants (JIA, pediatric SLE, JDM, and POMS).

The primary objective is to determine the proportions of adult and pediatric participants who have a protective antibody response at Week 4 assessed by the NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay.

Response will be assessed within subgroups defined by the magnitude of immune response to prior vaccines, age, categories of IS medications, type of vaccine, and whether IS medications are continued or withheld around administration of the additional homologous vaccine dose.

13.2 Endpoints

Primary, secondary, and exploratory endpoints are listed in Sections 3.2 Primary Endpoint, 3.3 Secondary Endpoints, and 3.4 Exploratory Endpoints, respectively.

13.3 Measures to Minimize Bias

Participants will be assigned to cohorts defined by IS medication (Cohort A and D: MMF/MPA; Cohort B and E: MTX; and Cohort C and F: BCDT) and by the initial COVID-19 vaccine regimen received (Moderna COVID-19 Vaccine, Pfizer-BioNTech COVID-19 Vaccine, or Janssen COVID-19 Vaccine). In Adult Stage 1 and the pediatric portion of the study, participants in Cohort C will be allocated to continue taking their prescribed IS medications throughout the trial. Participants in Cohort 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.

13.4 Analysis Plan

13.4.1 Analysis Populations

The following populations will be defined separately for Stage 1 and Stage 2.

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.

13.4.2 Primary Analysis of 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. Participants with missing Week 4 anti-COVID-19 antibody response data with a documented COVID infection 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). Intercurrent events which result in Week 4 anti-COVID-19 antibody response data being unevaluable for immune response, including receipt of monoclonal antibodies or plasma products directed against SARS-CoV-2 and any SARS-CoV-2 vaccine outside of the study, will also result in data be considered to be missing-completely-at-random (MCAR).

The primary analysis will be evaluated independently within each arm (defined by age, cohort, vaccine, and IS treatment plan) and within subgroups with either a negative or suboptimal response to prior vaccines (defined as Roche Elecsys® Anti-SARS-CoV-2 S result ≤200 U/mL) or with a low immune response (defined as Roche Elecsys® Anti-SARS-CoV-2 S result >200 U/mL and ≤2500 U/mL). The primary analysis will be performed in the vaccinated population. The proportion of participants meeting a protective antibody response criteria will be reported in each arm and subgroup 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 also be conducted 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.

13.4.3 Supportive Analyses of the Primary Endpoint

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). Descriptive statistics will be used to summarize antibody response to the additional homologous vaccine dose on a continuous scale. 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.

13.4.4 Analyses of Secondary and Other Endpoint(s)

For Stage 1, the multivariable logistic and linear regression models defined in Section 13.4.3 Supportive Analyses of the Primary Endpoint above will be used to compare response to additional homologous doses of COVID-19 vaccine for a variety of subgroups. Appropriate contrasts will be defined to compare vaccine response for the following:

- Continuing versus withholding IS medications will be compared within cohort (cohorts A and B only) and within and across type of vaccine.
- The types of additional vaccine dose administered will be compared within cohorts and across cohorts, and within and across IS treatment plan groups.
- Type of IS medications will be compared within and across each type of vaccine.
- Age groups and type of disease will be compared within and across each type of vaccine.
- Corticosteroid dose at baseline will be added as a covariate to the model to assess impact on vaccine response.
- Immune response to the initial COVID-19 vaccine regimen will be assessed within and across each type of vaccine.
- Additional covariates for disease activity, co-morbid illness, age, and sex may be added to assess whether the clinical parameters are associated with response to additional vaccine dose.

Data for the Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine may be combined in the comparisons above to assess the effect of mRNA vaccines together.

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 proteins) assay with thresholds <1204.7, 517.9, and 9779.6 AU/mL, respectively, and (b) the Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay with a threshold <0.80 U/mL. The proportions who seroconvert within and across arms will be summarized using 95% Clopper-Pearson confidence intervals, and comparisons will use a two-sample Binomial exact test with nominal two-sided alpha = 0.05.

For the subgroups of participants that are anti-COVID-19 antibody positive at baseline using separately, (a) the NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay, and (b) the Roche Elecsys® Anti-SARS-CoV-2 S electrochemiluminescence immunoassay with a threshold ≥0.80 U/mL. Fold improvement for each assay will be defined as:

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

Longitudinal changes in the anti-COVID-19 antibodies will be summarized over time by study visit using descriptive statistics. Details on handling missing data and intercurrent events, which result in anti-COVID-19 antibody response data being unevaluable for immune response, will be outlined in the statistical analysis plan.

Longitudinal changes in neutralization and pseudoneutralization assays will be summarized by study visit using descriptive statistics. For secondary continuous efficacy endpoints, descriptive statistics will be used to summarize the distribution of scores in each arm; for adult participants, this will include the H-SLEDAI (SLE participants), Tender/Swollen Joint Count (RA participants), PDAI (pemphigus participants), modified Rodnan Skin Score (SSc participants), CGI-C, PtGA, PGI-C, PGA, and PROMIS 29, and for pediatric participants, this will include the SLEDAI-2K (SLE), Tender/Swollen Joint Count (JIA participants), MMT-8 and CMAS (JDM participants), CGI-C, PtGA, PGI-C, PGA, and PedsQL. The proportion of participants who meet definition for disease-specific flares, including the Thanou modified SELENA-SLEDAI Flare Index (SLE participants), patient-reported flare assessment (SSc participants), and physician-assessed relapse (MS participants), will be summarized. The disease-specific flare endpoints will include Thanou modified SELENA-SLEDAI Flare Index (SLE participants), DAS28-CRP (RA participants), patient-reported flare assessment (SSc participants), flare assessment (pemphigus participants) and physician-assessed relapse (MS participants) in adults and the ACR Provisional Criteria for Global Flare in Childhood-onset SLE (for SLEDAI; pediatric SLE participants), physician-assessed relapse (POMS participants), and flare assessment (JDM participants).

Descriptive statistics will be used to summarize the proportions of participants in the safety arm who experience safety endpoints.

For Stage 2, analysis plans for primary and secondary endpoints will be repeated to evaluate the immune response to a subsequent alternative COVID-19 vaccine dose and to determine whether immunologic variables are associated with increased disease activity.

13.4.5 Descriptive Analyses

Summary descriptive statistics for baseline and demographic characteristics, disposition, and medication use will be provided for the safety and vaccinated populations. These data will be presented in the following manner:

- Continuous data (e.g., age, weight, and height) will be summarized by mean, standard deviation, median, and range.
- Categorical data (e.g., sex and race) will be presented as counts and percentages.

All medications taken by or administered to study participants beginning 30 days before the Screening Visit and continuing throughout the study will be collected. All medications used will be coded according to the World Health Organization (WHO) drug dictionary. The number and percentage of participants receiving prior and concomitant medications/therapies will be presented overall and by medication class.

13.5 Interim Analysis

13.5.1 Interim Analysis of Efficacy Data

No interim analysis of efficacy data is planned for the study.

13.5.2 Interim Analysis of Safety Data

No interim analysis of safety data is planned for the study. Routine reviews by the NIAID DSMB will be conducted as planned in Section 12.8.2 DSMB Review.

13.5.3 Futility Analysis

No early stopping for futility is planned for this study.

13.6 Statistical Hypotheses

The set of null hypotheses are that the true probability of a protective antibody response, π, is ≤ 0.25 in a given subpopulation, representing an inadequate improvement in anti-COVID-19 Antibody Response after administration of

an additional vaccine dose to warrant further investigation in that subpopulation. This will be tested within each arm indexed by cohort and age group (i), additional vaccine dose (j), and IS treatment plan (k)

$$H_{0,(i,j,k)}: \pi_{(i,j,k)} \leq 0.25$$

The set of alternative hypotheses are that the true vaccine response rate, π, is >0.25 and may warrant further investigation in that subpopulation

$$H_{1,(i,j,k)}: \pi_{(i,j,k)} > 0.25$$

13.7 Sample Size Considerations

Early reports show that a significant number of individuals taking IS medications respond poorly or not at all to COVID-19 vaccination. Ruddy et al. reported 26% of chronic inflammatory rheumatic disease patients had undetectable SARS-CoV-2 antibody response after their first mRNA vaccine dose, but many seroconverted with the second dose such that only 6% had persistent undetectable SARS-CoV-2 RBD antibodies [16]. However, those taking MMF or rituximab were at much higher risk of not mounting a detectable antibody response (89% and 67%, respectively)[17]. Another report has demonstrated diminished overall serologic response in adults with chronic inflammatory diseases, particularly in those treated with B-cell depletion or antimetabolites including MTX, with a 50-fold and 3-fold reduction in post-vaccine antibody titers relative to immunocompetent controls[80].

Based on the emerging evidence in individuals taking IS medications, an ineffective rate of achieving a protective immune response after the additional vaccine dose was defined to be less than or equal to 0.25 (null hypothesis). The study is powered to reject the null hypothesis in each arm when the true response rate is 0.5 or greater as preliminary evidence the additional vaccine dose is effective in specific study population.

The proportion of participants in each arm (cohort, additional vaccine dose, and IS treatment plan group) to receive an additional vaccine dose and achieve a protective antibody response at Week 4 will be evaluated using a one-sided exact test with alpha = 0.05 to test against a null hypothesis that the true response rate is ≤0.25. A sample size of 33 evaluable participants achieves at least 90% power to reject null hypothesis when the true response rate is 0.5 or greater.

Secondary analyses will compare the rate of achieving a protective immune response across arms using the multivariable logistic regression model. For comparisons of single arms, 33 evaluable participants per arm will provide 80% power to detect an odds ratio of 4.2 when the null hypothesis is true in one arm (improvement from 0.25 to 0.584). For comparisons that combine arms, pooling 3 arms (e.g., type of additional vaccine dose) will provide 80% power to detect an odds ratio of 2.3 (improvement to 0.394).

In order to account for up to 20% dropout within a given arm of participants missing Week 4 anti-COVID-19 antibody response data without a documented COVID infection, 40 participants within each subgroup defined by the Roche Elecsys® Anti-SARS-CoV-2 S assay. In each arm, the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results ≤200 U/mL will be capped at 40 participants, and the number of participants with Roche Elecsys® Anti-SARS-CoV-2 S results >200 U/mL and ≤2500 U/mL will be capped at 40 participants.

An adaptive design will be employed such that cohorts may be added or modified in light of emerging evidence on autoimmune disease vaccination or of the development and authorization of COVID-19 vaccines.

14. Identification and Access to Source Data

14.1 Source Data

Source documents and source data are considered to be the original documentation where participant information, visit consultations, examinations, and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

The investigator should retain all documentation relating to the study (including but not limited to informed consent forms, source documentation, study vaccine records, eCRFs, and essential documents) for a period of at least 2 years

after the last marketing application approval or, if no application will be filed or if the application is not approved, 2 years following the discontinuation of the investigation.

If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

At study closure, the investigator must inform DAIT/NIAID, or the SACCC as designee, of the long-term storage location of the study's records and must inform DAIT/NIAID if that location changes subsequently.

No study records should be destroyed without prior authorization from DAIT/NIAID.

14.2 Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID and authorized representatives of DAIT/NIAID, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15. Quality Assurance and Quality Control

The principal investigator (PI) is required to keep accurate records to ensure that the conduct of the study is fully documented. The PI is required to ensure that all eCRFs are completed for every participant entered in the trial. The period of record retention should be consistent with the record retention policies of the sponsoring agency or applicable regulatory agencies. However, in certain instances, documents should be retained for a longer period if required by the applicable regulatory agency or by the NIH.

Data will be obtained from a variety of sources including, but not limited to laboratory notebooks, automated instrument output files, and clinical participant charts. Data from these source materials will be transmitted to the SACCC via one of two mechanisms. Data collected electronically at central laboratories will be transferred electronically directly from the laboratory to the SACCC using standard secure data transfer procedures. Data collected at the clinical sites will be transmitted to the SACCC using an internet-based remote data entry system. Clinical site personnel use an internet browser to key data into eCRFs; each eCRF page is submitted to the clinical database electronically as the page is completed. Univariate data validation tests are performed as the data are keyed. The clinical database is backed up nightly; backup tapes are saved in a secure, off-site location. At any time, authorized site personnel may log in to the remote data entry system, review and correct previously entered data, or key additional data. The data will be further validated per the study data validation plan via a series of computerized and manual edit checks, and all relevant data queries will be raised and resolved on an ongoing basis. Complete, clean data will be frozen to prevent further inadvertent modifications. All discrepancies will be reviewed and any resulting queries will be resolved with the investigators and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

The SACCC is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

The SACCC will periodically visit the participating clinical sites and audit the source documents in order to validate the data in the SACCC central database. If on-site visits are not permitted at a site due to COVID-19 restrictions, source document review and other visit activities will be conducted remotely. Data will be provided using the participant's identification number, the SACCC will not collect personally identifying information such as the participant's name or social security number. Participants will provide demographic information such as race, ethnicity, and birth date.

Data collected by the SACCC will be held in the strictest confidence, and are protected from access that could reveal personally identifying information about any participant in the trial.

16. Protocol Deviations

16.1 Protocol Deviation Definitions

Protocol Deviation – Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. Protocol deviations occur for a variety of reasons, such as an investigator's intentional or unintentional departure from the protocol, the participant's lack of adherence to the protocol, or external/environmental factors (e.g., severe weather or holidays) that change the performance of a protocol. Some protocol deviations are anticipated and/or intentional; others are not. Some protocol deviations are known or identified before they occur; others are only discovered to have occurred after the fact. The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted or approved beforehand by the study Sponsor.

Major Protocol Deviation (Protocol Violation) – A Protocol Violation is a deviation from the IRB-approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol deviations include willful or knowing breaches of HSP regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation – A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

16.2 Reporting and Managing Protocol Deviations

The study site PI has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

When a deviation occurs, corrective actions may be necessary depending on the nature of the deviation. Risk assessment must occur by the PI and study Sponsor. The PI should ensure a procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study. The depth of Corrective Action/Preventive Action (CAPA) required should match the risk and impact on safety of participants and/or the quality of the data.

Upon determination that a protocol deviation has occurred, the PI/designated study staff will report the deviation according to the processes outlined for the study. A major deviation is to be reported within **3 business days** and reported by the PI to the IRB per IRB reporting requirements. The study Sponsor will determine reportability of the deviation to the DSMB and FDA as applicable.

17. Ethical Considerations and Compliance with Good Clinical Practice

17.1 Statement of Compliance

This clinical study will be conducted using GCP, as delineated in *FDA Guidance for Industry: E6R2 Good Clinical Practice: Integrated Addendum to ICH E6(R1)*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an Institutional Review Board. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

17.2 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The PI or designee listed on the FDA 1572 will review the consent and/or assent and answer questions. The prospective participant and if applicable, the participant's guardian will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (and/or their legal guardian) will read, sign, and date a consent and/or assent form before undergoing any

study procedures. Consent/assent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant. The consent/assent process will be documented in the research or medical records.

A separate assent form will be utilized to obtain assent from children 7-13 years of age, and participants 14 years of age and older will sign on the assent line on the main consent form. Consent will be obtained from participants who reach legal age of consent per state laws during participation in the trial.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

17.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers to the study sponsor or their representatives.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study Monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

18. Publication Policy

The ACE Publication Policy will apply to publication of study results. Authorized study personnel may find details regarding the policy on the ACE study portal. Site investigators are encouraged to communicate and publish study results with prior notification of and review by DAIT/NIAID.

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20. Appendices

20.1 Schedules of Events

Table 17. Schedule of Events for Adult Stage 1

Visit Number	PRESCRN	SCRN	Randomization	Week 0	Week 1	Week 4	Week 12	Week 24	Week 36	EOS	ET	UNS
Description	Pre-Screening	Screening	Randomization Phone Visit	Baseline	Vaccine Diary Review Phone Visit	Week 4	Week 12	Week 24	Week 36	Week 48	Early Termination	Unscheduled
Visit Window		-21 Days	At least 7 days prior to Vaccination	Week 0/Day 1	Day 8 – Day 12	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Clinical Blood Draw (mL)	**0**	**31**	**0**	**21**	**0**	**21**	**21**	**21**	**21**	**21**	**21**	**21**
Research Blood Draw (mL)	**0**		**0**	**61**	**0**	**55**	**55**	**55**	**55**	**55**	**55**	**55**
Visit Draw Total (mL)	**0**	**31**	**0**	**82**	**0**	**76**	**76**	**76**	**76**	**76**	**76**	**76**
General Assessments												
Pre-Screening Informed Consent[A]	X											
Informed Consent		X										
Demographics		X										
Medical History		X	X	X								
Concomitant Medications (including contraceptives)		X	X	X		X	X	X	X	X	X	X
Comprehensive Physical Exam[B]		X										
Targeted Physical Exam[C]				X		X	X	X	X	X	X	X
Neurological Exam[D]				X		X	X	X	X	X	X	X
Vital Signs		X[E]		X		X	X	X	X	X	X	X
Adverse Event Assessment					X[F,G]	X[F,G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]
Review of initial COVID-19 vaccination record and antibody response		X[H]										
Inclusion/Exclusion Criteria assessment		X	X									
Randomization/Allocation			X[I]									
Immunosuppressive Medication Call: MTX			X[J]		X[J]							
Immunosuppressive Medication Call: MMF/MPA			X[K]		X[K]							
Vaccine Reaction Diary[L]				X	X							
Disease-Specific Assessments												
SLE												
Confirmation of 2019 ACR/EULAR or 2012 SLICC classification criteria for SLE		X										
H-SLEDAI		X[M]		X[N]		X	X	X	X	X	X	X[U]
Thanou modified SELENA-SLEDAI Flare Index				X		X	X	X	X	X	X	X[U]
RA												
Confirmation of 2010 ACR/EULAR classification criteria for RA		X										
Tender/Swollen Joint Count		X[M]		X[N]		X	X	X	X	X	X	X[U]
SSc												
Confirmation of 2013 EULAR/ACR classification criteria for SSc		X										

Visit Number	PRESCRN	SCRN	Randomization	Week 0	Week 1	Week 4	Week 12	Week 24	Week 36	EOS	ET	UNS
Description	Pre-Screening	Screening	Randomization Phone Visit	Baseline	Vaccine Diary Review Phone Visit	Week 4	Week 12	Week 24	Week 36	Week 48	Early Termination	Unscheduled
Visit Window		-21 Days	At least 7 days prior to Vaccination	Week 0/Day 1	Day 8 – Day 12	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Patient self-reported disease flare for SSc		X		X		X	X	X	X	X	X	X[U]
Modified Rodnan Skin Score		X		X		X	X	X	X	X	X	X[U]
MS												
Confirmation of 2017 McDonald diagnostic criteria for MS		X										
Physician-assessed relapse for MS		X				X	X	X	X	X	X	X[U]
EDSS				X		X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]
Pemphigus												
Confirmation of International consensus criteria for pemphigus		X										
PDAI		X		X[N]		X	X	X	X	X	X	X[U]
Flare Assessment for pemphigus				X		X	X	X	X	X	X	X[U]
Participant & Clinician Reported Outcomes												
PROMIS-29				X		X	X	X	X	X	X	X
PtGA		X[M]		X		X	X	X	X	X	X	X
PGIC						X	X	X	X	X	X	X
PGA		X[M]		X		X	X	X	X	X	X	X
CGI-C						X	X	X	X	X	X	X
Local Laboratory Assessments												
Pre-Screening Rapid Result/Antibody Test - OPTIONAL	X[A]											
Urine Pregnancy[P]		X		X								
Molecular COVID-19 Testing		X		X								
Central Laboratory Assessments												
Elecsys® Anti-SARS-CoV-2 S	X[A]	X[H]				X	X	X	X	X	X	X
Hematology (CBC with differential)		X		X		X	X	X	X	X	X	X
Blood Chemistry (CMP, eGFR)		X		X		X	X	X	X	X	X	X
Infectious Disease												
HIV Testing		X										
Hepatitis B Surface Antigen		X										
Hepatitis C antibody (with viral load if indicated)		X										
RA												
CRP		X		X		X	X	X	X	X	X	X[U]
SLE												
Anti-dsDNA, C3, C4		X		X		X	X	X	X	X	X	X[U]
Random urine protein-creatinine ratio		X		X		X	X	X	X	X	X	X[U]
Urinalysis (microscopic)		X		X		X	X	X	X	X	X	X[U]
Cohort C: B-cell depleting therapy												
CD19+ B cells[Q]		X		X		X	X	X	X	X	X	X[U]
Pemphigus												
Anti-desmoglein 1/3 IgG autoantibodies by ELISA		X		X		X	X	X	X	X	X	X[U]

Visit Number	PRESCRN	SCRN	Randomization	Week 0	Week 1	Week 4	Week 12	Week 24	Week 36	EOS	ET	UNS
Description	Pre-Screening	Screening	Randomization Phone Visit	Baseline	Vaccine Diary Review Phone Visit	Week 4	Week 12	Week 24	Week 36	Week 48	Early Termination	Unscheduled
Visit Window		-21 Days	At least 7 days prior to Vaccination	Week 0/Day 1	Day 8 – Day 12	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Mechanistic Assessments												
Serum[R]				X[S]		X	X	X	X	X	X	X
Whole Blood/PBMC/Plasma/DNA				X		X	X	X	X	X	X	X
RNA Assays				X		X	X	X	X	X	X	X
Background Immunosuppressive Medication Testing (MTX, MPA)				X								
Study Treatment / Investigational Agent												
Additional homologous vaccine dose eligibility confirmation				X[T]								
~~Moderna COVID-19 Vaccine~~				X[T]								
~~Pfizer-BioNTech COVID-19 Vaccine~~				X[T]								
~~Janssen COVID-19 Vaccine~~				X[T]								

[A]If a site is conducting optional pre-screening rapid result/antibody testing; the site will review the pre-screening consent with the participant and obtain his/her signature prior to conducting any pre-screening activities. Pre-screening is optional for all participants. The site may send an Elecsys® Anti-SARS-CoV-2 S (RBD) sample to the central lab as one of 3 potential pre-screening tests, as outlined in the ACV01 lab manual.

[B]Comprehensive physical exams include the following systems (at a minimum): general appearance, skin, head/eyes/ears/nose/neck/throat, respiratory/chest, cardiovascular, abdominal, neurological, & musculoskeletal/extremities.

[C]Targeted physical exams will be guided by participant complaints and prior abnormalities.

[D]Neurological Exam will be conducted for all MS participants and for participants with other diagnoses who have a neurological complaint after Screening and Randomization/Allocation.

[E]Height will be collected at Screening only. Weight, temperature, pulse, and blood pressure will be collected at each visit.

[F]Solicited AEs will be collected for 7 days post study vaccination. Unsolicited AEs will be collected until 28 days post study vaccination.

[G]SAEs, MAAEs, NOCMCs, AESIs, COVID-19 diagnoses, and flares of a secondary autoimmune disease will be collected from Day 1 through the end of the participant's study participation.

[H]Eligibility confirmed by CDC card or documentation in medical records and results of response to initial COVID-19 vaccine regimen assessed by Elecsys® Anti-SARS-CoV-2 S assay.

[I]Randomization for Cohorts A and B must occur within 21 days of Screening and at least 7 days prior to Week 0/Day 1. During the randomization visit, sites will call participants to confirm medical history and concomitant medication data still meet eligibility criteria. Participants in Cohort C will not be randomized. These participants must have study eligibility confirmed and have the Baseline/Week 0 visit occur within 28 days of Screening. Unsolicited AEs that are Grade 3 or higher will be collected for all Cohorts between Randomization/Allocation and vaccine administration.

[J]Participants in Cohort B (MTX) randomized to the withhold IS treatment plan will withhold their MTX for at least 7 days prior to and at least 7 days after receipt of an additional homologous vaccine dose at Baseline (not to exceed 21 days holding MTX). The site will call the participant prior to Baseline to remind the participant to withhold his/her MTX and after Baseline to remind the participant to restart his/her MTX.

[K]Participants in Cohort A (MMF/MPA) randomized to the withhold IS treatment plan will withhold their MMF/MPA for 3 days prior to and 10 days after receipt of an additional homologous vaccine dose at Baseline. The site will call the participant prior to Baseline to remind the participant to withhold his/her MMF/MPA and after Baseline to remind the participant to restart his/her MMF/MPA.

[L]The vaccine diary will be completed for 7 days after the additional homologous vaccine dose.

[M]The H-SLEDAI and PGA will be collected at Screening for all SLE participants to assess disease activity. The Tender/Swollen Joint Count and PtGA will be collected at Screening for all RA participants to assess disease activity using DAS28-CRP.

[N]If the Baseline/Week 0 visit occurs less than 10 days from the Screening visit, the following disease activity assessments do not need to be repeated: H-SLEDAI, DAS28-CRP, and PDAI.

[O]The EDSS will be collected whenever a MS relapse is suspected, and if applicable, at the time of relapse recovery (to occur 8-12 weeks after the suspected relapse EDSS assessment).

[P]For women of childbearing potential, a stat urine HCG prior to vaccination will be performed locally with point of care testing.

[Q]If a participant is on a CD20 depleting agent, CD19+ B cells will be collected.

[R]Antibody levels will be tested at each time point to test for IgG and IgM responses against SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins.

[S]Cohort A (MMF/MPA) participants who are randomized to the Continue IS treatment arm will hold their morning dose of MMF/MPA until after the serum blood draw.

[T]All Week 0 assessments (including confirmation of additional homologous vaccine dose eligibility) must be completed prior to administration of the additional homologous vaccine dose. If the additional homologous vaccine dose cannot be administered at Baseline/Week 0, the additional homologous vaccine dose eligibility confirmation and administration of the additional homologous vaccine dose may occur 2-3 days after the Baseline/Week 0 visit. Administration of the additional homologous vaccine dose must occur within 28 days of the Screening visit.

[U]For unscheduled visits conducted for disease activity increases, all disease-specific assessments and corresponding clinical laboratories are to be performed. For unscheduled visits conducted for a reason other than a disease activity increases, participants should be evaluated per clinical judgement of the investigator.

Table 18. Schedule of Events for Adult Stage 2 Newly Recruited Participants

Visit Number	S2 PRESCRN	S2 SCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Pre-Screening	S2 Screening	S2 Baseline	S2 Vaccine Diary Review Phone Visit	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window		-21 Days; At least 7 days prior to Vaccination	Week 0/Day 1	Day 8 – Day 12	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Clinical Blood Draw (mL)	**0**	**31**	**21**	**0**	**21**	**21**	**21**	**21**	**21**	**21**	**21**
Research Blood Draw (mL)	**0**		**55**	**0**	**55**	**55**	**55**	**55**	**55**	**55**	**55**
Visit Draw Total (mL)	**0**	**31**	**76**	**0**	**76**	**76**	**76**	**76**	**76**	**76**	**76**
General Assessments											
Pre-Screening Informed Consent[A]	X										
Informed Consent		X									
Demographics		X									
Medical History		X	X								
Concomitant Medications (including contraceptives)		X	X		X	X	X	X	X	X	X
Comprehensive Physical Exam[B]		X									
Targeted Physical Exam[C]			X		X	X	X	X	X	X	X
Neurological Exam[D]			X		X	X	X	X	X	X	X
Vital Signs		X[E]	X		X	X	X	X	X	X	X
Adverse Event Assessment				X[F,G]	X[F,G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]
Review of COVID-19 vaccination record and antibody response		X[H]									
Inclusion/Exclusion Criteria assessment		X									
Immunosuppressive Medication Call: MTX		X[I]		X[I]							
Immunosuppressive Medication Call: MMF/MPA		X[J]		X[J]							
Vaccine Reaction Diary[K]			X	X							
Disease-specific Assessments											
SLE											
Confirmation of 2019 ACR/EULAR or 2012 SLICC classification criteria for SLE		X									
H-SLEDAI		X[L]	X[M]		X	X	X	X	X	X	X[T]
Thanou modified SELENA-SLEDAI Flare Index			X		X	X	X	X	X	X	X[T]
RA											
Confirmation of 2010 ACR/EULAR classification criteria for RA		X									
Tender/Swollen Joint Count		X[L]	X[M]		X	X	X	X	X	X	X[T]
SSc											
Confirmation of 2013 EULAR/ACR classification criteria for SSc		X									
Patient self-reported disease flare for SSc		X	X		X	X	X	X	X	X	X[T]
Modified Rodnan Skin Score		X	X		X	X	X	X	X	X	X[T]

Visit Number	S2 PRESCRN	S2 SCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Pre-Screening	S2 Screening	S2 Baseline	S2 Vaccine Diary Review Phone Visit	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window		-21 Days; At least 7 days prior to Vaccination	Week 0/Day 1	Day 8 – Day 12	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
MS											
Confirmation of 2017 McDonald diagnostic criteria for MS		X									
Physician-assessed relapse for MS		X			X	X	X	X	X	X	X[T]
EDSS			X		X[N]	X[N]	X[N]	X[N]	X[N]	X[N]	X[N]
Pemphigus											
Confirmation of International consensus criteria for pemphigus		X									
PDAI		X	X[M]		X	X	X	X	X	X	X[T]
Flare Assessment for pemphigus			X		X	X	X	X	X	X	X[T]
Participant- and Clinician-reported Outcomes											
PROMIS-29			X		X	X	X	X	X	X	X
PtGA		X[L]	X		X	X	X	X	X	X	X
PGIC					X	X	X	X	X	X	X
PGA		X[L]	X		X	X	X	X	X	X	X
CGI-C					X	X	X	X	X	X	X
Local Laboratory Assessments											
Pre-Screening Rapid Result/Antibody Test - OPTIONAL	X[A]										
Urine Pregnancy[O]		X	X								
Molecular COVID-19 Testing		X	X								
Central Laboratory Assessments											
Elecsys® Anti-SARS-CoV-2 S (RBD)	X[A]	X[H]			X	X	X	X	X	X	X
Hematology (CBC with differential)		X	X		X	X	X	X	X	X	X
Blood Chemistry (CMP, eGFR)		X	X		X	X	X	X	X	X	X
Infectious Disease											
HIV Testing		X									
Hepatitis B Surface Antigen		X									
Hepatitis C antibody (with viral load if indicated)		X									
RA											
CRP		X	X		X	X	X	X	X	X	X[T]
SLE											
Anti-dsDNA, C3, C4		X	X		X	X	X	X	X	X	X[T]
Random urine protein-creatinine ratio		X	X		X	X	X	X	X	X	X[T]
Urinalysis (microscopic)		X	X		X	X	X	X	X	X	X[T]
Cohort C: B-cell depleting therapy											
CD19+ B cells[P]		X	X		X	X	X	X	X	X	X[T]
Pemphigus											
Anti-desmoglein 1/3 IgG autoantibodies by ELISA		X	X		X	X	X	X	X	X	X[U]

Visit Number	S2 PRESCRN	S2 SCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Pre-Screening	S2 Screening	S2 Baseline	S2 Vaccine Diary Review Phone Visit	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window		-21 Days; At least 7 days prior to Vaccination	Week 0/Day 1	Day 8 – Day 12	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Mechanistic Assessments											
Serum[Q]			X		X	X	X	X	X	X	X
Whole Blood/PBMC/Plasma/DNA			X		X	X	X	X	X	X	X
RNA Assays			X		X	X	X	X	X	X	X
Background Immunosuppressive Medication Testing (MTX, MPA)			X								
Study Treatment / Investigational Agent											
Alternative vaccine dose eligibility confirmation			X[R]								
Determine alternative COVID-19 vaccine		X									
mRNA COVID-19 vaccine[S]			X[R]								
Sanofi-GSK COVID-19 vaccine			X[R]								

[A]If a site is conducting optional pre-screening rapid result/antibody testing, the site will review the pre-screening consent with the participant and obtain his/her signature prior to conducting any pre-screening activities. Pre-screening is optional for all participants. The site may send an Elecsys® Anti-SARS-CoV-2 S (RBD) sample to the central lab as one of 3 potential pre-screening tests, as outlined in the ACV01 lab manual.

[B]Comprehensive physical exams include the following systems (at a minimum): general appearance, skin, head/eyes/ears/nose/neck/throat, respiratory/chest, cardiovascular, abdominal, neurological, & musculoskeletal/extremities.

[C]Targeted physical exams will be guided by participant complaints and prior abnormalities.

[D]Neurological Exam: for all MS participants and for participants with other diagnoses who have a neurological complaint after Stage 2 Screening.

[E]Height will be collected at Stage 2 Screening only. Weight, temperature, pulse, and blood pressure will be collected at each visit.

[F]Solicited AEs will be collected for 7 days post study vaccination. Unsolicited AEs will be collected until 28 days post study vaccination.

[G]SAEs, MAAEs, NOCMCs, AESIs, COVID-19 diagnoses, and flares of a secondary autoimmune disease will be collected from Day 1 through the end of the participant's study participation.

[H]Eligibility confirmed by CDC card or documentation in medical records and results of response to a previous COVID-19 vaccine dose assessed by Elecsys® Anti-SARS-CoV-2 S (RBD) assay.

[I]Participants in Cohort E (MTX) and participants in Cohort F (BCDT) who are also taking MTX will withhold their immunosuppressive medication for at least 7 days prior to and at least 7 days after receipt of the alternative vaccine dose at Stage 2 Baseline (not to exceed 21 days withholding of MTX). If necessary, the site will call the participant between Stage 2 Screening and Stage 2 Baseline to remind the participant to withhold his/her MTX. The site will call the participant after Stage 2 Baseline to remind the participant to restart his/her MTX.

[J]Participants in Cohort D (MMF/MPA) and participants in Cohort F (BCDT) who are also taking MMF/MPA will withhold their immunosuppressive medication for 3 days prior to and 10 days after receipt of the alternative vaccine dose at Stage 2 Baseline. If necessary, the site will call the participant between Stage 2 Screening and Stage 2 Baseline to remind the participant to withhold his/her MMF/MPA. The site will call the participant after Stage 2 Baseline to remind the participant to restart his/her MMF/MPA.

[K]The vaccine diary will be completed for 7 days after the alternative vaccine dose.

[L]The H-SLEDAI and PGA will be collected at Stage 2 Screening for all SLE participants to assess disease activity. The Tender/Swollen Joint Count and PtGA at Stage 2 Screening will be collected for all RA participants to assess disease activity using DAS28-CRP.

[M]If the Stage 2 Baseline/Stage 2 Week 0 visit occurs less than 10 days from the Screening visit, the following disease activity assessments do not need to be repeated: H-SLEDAI, DAS28-CRP, and PDAI.

[N]The EDSS will be collected whenever a MS relapse is suspected, and if applicable, at the time of relapse recovery (to occur 8-12 weeks after the suspected relapse EDSS assessment).

[O]For women of childbearing potential. Stat urine HCG prior to vaccination may be performed locally with point of care testing.

[P]If a participant is on a CD20 depleting agent, CD19+ B cells will be collected.

[Q]Antibody levels will be tested at each time point to test for IgG and IgM responses against SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins.

[R]All Stage 2 Week 0 assessments (including confirmation of additional vaccine dose eligibility) must be completed prior to administration of the alternative vaccine dose. If the alternative vaccine dose cannot be administered at Stage 2 Baseline/Stage 2 Week 0, the alternative vaccine dose eligibility confirmation and administration of the alternative vaccine dose may occur 2-3 days after the Stage 2 Baseline/Stage 2 Week 0 visit. Administration of the alternative vaccine dose must occur within 28 days of the Stage 2 Screening visit.

[S]Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine.

[T]For unscheduled visits conducted for disease activity increases, all disease-specific assessments and corresponding clinical laboratories are to be performed. For unscheduled visits conducted for a reason other than a disease activity increases, participants should be evaluated per clinical judgement of the investigator.

Table 19. Schedule of Events for Adult Stage 2 Rollover Participants

Visit Number	S2 PHNSCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Screening Phone Visit[A]	S2 Baseline	S2 Vaccine Diary Review Phone Visit	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window	-21 days; At least 7 days prior to Vaccination[A]	Week 0/Day 1*	Day 8 – Day 12	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Clinical Blood Draw (mL)	**0**	**16**	**0**	**12**	**10**	**10**	**10**	**10**	**10**	**10**
Research Blood Draw (mL)	**0**	**56**	**0**	**56**	**56**	**56**	**56**	**56**	**56**	**56**
Visit Draw Total (mL)	**0**	**72**	**0**	**68**	**66**	**66**	**66**	**66**	**66**	**66**
General Assessments										
Verbal agreement to roll over to Stage 2[B]	X									
Medical History	X	X								
Concomitant Medications (including contraceptives)	X	X		X	X	X	X	X	X	X
Targeted Physical Exam[C]	X[D]	X		X	X	X	X	X	X	X
Neurological Exam[E]	X[D]	X		X	X	X	X	X	X	X
Vital Signs	X[D]	X[F]		X	X	X	X	X	X	X
Adverse Event Assessment	X[G]	X[G]	X[G,H]	X[G,H]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]
Inclusion/Exclusion Criteria assessment	X									
Immunosuppressive Medication Instructions	X[I, J]		X[I,J]							
Vaccine Reaction Diary[K]		X	X							
Disease-specific Assessments										
SLE										
H-SLEDAI	X[D, L]	X		X	X	X	X	X	X	X[T]
Thanou modified SELENA-SLEDAI Flare Index		X		X	X	X	X	X	X	X[T]
RA										
Tender/Swollen Joint Count	X[D,L]	X		X	X	X	X	X	X	X[T]
SSc										
Patient self-reported disease flare for SSc	X[D]	X		X	X	X	X	X	X	X[T]
Modified Rodnan Skin Score	X[D]	X		X	X	X	X	X	X	X[T]
MS										
Physician-assessed relapse for MS	X[D]			X	X	X	X	X	X	X[T]
EDSS		X		X[M]	X[M]	X[M]	X[M]	X[M]	X[M]	X[M]
Pemphigus										
PDAI	X[D]	X		X	X	X	X	X	X	X[T]
Flare Assessment for pemphigus		X		X	X	X	X	X	X	X[T]
Participant- & Clinician-reported Outcomes										
PROMIS-29		X		X	X	X	X	X	X	X
PtGA	X[L]	X		X	X	X	X	X	X	X
PGIC				X	X	X	X	X	X	X
PGA	X[L]	X		X	X	X	X	X	X	X
CGI-C				X	X	X	X	X	X	X

Visit Number	S2 PHNSCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Screening Phone Visit[A]	S2 Baseline	S2 Vaccine Diary Review Phone Visit	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window	-21 days; At least 7 days prior to Vaccination[A]	Week 0/Day 1*	Day 8 – Day 12	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Local Laboratory Assessments										
Urine Pregnancy[N]	X[O]	X								
Molecular COVID-19 Testing	X[O]	X								
Central Laboratory Assessments										
Elecsys® Anti-SARS-CoV-2 S (RBD)	X[D]			X	X	X	X	X	X	X
Hematology (CBC with differential)	X[D]	X		X	X	X	X	X	X	X
Blood Chemistry (CMP, eGFR)	X[D]	X		X	X	X	X	X	X	X
RA										
CRP	X[D]	X		X	X	X	X	X	X	X[T]
SLE										
Anti-dsDNA, C3, C4	X[D]	X		X	X	X	X	X	X	X[T]
Random urine protein-creatinine ratio	X[D]	X		X	X	X	X	X	X	X[T]
Urinalysis (microscopic)	X[D]	X		X	X	X	X	X	X	X
Cohort C: B-cell depleting therapy										
CD19+ B cells[P]	X[D]	X		X	X	X	X	X	X	X[T]
Pemphigus										
Anti-desmoglein 1/3 IgG autoantibodies by ELISA	X[D]	X		X	X	X	X	X	X	X[T]
Mechanistic Assessments										
Serum[Q]		X		X	X	X	X	X	X	X
Whole Blood/PBMC/Plasma/DNA		X		X	X	X	X	X	X	X
RNA Assays		X		X	X	X	X	X	X	X
Background Immunosuppressive Medication Testing (MTX, MPA)		X								
Study Treatment / Investigational Agent										
Alternative vaccine dose eligibility confirmation		X[R]								
Determine alternative COVID-19 vaccine	X									
mRNA COVID-19 vaccine[S]		X[R]								
Sanofi COVID-19 vaccine		X[R]								

[A]When possible, screening for rollover subjects will utilize information collected at the participant's most recent Stage 1 or Stage 2 follow-up visit. If the last Stage 1 or Stage 2 follow-up visit was within the previous 21 days, Screening may occur remotely via review of the data from the previous visit and a phone call with the participant to confirm rollover to (or restarting of) Stage 2. If the needed data are not available from the previous Stage 1 or Stage 2 visit or 28 days will have passed when the S2 Baseline Week 0 visit is reached, then this visit must be conducted at the clinical site.

[B]The site will review the Stage 2 procedures and the previously signed informed consent document with the participant and record formal participant agreement to (re-)enter Stage 2.

[C]Targeted physical exams will be guided by participant complaints and prior abnormalities.

[D]Remote screening of these parameters will utilize information collected at the participant's most recent Stage 1 or Stage 2 follow-up visit. If these data are not available from a previous visit conducted within the past 21 days, then new information for these parameters must be collected during an in-person visit to the clinical site. For rollover participants, the comprehensive physical exam is replaced by the targeted physical and neurological exams at the previous Stage 1 or Stage 2 visit.

[E]Neurological Exam: for all MS participants and for participants with other diagnoses who have a neurological complaint after Screening and enrollment.

[F]For rollover participants, height will be collected at Screening for Stage 1 only. Weight, temperature, pulse, and blood pressure will be collected at each visit.

[G]SAEs, MAAEs, NOCMCs, AESIs, COVID-19 diagnoses, and flares of a secondary autoimmune disease will be collected from Day 1 through the end of the participant's study participation.

[H]Solicited AEs will be collected for 7 days post study vaccination. Unsolicited AEs will be collected until 28 days post study vaccination.

[I]Participants in Cohort E (MTX) and participants in Cohort F (BCDT) who are also taking MTX will withhold their IS medication for at least 7 days prior to and at least 7 days after receipt of the alterative vaccine dose at Stage 2 Baseline Week 0 (not to exceed 21 days withholding of MTX). If necessary, the site will call the participant between Stage 2 Screening and Stage 2 Baseline Week 0 to remind the participant to withhold his/her MTX. The site will call the participant after Stage 2 Baseline Week 0 to remind the participant to restart his/her MTX.

[J]Participants in Cohort D (MMF/MPA) and participants in Cohort F (BCDT) who are also taking MMF/MPA will withhold their IS medication for 3 days prior to and 10 days after receipt of the alternative vaccine dose at Stage 2 Baseline Week 0. If necessary, the site will call the participant between Stage 2 Screening and Stage 2 Baseline Week 0 to remind the participant to withhold his/her MMF/MPA. The site will call the participant after S2 Baseline Week 0 to remind the participant to restart his/her MMF/MPA.

[K]The vaccine diary will be completed for 7 days after the alternative vaccine dose.

[L]The H-SLEDAI and PGA will be collected at Stage 2 Screening for all SLE participants to assess disease activity. The Tender/Swollen Joint Count and PtGA at Stage 2 Screening will be collected for all RA participants to assess disease activity using DAS28-CRP.

[M]The EDSS will be collected whenever a MS relapse is suspected, and if applicable, at the time of relapse recovery (to occur 8-12 weeks after the suspected relapse EDSS assessment).

[N] For women of childbearing potential. Stat urine HCG prior to vaccination may be performed locally with point of care testing.

[O]If the S2 Screening visit occurs onsite, the molecular COVID-19 test and urine pregnancy test will be conducted. If Stage 1 or Stage 2 visit data is being used to assess Stage 2 eligibility and screening, the molecular COVID-19 test and urine pregnancy tests will be conducted at the S2 Baseline visit only.

[P]If a participant is on a CD20 depleting agent, CD19+ B cells will be collected.

[Q]Antibody levels will be tested at each time point to test for IgG and IgM responses against SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins.

[R]All Stage 2 Baseline Week 0 assessments (including confirmation of alternative vaccine dose eligibility) must be completed prior to administration of the alternative vaccine dose. If the alternative vaccine dose cannot be administered at Stage 2 Baseline Week 0, the alternative vaccine dose eligibility confirmation and administration of the alternative vaccine dose may occur 2-3 days after the Stage 2 Baseline Week 0 visit. Administration of the alternative vaccine dose must occur within 28 days of when the data used for screening were obtained.

[S]Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine.

[T]For unscheduled visits conducted for disease activity increases, all disease-specific assessments and corresponding clinical laboratories are to be performed. For unscheduled visits conducted for a reason other than a disease activity increases, participants should be evaluated per clinical judgement of the investigator.

Table 20. Schedule of Events for Pediatric Stage 1

Visit Number	PRESCRN	SCRN	Randomization	Week 0	Week 1	Week 4	Week 12	Week 24	Week 36	EOS	ET	UNS
Description	Pre-Screening	Screening	Randomization Phone Visit	Baseline	Vaccine Diary Review Visit[A]	Week 4	Week 12	Week 24	Week 36	Week 48	Early Termination	Unscheduled
Visit Window		-21 Days	At least 7 days prior to Vaccination	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Pediatric Participant Blood Draw Limits	**No more than 5mL/kg may be drawn for research purposes in a single day, and no more than 9.5mL/kg may be drawn over any 8-week period. Pediatric blood draw details and prioritization are listed in the ACV01 lab manual.**											
General Assessments												
Pre-Screening Informed Consent[B]	X											
Informed Consent/Assent		X										
Demographics		X										
Medical History		X	X	X								
Concomitant Medications (including contraceptives)		X	X	X	X	X	X	X	X	X	X	X
Comprehensive Physical Exam[C]		X										
Targeted Physical Exam[D]				X		X	X	X	X	X	X	X
Neurological Exam[E]				X		X	X	X	X	X	X	X
Vital Signs[F]		X		X		X	X	X	X	X	X	X
Adverse Event Assessment					X[G, H]	X[G, H]	X[H]	X[H]	X[H]	X[H]	X[H]	X[H]
Review of initial COVID-19 vaccination record and antibody response		X[I]										
Inclusion/Exclusion criteria assessment		X	X									
Randomization			X[J]									
Immunosuppressive Medication Call: MTX			X[K]		X[K]							
Immunosuppressive Medication Call: MMF/MPA			X[L]		X[L]							
Pediatric Vaccine Reaction Diary[M]				X	X							
Disease-Specific Assessments												
SLE												
Confirmation of 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups		X										
SLEDAI-2K		X[N]		X[O]		X	X	X	X	X	X	X[X]
ACR Provisional Criteria for Global Flare in Childhood-onset SLE				X		X	X	X	X	X	X	X
JIA												
Confirmation of ILAR classification for JIA		X										
Tender/Swollen Joint Count		X[N]		X[O]		X	X	X	X	X	X	X[X]
PASI[P]				X		X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]
JDM												
Confirmation of Peter criteria or the 2017 EULAR/ACR classification criteria for JDM		X										
Flare Assessment for JDM (Disease Activity Score [DAS])		X		X		X	X	X	X	X	X	X[X]
CMAS[Y]		X		X[O]		X	X	X	X	X	X	X[X]
POMS												
Confirmation of 2017 McDonald diagnostic criteria for MS		X										

Visit Number	PRESCRN	SCRN	Randomization	Week 0	Week 1	Week 4	Week 12	Week 24	Week 36	EOS	ET	UNS
Description	Pre-Screening	Screening	Randomization Phone Visit	Baseline	Vaccine Diary Review Visit[A]	Week 4	Week 12	Week 24	Week 36	Week 48	Early Termination	Unscheduled
Visit Window		-21 Days	At least 7 days prior to Vaccination	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Physician-assessed relapse for MS		X		X[O]		X	X	X	X	X	X	X[X]
EDSS				X		X[R]	X[R]	X[R]	X[R]	X[R]	X[R]	X[R]
Participant & Clinician Reported Outcomes												
PedsQL				X		X	X	X	X	X	X	X
PtGA		X[N]		X		X	X	X	X	X	X	X
PGI-C						X	X	X	X	X	X	X
PGA		X[N]		X		X	X	X	X	X	X	X
CGI-C						X	X	X	X	X	X	X
Local Laboratory Assessments												
Pre-Screening Rapid Result/Antibody Test - OPTIONAL	X[B]											
Urine Pregnancy[S]		X		X								
Molecular COVID-19 Testing		X		X								
ESR (pediatric SLE participants only)		X		X		X	X	X	X	X	X	X[X]
Central Laboratory Assessments												
Elecsys® Anti-SARS-CoV-2 S (RBD)	X[B]	X[I]				X	X	X	X	X	X	X
Hematology (CBC with differential)		X		X		X	X	X	X	X	X	X
Blood Chemistry (CMP, eGFR)		X		X		X	X	X	X	X	X	X
JIA												
CRP		X		X		X	X	X	X	X	X	X[X]
SLE												
Anti-dsDNA, C3, C4		X		X		X	X	X	X	X	X	X[X]
Random urine protein-creatinine ratio		X		X		X	X	X	X	X	X	X[X]
Urinalysis (microscopic)		X		X		X	X	X	X	X	X	X
Cohort C: B-cell depleting therapy												
CD19+ B cells[T]		X		X		X	X	X	X	X	X	X[X]
JDM												
Aldolase		X		X		X	X	X	X	X	X	X[X]
Mechanistic Assessments												
Serum[U]				X[V]	X[A]	X	X	X	X	X	X	X
Whole Blood/PBMC/Plasma				X	X[A]	X	X	X	X	X	X	X
RNA Assays				X	X[A]	X	X	X	X	X	X	X
Background Immunosuppressive Medication Testing (MTX, MPA)				X								
Study Treatment / Investigational Agent												
Additional homologous vaccine dose eligibility confirmation				X[W]								
Moderna COVID-19 vaccine				X[W]								
Pfizer-BioNTech COVID-19 vaccine				X[W]								

Visit Number	PRESCRN	SCRN	Randomization	Week 0	Week 1	Week 4	Week 12	Week 24	Week 36	EOS	ET	UNS
Description	Pre-Screening	Screening	Randomization Phone Visit	Baseline	Vaccine Diary Review Visit[A]	Week 4	Week 12	Week 24	Week 36	Week 48	Early Termination	Unscheduled
Visit Window		-21 Days	At least 7 days prior to Vaccination	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		

[A]If participants choose to participate in the optional mechanistic blood draw visit at Week 1, the visit will occur at the clinic and the vaccine reaction diary review (along with a review of concomitant medications) will occur in person. If the participant declines to participate in the optional mechanistic blood draw visit at Week 1, the vaccine reaction diary review will occur over the phone and no in person clinic visit is needed.
[B]If a site is conducting optional pre-screening rapid result/antibody testing; the site will review the pre-screening consent with the participant and obtain his/her signature prior to conducting any pre-screening activities. Pre-screening is optional for all participants. The site may send an Elecsys® Anti-SARS-CoV-2 S (RBD) sample to the central lab as one of 3 potential pre-screening tests, as outlined in the ACV01 lab manual.
[C]Comprehensive physical exams include the following systems (at a minimum): general appearance, skin, head/eyes/ears/nose/neck/throat, respiratory/chest, cardiovascular, abdominal, neurological, & musculoskeletal/extremities.
[D]Targeted physical exams will be guided by participant complaints and prior abnormalities.
[E]Neurological Exam: for all POMS participants and for participants with other diagnoses who have a neurological complaint after Screening and allocation/randomization.
[F]Weight, height, temperature, pulse, and blood pressure will be collected at each visit.
[G]Solicited AEs will be collected for 7 days post study vaccination. Unsolicited AEs will be collected until 28 days post study vaccination.
[H]SAEs, MAAEs, NOCMCs, AESIs, COVID-19 diagnoses, and flares of a secondary autoimmune disease will be collected from Day 1 through the end of the participant's study participation.
[I]Eligibility confirmed by CDC card or documentation in medical records and results of response to initial COVID-19 vaccine regimen assessed by Elecsys® Anti-SARS-CoV-2 S (RBD) assay.
[J]Randomization for Cohorts A and B must occur within 21 days of Screening and at least 7 days prior to Week 0/Day 1. During the randomization visit, sites will call participants to confirm medical history and concomitant medication data still meet eligibility criteria. Participants in Cohort C will not be randomized. These participants must have study eligibility confirmed and have the Baseline/Week 0 visit occur within 28 days of Screening.
[K]Participants in Cohort B (MTX) randomized to the withhold IS treatment plan will withhold their MTX for at least 7 days prior to and at least 7 days after receipt of vaccine booster at Baseline (not to exceed 21 days holding MTX). The site will call the participant prior to Baseline to remind the participant to withhold his/her MTX and after Baseline to remind the participant to restart his/her MTX.
[L]Participants in Cohort A (MMF/MPA) randomized to the withhold IS treatment plan will withhold their MMF/MPA for 3 days prior to and 10 days after receipt of vaccine booster at Baseline. The site will call the participant prior to Baseline to remind the participant to withhold his/her MMF/MPA and after Baseline to remind the participant to restart his/her MMF/MPA.
[M]The vaccine diary will be completed for 7 days after vaccine booster. If the participant consents to an optional mechanistic specimen collection at Week 1, the site will complete the review of the vaccine reaction diary prior to collecting specimens.
[N]The Tender/Swollen Joint Count, PGA, and PtGA at Screening will be collected for all JIA participants to assess disease activity using JADAS-10. The PGA and the SLEDAI-2K will be collected for pediatric SLE participants at screening for evaluation of the childhood-onset SLE criteria of global flare.
[O]If the Baseline/Week 0 visit occurs less than 10 days from the Screening visit, the following disease activity assessments do not need to be repeated: SLEDAI-2K, Tender/Swollen Joint count, CMAS, and physician-assessed relapse for MS.
[P]The PASI will only be assessed if a JIA participant has psoriatic arthritis.
[Q]The PASI will be assessed post-Baseline if a psoriatic arthritis flare is suspected.
[R]The EDSS will be collected whenever a POMS relapse is suspected, and if applicable, at the time of relapse recovery (to occur 8-12 weeks after the suspected relapse EDSS assessment).
[S]For postmenarchal females only. Stat urine HCG prior to vaccination may be performed locally with point of care testing.
[T]If a participant is on a CD20 depleting agent, CD19+ B cells will be collected.
[U]Antibody levels will be tested at each time point to test for IgG and IgM responses against SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins.
[V]Cohort A (MMF/MPA) participants who are randomized to the Continue IS treatment arm will hold their morning dose of MMF/MPA until after the serum blood draw.
[W]All Week 0 assessments (including confirmation of additional homologous vaccine dose eligibility) must be completed prior to administration of the additional homologous vaccine dose. If the additional homologous vaccine dose cannot be administered at Baseline/Week 0, the additional homologous vaccine dose eligibility confirmation and administration of the additional homologous vaccine dose may occur 2-3 days after the Baseline/Week 0 visit. Administration of the additional homologous vaccine dose must occur within 28 days of the Screening visit.
[X]For unscheduled visits conducted for disease activity increases, all disease-specific assessments and corresponding clinical laboratories are to be performed. For unscheduled visits conducted for a reason other than a disease activity increases, participants should be evaluated per clinical judgement of the investigator.
[Y]The CMAS is required for JDM participants 6-17 years of age. The CMAS is optional for JDM participants who are 2- 5 years of age.

Table 21. Schedule of Events for Pediatric Stage 2 Newly Recruited Participants

Visit Number	S2 PRESCRN	S2 SCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Pre-Screening	S2 Screening	S2 Baseline	S2 Vaccine Diary Review Phone Visit[A]	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window		-21 Days; At least 7 days prior to Vaccination	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Pediatric Participant Blood Draw Limits	**No more than 5mL/kg may be drawn for research purposes in a single day, and no more than 9.5mL/kg may be drawn over any 8-week period. Pediatric blood draw details and prioritization are listed in the ACV01 lab manual.**										
General Assessments											
Pre-Screening Informed Consent[B]	X										
Informed Consent/Assent		X									
Demographics		X									
Medical History		X	X								
Concomitant Medications (including contraceptives)		X	X	X	X	X	X	X	X	X	X
Comprehensive Physical Exam[C]		X									
Targeted Physical Exam[D]			X		X	X	X	X	X	X	X
Neurological Exam[E]			X		X	X	X	X	X	X	X
Vital Signs[F]		X	X		X	X	X	X	X	X	X
Adverse Event Assessment				X[G, H]	X[G, H]	X[H]	X[H]	X[H]	X[H]	X[H]	X[H]
Review of COVID-19 vaccination record and antibody response		X[I]									
Inclusion/Exclusion criteria assessment		X									
Immunosuppressive Medication Instructions		X[J,K]		X[J,K]							
Pediatric Vaccine Reaction Diary[L]			X	X							
Disease-Specific Assessments											
SLE											
Confirmation of 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups		X									
SLEDAI-2K		X[M]	X[N]		X	X	X	X	X	X	X[X]
ACR Provisional Criteria for Global Flare in Childhood-onset SLE			X		X	X	X	X	X	X	X
JIA											
Confirmation of ILAR classification for JIA		X									
Tender/Swollen Joint Count		X[M]	X[N]		X	X	X	X	X	X	X[X]
PASI[O]			X		X[P]	X[P]	X[P]	X[P]	X[P]	X[P]	X[P]
JDM											
Confirmation of Peter criteria or the 2017 EULAR/ACR classification criteria for JDM		X									
Flare Assessment for JDM		X	X		X	X	X	X	X	X	X[X]
CMAS[Q]		X	X[N]		X	X	X	X	X	X	X[X]
POMS											

Visit Number	S2 PRESCRN	S2 SCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Pre-Screening	S2 Screening	S2 Baseline	S2 Vaccine Diary Review Phone Visit[A]	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window		-21 Days; At least 7 days prior to Vaccination	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Confirmation of 2017 McDonald diagnostic criteria for MS		X									
Physician-assessed relapse for MS		X	X[N]		X	X	X	X	X	X	X[X]
EDSS			X		X[R]	X[R]	X[R]	X[R]	X[R]	X[R]	X[R]
Participant & Clinician Reported Outcomes											
PedsQL			X		X	X	X	X	X	X	X
PtGA		X[M]	X		X	X	X	X	X	X	X
PGI-C					X	X	X	X	X	X	X
PGA		X[M]	X		X	X	X	X	X	X	X
CGI-C					X	X	X	X	X	X	X
Local Laboratory Assessments											
Pre-Screening Rapid Result/Antibody Test - OPTIONAL	X[B]										
Urine Pregnancy[S]		X	X								
Molecular COVID-19 Testing		X	X								
ESR (pediatric SLE participants only)		X	X		X	X	X	X	X	X	X[X]
Central Laboratory Assessments											
Elecsys® Anti-SARS-CoV-2 S (RBD)	X[B]	X[I]			X	X	X	X	X	X	X
Hematology (CBC with differential)		X	X		X	X	X	X	X	X	X
Blood Chemistry (CMP, eGFR)		X	X		X	X	X	X	X	X	X
JIA											
CRP		X	X		X	X	X	X	X	X	X[X]
SLE											
Anti-dsDNA, C3, C4		X	X		X	X	X	X	X	X	X[X]
Random urine protein-creatinine ratio		X	X		X	X	X	X	X	X	X[X]
Urinalysis (microscopic)		X	X		X	X	X	X	X	X	X
Cohort C: B-cell depleting therapy											
CD19+B cells[T]		X	X		X	X	X	X	X	X	X[X]
JDM											
Aldolase		X	X		X	X	X	X	X	X	X[X]
Mechanistic Assessments											
Serum[U]			X[V]	X[A]	X	X	X	X	X	X	X
Whole Blood/PBMC/Plasma			X	X[A]	X	X	X	X	X	X	X
RNA Assays			X	X[A]	X	X	X	X	X	X	X
Background Immunosuppressive Medication Testing (MTX, MPA)			X								
Study Treatment / Investigational Agent											
Alternative vaccine dose eligibility confirmation			X[W]								
Moderna COVID-19 vaccine			X[W]								

Visit Number	S2 PRESCRN	S2 SCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Pre-Screening	S2 Screening	S2 Baseline	S2 Vaccine Diary Review Phone Visit[A]	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window		-21 Days; At least 7 days prior to Vaccination	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Pfizer-BioNTech COVID-19 vaccine			X[W]								

[A]If participants choose to participate in the optional mechanistic blood draw visit at Week 1, the visit will occur at the clinic and the vaccine reaction diary review (along with a review of concomitant medications) will occur in person. If the participant declines to participate in the optional mechanistic blood draw visit at Week 1, the vaccine reaction diary review will occur over the phone and no in person clinic visit is needed.

[B]If a site is conducting optional pre-screening rapid result/antibody testing; the site will review the pre-screening consent with the participant and obtain his/her signature prior to conducting any pre-screening activities. Pre-screening is optional for all participants. The site may send an Elecsys® Anti-SARS-CoV-2 S (RBD) sample to the central lab as one of 3 potential pre-screening tests, as outlined in the ACV01 lab manual.

[C]Comprehensive physical exams include the following systems (at a minimum): general appearance, skin, head/eyes/ears/nose/neck/throat, respiratory/chest, cardiovascular, abdominal, neurological, & musculoskeletal/extremities.

[D]Targeted physical exams will be guided by participant complaints and prior abnormalities.

[E]Neurological Exam: for all POMS participants and for participants with other diagnoses who have a neurological complaint after Screening and enrollment/randomization.

[F]Weight, height, temperature, pulse, and blood pressure will be collected at each visit.

[G]Solicited AEs will be collected for 7 days post study vaccination. Unsolicited AEs will be collected until 28 days post study vaccination.

[H]SAEs, MAAEs, NOCMCs, AESIs, COVID-19 diagnoses, and flares of a secondary autoimmune disease will be collected from Day 1 through the end of the participant's study participation.

[I]Eligibility confirmed by CDC card or documentation in medical records and results of response to initial COVID-19 vaccine regimen assessed by Elecsys® Anti-SARS-CoV-2 S (RBD) assay.

[J]Participants in Cohort E (MTX) will withhold their immunosuppressive medication for at least 7 days prior to and at least 7 days after receipt of the alternative vaccine dose at Stage 2 Baseline (not to exceed 21 days withholding of MTX). If necessary, the site will call the participant between Stage 2 Screening and Stage 2 Baseline to remind the participant to withhold his/her MTX. The site will call the participant after Stage 2 Baseline to remind the participant to restart his/her MTX.

[K]Participants in Cohort D (MMF/MPA) will withhold their immunosuppressive medication for 3 days prior to and 10 days after receipt of the alternative vaccine dose at Stage 2 Baseline. If necessary, the site will call the participant between Stage 2 Screening and Stage 2 Baseline to remind the participant to withhold his/her MMF/MPA. The site will call the participant after Stage 2 Baseline to remind the participant to restart his/her MMF/MPA.

[L]The vaccine diary will be completed for 7 days after vaccine booster. If the participant consents to an optional mechanistic specimen collection at Week 1, he site will complete the review of the vaccine reaction diary prior to collecting specimens.

[M]The Tender/Swollen Joint Count, PGA, and PtGA at Screening will be collected for all JIA participants in order to assess disease activity using JADAS-10. The PGA and the SLEDAI-2K will be collected for pediatric SLE participants at screening for evaluation of the childhood-onset SLE criteria of global flare.

[N]If the Baseline/Week 0 visit occurs less than 10 days from the Screening visit, the following disease activity assessments do not need to be repeated: SLEDAI-2K, Tender/Swollen Joint count, CMAS, and physician-assessed relapse for MS.

[O]The PASI will only be assessed if a JIA participant has psoriatic arthritis.

[P]The PASI will be assessed post-Baseline if a psoriatic arthritis flare is suspected.

[Q]The CMAS is required for JDM participants 6 -17 years of age. The CMAS is optional for JDM participants who are 2-5 years of age.

[R]The EDSS will be collected whenever a POMS relapse is suspected, and if applicable, at the time of relapse recovery (to occur 8-12 weeks after the suspected relapse EDSS assessment)

[S]For postmenarchal females only. Stat urine HCG prior to vaccination may be performed locally with point of care testing.

[T]If a participant is on a CD20 depleting agent, CD19+ B cells will be collected.

[U]Antibody levels will be tested at each time point to test for IgG and IgM responses against SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins

[W]All Stage 2 Week 0 assessments (including confirmation of additional vaccine dose eligibility) must be completed prior to administration of the alternative vaccine dose. If the alternative vaccine dose cannot be administered at Stage 2 Baseline/Stage 2 Week 0, the alternative vaccine dose eligibility confirmation and administration of the alternative vaccine dose may occur 2-3 days after the Stage 2 Baseline/Stage 2 Week 0 visit. Administration of the alternative vaccine dose must occur within 28 days of the Stage 2 Screening visit.

[X]For unscheduled visits conducted for disease activity increases, all disease-specific assessments and corresponding clinical laboratories are to be performed. For unscheduled visits conducted for a reason other than a disease activity increases, participants should be evaluated per clinical judgement of the investigator.

Table 22. Schedule of Events for Pediatric Stage 2 Rollover Participants

Visit Number	S2 PHNSCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Screening Phone Visit[A]	S2 Baseline	S2 Vaccine Diary Review Phone Visit[B]	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window	-21 Days; At least 7 days prior to Vaccination[A]	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Pediatric Participant Blood Draw Limits	**No more than 5mL/kg may be drawn for research purposes in a single day, and no more than 9.5mL/kg may be drawn over any 8-week period. Pediatric blood draw details and prioritization are listed in the ACV01 lab manual.**									
General Assessments										
Verbal agreement to roll over to Stage 2[B]										
Informed Consent/Assent	X									
Medical History	X	X								
Concomitant Medications (including contraceptives)	X	X	X	X	X	X	X	X	X	X
Targeted Physical Exam[C]	X[D]	X		X	X	X	X	X	X	X
Neurological Exam[E]	X[D]	X		X	X	X	X	X	X	X
Vital Signs[F]	X[D]	X		X	X	X	X	X	X	X
Adverse Event Assessment			X[G, H]	X[G, H]	X[H]	X[H]	X[H]	X[H]	X[H]	X[H]
Inclusion/Exclusion criteria assessment	X									
Immunosuppressive Medication Instructions	X[I, J]		X[I,J]							
Vaccine Reaction Diary[K]		X	X							
Disease-Specific Assessments										
SLE										
SLEDAI-2K	X[D,L]	X[M]		X	X	X	X	X	X	X[W]
ACR Provisional Criteria for Global Flare in Childhood-onset SLE		X		X	X	X	X	X	X	X
JIA										
Tender/Swollen Joint Count	X[D,L]	X[M]		X	X	X	X	X	X	X[W]
PASI[N]		X		X[O]	X[O]	X[O]	X[O]	X[O]	X[O]	X[O]
JDM										
Flare Assessment for JDM	X[D]	X		X	X	X	X	X	X	X[W]
CMAS[P]	X[D]	X[M]		X	X	X	X	X	X	X[W]
POMS										
Physician-assessed relapse for MS	X[D]	X[M]		X	X	X	X	X	X	X[W]
EDSS		X		X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]	X[Q]
Participant & Clinician Reported Outcomes										
PedsQL		X		X	X	X	X	X	X	X
PtGA	X[L]	X		X	X	X	X	X	X	X
PGI-C				X	X	X	X	X	X	X
PGA	X[L]	X		X	X	X	X	X	X	X
CGI-C				X	X	X	X	X	X	X
Local Laboratory Assessments										
Urine Pregnancy[R]	X[S]	X								

Visit Number	S2 PHNSCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Screening Phone Visit[A]	S2 Baseline	S2 Vaccine Diary Review Phone Visit[B]	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window	-21 Days; At least 7 days prior to Vaccination[A]	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		
Molecular COVID-19 Testing	X[S]	X								
ESR (pediatric SLE participants only)	X[D]	X		X	X	X	X	X	X	X[W]
Central Laboratory Assessments										
Elecsys® Anti-SARS-CoV-2 S (RBD)	X[D]			X	X	X	X	X	X	X
Hematology (CBC with differential)	X[D]	X		X	X	X	X	X	X	X
Blood Chemistry (CMP, eGFR)	X[D]	X		X	X	X	X	X	X	X
JIA										
CRP	X[D]	X		X	X	X	X	X	X	X[W]
SLE										
Anti-dsDNA, C3, C4	X[D]	X		X	X	X	X	X	X	X[W]
Random urine protein-creatinine ratio	X[D]	X		X	X	X	X	X	X	X[W]
Urinalysis (microscopic)	X[D]	X		X	X	X	X	X	X	X[W]
Cohort C: B-cell depleting therapy										
CD19+B cells[T]	X[D]	X		X	X	X	X	X	X	X[W]
JDM										
Aldolase	X[D]	X		X	X	X	X	X	X	X[W]
Mechanistic Assessments										
Serum[U]		X[U]	X	X	X	X	X	X	X	X
Whole Blood/PBMC/Plasma		X	X	X	X	X	X	X	X	X
RNA Assays		X	X	X	X	X	X	X	X	X
Background Immunosuppressive Medication Testing (MTX, MPA)		X								
Study Treatment / Investigational Agent										
Additional homologous vaccine dose eligibility confirmation		X[V]								
Moderna COVID-19 vaccine		X[V]								
Pfizer-BioNTech COVID-19 vaccine		X[V]								

Visit Number	S2 PHNSCRN	S2 Week 0	S2 Week 1	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 EOS	S2 ET	S2 UNS
Description	S2 Screening Phone Visit[A]	S2 Baseline	S2 Vaccine Diary Review Phone Visit[B]	S2 Week 4	S2 Week 12	S2 Week 24	S2 Week 36	S2 Week 48	S2 Early Termination	S2 Unscheduled
Visit Window	-21 Days; At least 7 days prior to Vaccination[A]	Week 0/Day 1	Day 7– Day 15	+/- 1 week	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks		

[A]If participants choose to participate in the optional mechanistic blood draw visit at Week 1, the visit will occur at the clinic and the vaccine reaction diary review (along with a review of concomitant medications) will occur in person. If the participant declines to participate in the optional mechanistic blood draw visit at Week 1, the vaccine reaction diary review will occur over the phone and no in person clinic visit is needed.

[B]If a site is conducting optional pre-screening rapid result/antibody testing; the site will review the pre-screening consent with the participant and obtain his/her signature prior to conducting any pre-screening activities. Pre-screening is optional for all participants. The site may send an Elecsys® Anti-SARS-CoV-2 S (RBD) sample to the central lab as one of 3 potential pre-screening tests, as outlined in the ACV01 lab manual.

[C]Targeted physical exams will be guided by participant complaints and prior abnormalities.

[D]Remote screening of these parameters will utilize information collected at the participant's most recent Stage 1 or Stage 2 follow-up visit. If these data are not available from a previous visit conducted within the past 21 days, then new information for these parameters must be collected during an in-person visit to the clinical site. For rollover participants, the comprehensive physical exam is replaced by the targeted physical and neurological exams at the previous Stage 1 or Stage 2 visit.

[E]Neurological Exam: for all POMS participants and for participants with other diagnoses who have a neurological complaint after Screening and enrollment/randomization.

[F]Weight, height, temperature, pulse, and blood pressure will be collected at each visit.

[G]Solicited AEs will be collected for 7 days post study vaccination. Unsolicited AEs will be collected until 28 days post study vaccination.

[H]SAEs, MAAEs, NOCMCs, AESIs, COVID-19 diagnoses, and flares of a secondary autoimmune disease will be collected from Day 1 through the end of the participant's study participation.

[I]Participants in Cohort E (MTX) and participants in Cohort F (BCDT) who are also taking MTX will withhold their IS medication for at least 7 days prior to and at least 7 days after receipt of the alterative vaccine dose at Stage 2 Baseline Week 0 (not to exceed 21 days withholding of MTX). If necessary, the site will call the participant between Stage 2 Screening and Stage 2 Baseline Week 0 to remind the participant to withhold his/her MTX. The site will call the participant after Stage 2 Baseline Week 0 to remind the participant to restart his/her MTX.

[J]Participants in Cohort D (MMF/MPA) and participants in Cohort F (BCDT) who are also taking MMF/MPA will withhold their IS medication for 3 days prior to and 10 days after receipt of the alternative vaccine dose at Stage 2 Baseline Week 0. If necessary, the site will call the participant between Stage 2 Screening and Stage 2 Baseline Week 0 to remind the participant to withhold his/her MMF/MPA. The site will call the participant after S2 Baseline Week 0 to remind the participant to restart his/her MMF/MPA.

[K]The vaccine diary will be completed for 7 days after vaccine booster. If the participant consents to an optional mechanistic specimen collection at Week 1, he site will complete the review of the vaccine reaction diary prior to collecting specimens.

[L]The Tender/Swollen Joint Count, PGA, and PtGA at Screening will be collected for all JIA participants in order to assess disease activity using JADAS-10. The PGA and the SLEDAI-2K will be collected for pediatric SLE participants at screening for evaluation of the childhood-onset SLE criteria of global flare.

[M]If the Baseline/Week 0 visit occurs less than 10 days from the Screening visit, the following disease activity assessments do not need to be repeated: SLEDAI-2K, Tender/Swollen Joint count, CMAS, and physician-assessed relapse for MS.

[N]The PASI will only be assessed if a JIA participant has psoriatic arthritis.

[O]The PASI will be assessed post-Baseline if a psoriatic arthritis flare is suspected.

[P] The CMAS is required for JDM participants 6 -17 years of age. The CMAS is optional for JDM participants who are 2-5 years of age.

[Q]The EDSS will be collected whenever a POMS relapse is suspected, and if applicable, at the time of relapse recovery (to occur 8-12 weeks after the suspected relapse EDSS assessment)

[R] For postmenarchal females only. Stat urine HCG prior to vaccination may be performed locally with point of care testing.

[S]If the S2 Screening visit occurs onsite, the molecular COVID-19 test and urine pregnancy test will be conducted. If Stage 1 or Stage 2 visit data is being used to assess Stage 2 eligibility and screening, the molecular COVID-19 test and urine pregnancy tests will be conducted at the S2 Baseline visit only.

[T]If a participant is on a CD20 depleting agent, CD19+ B cells will be collected.

[U]Antibody levels will be tested at each time point to test for IgG and IgM responses against SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins

[V]All Stage 2 Week 0 assessments (including confirmation of additional vaccine dose eligibility) must be completed prior to administration of the alternative vaccine dose. If the alternative vaccine dose cannot be administered at Stage 2 Baseline/Stage 2 Week 0, the alternative vaccine dose eligibility confirmation and administration of the alternative vaccine dose may occur 2-3 days after the Stage 2 Baseline/Stage 2 Week 0 visit. Administration of the alternative vaccine dose must occur within 28 days of the Stage 2 Screening visit.

[W]For unscheduled visits conducted for disease activity increases, all disease-specific assessments and corresponding clinical laboratories are to be performed. For unscheduled visits conducted for a reason other than a disease activity increases, participants should be evaluated per clinical judgement of the investigator.

20.2 CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Reaction involving **one of the following organ systems in which the symptoms are mild**: <u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (no change in activity level), single episode of vomiting and/or single episode of diarrhea	Reaction involving **two or more of the following organ systems in which the symptoms are mild**: <u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (no change in activity level), single episode of vomiting, and/or single episode of diarrhea **OR** Reaction involving **at least one of the following organ systems in which the symptoms are moderate:**	Reaction involving **one or more of the following organ systems**: <u>Lower respiratory</u> Throat tightness, wheezing, chest tightness, dyspnea, cough that respond to short-acting bronchodilator treatment (including IM epinephrine) with or without supplemental oxygen <u>GI</u> Severe abdominal pain, more than two episodes of vomiting and/or diarrhea	**Life-threatening reaction** involving **one or more of the following organ systems** with or without other symptoms listed in Grades 1 to 3: <u>Lower respiratory</u> Throat tightness with stridor, wheezing, chest tightness, dyspnea, or cough associated with a requirement for supplemental oxygen and refractoriness to short-acting bronchodilator treatment (including IM epinephrine)[1] **OR** Respiratory compromise requiring mechanical support <u>Cardiovascular</u> Reduced BP with associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope) defined as: • Children: low systolic BP (age specific[2]) or	Death

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	<u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (with change in activity level), two episodes of vomiting and/or diarrhea		>30% decrease in systolic BP • Adults: systolic BP of less than 90 mmHg or >30% decrease from baseline	

1. Examples of refractoriness could include continuous albuterol nebulizer or epinephrine IV infusion or more than three IM epinephrine injections.
2. Low systolic BP for children is defined as: less than 70 mmHg from 1 month to 1 year of age, less than (70 mmHg + [2 x age]) from 1 to 10 years of age, and less than 90 mmHg from 11 to 17 years of age.

20.3 Adult Vaccine Reaction Diary

ACV01 Vaccine Reaction Diary Card

Participant ID: _____

Study Doctor: _____ Phone Number: _____

Call the Study Doctor listed above:

- If you have a temperature equal to or greater than 102.4 °F
- If you have any severe symptom that prevents daily activity or requires medical care
- If injection site symptoms are noted larger than ring B on the measuring tool
- If you have any concerns or questions about completing the Diary Card or about any symptoms you are experiencing

PLEASE HAVE THIS DIARY CARD WITH YOU DURING EACH SCHEDULED CALL WITH STUDY STAFF

YOUR CALL IS SCHEDULED ON: _____ **AT:** _____ **AM / PM**

TEMPERATURE RECORDING: Take and record your oral temperature daily. Aim to take your temperature at the same time each day. Record all temperatures in degrees Fahrenheit (°F).

Directions:

1. Wipe the thermometer clean with rubbing alcohol and rinse with cold tap water before and after each use.
2. Do not eat, drink any liquids, exercise, bathe, or smoke for at least 15 minutes before taking your temperature.
3. Press the On/Off button. You will see the last recorded temperature briefly. The thermometer is ready to use when it reads "Lo" and a blinking "°F" is visible.
4. Place the thermometer under your tongue as far back as you can comfortably put it. Keep your mouth closed and hold the thermometer in the same spot until the thermometer beeps.
5. Record the date, time (using a 12-hour clock with AM or PM), and temperature reading in the table below.
6. If you take your temperature more than once in a day, record the highest temperature.

	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/ __ __ __/ 202_	__ __/ __ __ __/ 202_	__ __/ __ __ __/ 202_	__ __/ __ __ __/ 202_	__ __/ __ __ __/ 202_	__ __/ __ __ __/ 202_	__ __/ __ __ __/ 202_
Time (HH:MM)	__ __ : __ __ □ AM □ PM	__ __ : __ __ □ AM □ PM	__ __ : __ __ □ AM □ PM	__ __ : __ __ □ AM □ PM	__ __ : __ __ □ AM □ PM	__ __ : __ __ □ AM □ PM	__ __ : __ __ □ AM □ PM
Temperature (°F)	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F

ACV01 Vaccine Reaction Diary Card

Participant ID: _____

INJECTION SITE SYMPTOM RECORD: Using the measuring tool provided at the time of your injection, rate the symptoms you experience in the table below. For each injection site symptom listed, mark either *Not Present* or circle the appropriate letter. Every day you must select either *Not Present* or record a rating for each symptom listed.

Directions:

1. Center the measuring tool over the injection site.
2. Note the letter (A, B, C or D) of the ring that holds the widest point of redness and/or swelling / hardness.
3. Circle the letter corresponding to each symptom in the table below. **Please select only one answer per box.**

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_
Injection Site Redness	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D
Injection Site Swelling / Hardness	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D

MEDICATION CHANGES: Have you changed or added any new medications this week (prescription and/or over-the-counter)? □ Yes □ No

If yes, record each new or updated medication below. If you need more space, record medications on a separate piece of paper and keep it with your diary.

Medication Name	Dose	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Reason

ACV01 Vaccine Reaction Diary Card Participant ID: _____

SYMPTOMS EXPERIENCED: Using the participant symptom rating scale provided, rate the symptoms you experience in the table below. If you have no symptoms, place an "X" in the *No Symptoms* box and leave all other boxes for that day blank. If you have one or more of the listed symptoms, use the rating scale to rate each symptom. Every day you must check either *No Symptoms* or record a rating (at minimum the applicable number: 0, 1, 2, 3; you may also write none, mild, moderate, or severe) for all of the symptoms listed. **CALL THE STUDY DOCTOR IF YOU EXPERIENCE ANY SEVERE (RATING #3) SYMPTOMS.**

SYMPTOM RATING SCALE:

0 No symptoms
1 Mild (present, but did not require over-the-counter or prescription medications; did not interfere with daily activities)
2 Moderate (required over-the-counter or prescription medications; caused some interference with daily activities)
3 Severe (required over-the-counter or prescription medications; significant, incapacitating discomfort preventing daily activities)

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202	__ __/__ __ __/202
No Symptoms							
Injection Site Reactions:							
Pain at Injection Site							
Redness at Injection Site							
Swelling / Hardness at Injection Site							
Papules							
Ulceration							

ACV01 Vaccine Reaction Diary Card

Participant ID: _____

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Other:							
Lymph Node – Arm pit							
Chills							
Muscle Aches/Pain							
Joint Pain							
Tiredness / Fatigue							
Headache							
Nausea							
Vomiting							
Hives							
Diarrhea							
Shortness of Breath							
Chest Pain							
Pain (in arm)							
Pain (in leg)							
Swelling (in arm)							
Swelling (in leg)							

ACV01 Vaccine Reaction Diary Card

Participant ID: _____

ADDITIONAL SYMPTOMS:

Have you experienced any other symptoms (including an increase in symptoms in your underlying autoimmune disease) not listed above? □ Yes □ No

If Yes, record the symptoms you experienced. If you need more space, record symptoms on a separate piece of paper and keep it with your diary.

Symptom Experienced	Highest Rating Experienced*	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)

**** Use the Symptom Rating Scale on page 3 and record only the highest rating experienced for that symptom between the start and stop dates (i.e., a headache rated 2 on Day 1 that increases to a 3 on Day 2 would be marked as a 3).***

20.4 Pediatric Vaccine Reaction Diary (2 year old)

ACV01 Pediatric Diary Card (2 year old) Participant ID: _____

Study Doctor: _____ Phone Number: _____

Call the Study Doctor listed above:

- If your child has a temperature equal to or greater than 102.4 °F
- If your child has any severe symptom that prevents daily activity or requires medical care
- If injection site symptoms are noted larger than ring B on the measuring tool
- If you have any concerns or questions about completing the Pediatric Diary Card or about any symptoms your child is experiencing

PLEASE HAVE THIS DIARY CARD WITH YOU DURING EACH SCHEDULED CALL WITH STUDY STAFF

YOUR CALL IS SCHEDULED ON: _____ **AT:** _____ **AM / PM**

TEMPERATURE RECORDING: Take and record your child's oral temperature daily. Aim to take your child's temperature at the same time each day. Record all temperatures in degrees Fahrenheit (°F).

Directions:

1. Wipe the thermometer clean with rubbing alcohol and rinse with cold tap water before and after each use.
2. Do not have them eat, drink any liquids, exercise, or bathe for at least 15 minutes before taking their temperature.
3. Press the On/Off button. You will see the last recorded temperature briefly. The thermometer is ready to use when it reads "Lo" and a blinking "°F" is visible.
4. Place the thermometer under your child's tongue as far back as you can comfortably put it. Keep your child's mouth closed and hold the thermometer in the same spot until the thermometer beeps.
5. Record the date, time (using a 12-hour clock with AM or PM), and temperature reading in the table below.
6. If you take your child's temperature more than once in a day, record the highest temperature.

	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_
Time (HH:MM)	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM
Temperature (°F)	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F

ACV01 Pediatric Diary Card (2 year old) Participant ID: _____

INJECTION SITE SYMPTOM RECORD: The site coordinator will provide you with the appropriate measuring tool based upon participant age (2-4 year old measuring tool). Using the measuring tool provided at the time of your child's injection, rate the symptoms you experience in the table below. For each injection site symptom listed, mark either *Not Present* or circle the appropriate letter. Every day you must select either *Not Present* or record a rating for each symptom listed.

Directions:

1. Center the measuring tool over the injection site.
2. Note the letter (A, B, C or D) of the ring that holds the widest point of redness and/or swelling / hardness.
3. Circle the letter corresponding to each symptom in the table below. **Please select only one answer per box.**

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_
Injection Site Redness	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D
Injection Site Swelling / Hardness	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D	☐ Not Present A B C D

MEDICATION CHANGES: Has your child changed or added any new medications this week (prescription and/or over-the-counter)? ☐ Yes ☐ No

If yes, record each new or updated medication below. If you need more space, record medications on a separate piece of paper and keep it with your diary.

Medication Name	Dose	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Reason

ACV01 Pediatric Diary Card (2 year old) Participant ID: _____

SYMPTOMS EXPERIENCED: Using the symptom rating scale provided, rate the symptoms your child experiences in the table below. If your child has no symptoms, place an "X" in the *No Symptoms* box and leave all other boxes for that day blank. If your child has one or more of the listed symptoms, use the rating scale to rate each symptom. Every day you must check either *No Symptoms* or record a rating (at minimum the applicable number: 0, 1, 2, 3; you may also write none, mild, moderate, or severe) for all of the symptoms listed. **CALL THE STUDY DOCTOR IF YOUR CHILD EXPERIENCES ANY SEVERE (RATING #3) SYMPTOMS.**

GENERAL SYMPTOM RATING SCALE:

0 No symptoms
1 Mild (present, but did not require over-the-counter or prescription medications; did not interfere with daily activities)
2 Moderate (required over-the-counter or prescription medications; caused some interference with daily activities)
3 Severe (required over-the-counter or prescription medications; significant, incapacitating discomfort preventing daily activities)

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202	__ __/__ __ __/202
No Symptoms							
Injection Site Reactions:							
Pain at Injection Site							
Redness at Injection Site							
Swelling / Hardness at Injection Site							
Papules							
Ulceration							

Instructions for Other Symptoms:	SYMPTOM-SPECIFIC RATING SCALE: VOMITING	SYMPTOM-SPECIFIC RATING SCALE: DIARRHEA
Grade using the General Symptom Rating Scale above, with the following exceptions:	0 No symptoms 1 Mild: 1 to 2 times in 24 hours 2 Moderate: >2 times in 24 hours 3 Severe: Prevents daily activity	0 No symptoms 1 Mild: 2 to 3 loose stools in 24 hours 2 Moderate: 4 to 5 loose stools in 24 hours 3 Severe: 6 or more loose stools in 24 hours

ACV01 Pediatric Diary Card (2 year old) Participant ID: _____

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Other:							
Lymph Node – Arm pit							
Chills							
Muscle Aches/Pain							
Joint Pain							
Sleepiness (Tiredness / Fatigue)							
Irritability/Crying (Headache)							
Loss of Appetite (Nausea)							
Vomiting							
Hives							
Diarrhea							
Shortness of Breath							
Swelling in arm							
Swelling in leg							

ADDITIONAL SYMPTOMS: Has your child experienced any other symptoms (including an increase in symptoms in their underlying autoimmune disease) not listed above? ☐ Yes ☐ No

ACV01 Pediatric Diary Card (2 year old) Participant ID: _____

If Yes, record the symptoms they experienced. If you need more space, record symptoms on a separate piece of paper and keep it with your diary.

Symptom Experienced	Highest Rating Experienced*	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)

**** Use the Symptom Rating Scale on page 3 and record only the highest rating experienced for that symptom between the start and stop dates (i.e., a headache rated 2 on Day 1 that increases to a 3 on Day 2 would be marked as a 3).***

20.5 Pediatric Vaccine Reaction Diary (3 – 4 year old)

ACV01 Pediatric Diary Card (3 - 4 year old) Participant ID: _____

Study Doctor: _____ Phone Number: _____

Call the Study Doctor listed above:

- If your child has a temperature equal to or greater than 102.4 °F
- If your child has any severe symptom that prevents daily activity or requires medical care
- If injection site symptoms are noted larger than ring B on the measuring tool
- If you have any concerns or questions about completing the Pediatric Diary Card or about any symptoms your child is experiencing

PLEASE HAVE THIS DIARY CARD WITH YOU DURING EACH SCHEDULED CALL WITH STUDY STAFF

YOUR CALL IS SCHEDULED ON: _____ **AT:** _____ **AM / PM**

TEMPERATURE RECORDING: Take and record your child's oral temperature daily. Aim to take your child's temperature at the same time each day. Record all temperatures in degrees Fahrenheit (°F).

Directions:

1. Wipe the thermometer clean with rubbing alcohol and rinse with cold tap water before and after each use.
2. Do not have them eat, drink any liquids, exercise, or bathe for at least 15 minutes before taking their temperature.
3. Press the On/Off button. You will see the last recorded temperature briefly. The thermometer is ready to use when it reads "Lo" and a blinking "°F" is visible.
4. Place the thermometer under your child's tongue as far back as you can comfortably put it. Keep your child's mouth closed and hold the thermometer in the same spot until the thermometer beeps.
5. Record the date, time (using a 12-hour clock with AM or PM), and temperature reading in the table below.
6. If you take your child's temperature more than once in a day, record the highest temperature.

	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_
Time (HH:MM)	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM
Temperature (°F)	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F

ACV01 Pediatric Diary Card (3 - 4 year old) Participant ID: _____

INJECTION SITE SYMPTOM RECORD: The site coordinator will provide you with the appropriate measuring tool based upon participant age (2-4 year old measuring tool). Using the measuring tool provided at the time of your child's injection, rate the symptoms you experience in the table below. For each injection site symptom listed, mark either *Not Present* or circle the appropriate letter. Every day you must select either *Not Present* or record a rating for each symptom listed.

Directions:

1. Center the measuring tool over the injection site.
2. Note the letter (A, B, C or D) of the ring that holds the widest point of redness and/or swelling / hardness.
3. Circle the letter corresponding to each symptom in the table below. **Please select only one answer per box.**

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_
Injection Site Redness	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D
Injection Site Swelling / Hardness	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D	□ Not Present A B C D

MEDICATION CHANGES: Has your child changed or added any new medications this week (prescription and/or over-the-counter)? □ Yes □ No

If yes, record each new or updated medication below. If you need more space, record medications on a separate piece of paper and keep it with your diary.

Medication Name	Dose	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Reason

ACV01 Pediatric Diary Card (3 - 4 year old) Participant ID: _____

SYMPTOMS EXPERIENCED: Using the symptom rating scale provided, rate the symptoms your child experiences in the table below. If your child has no symptoms, place an "X" in the *No Symptoms* box and leave all other boxes for that day blank. If your child has one or more of the listed symptoms, use the rating scale to rate each symptom. Every day you must check either *No Symptoms* or record a rating (at minimum the applicable number: 0, 1, 2, 3; you may also write none, mild, moderate, or severe) for all of the symptoms listed. **CALL THE STUDY DOCTOR IF YOUR CHILD EXPERIENCES ANY SEVERE (RATING #3) SYMPTOMS.**

GENERAL SYMPTOM RATING SCALE:

0 No symptoms
1 Mild (present, but did not require over-the-counter or prescription medications; did not interfere with daily activities)
2 Moderate (required over-the-counter or prescription medications; caused some interference with daily activities)
3 Severe (required over-the-counter or prescription medications; significant, incapacitating discomfort preventing daily activities)

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202	__ __/__ __ __/202
No Symptoms							
Injection Site Reactions:							
Pain at Injection Site							
Redness at Injection Site							
Swelling / Hardness at Injection Site							
Papules							
Ulceration							

Instructions for Other Symptoms:	SYMPTOM-SPECIFIC RATING SCALE:	SYMPTOM-SPECIFIC RATING SCALE:
Grade using the General Symptom Rating Scale above, with the following exceptions:	NAUSEA / VOMITING 0 No symptoms 1 Mild: 1 to 2 times in 24 hours 2 Moderate: >2 times in 24 hours 3 Severe: Prevents daily activity	DIARRHEA 0 No symptoms 1 Mild: 2 to 3 loose stools in 24 hours 2 Moderate: 4 to 5 loose stools in 24 hours 3 Severe: 6 or more loose stools in 24 hours

ACV01 Pediatric Diary Card (3 - 4 year old) Participant ID: _____

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Other:							
Lymph Node – Arm pit							
Chills							
Muscle Aches/Pain							
Joint Pain							
Tiredness / Fatigue							
Headache							
Nausea							
Vomiting							
Hives							
Diarrhea							
Shortness of Breath							
Swelling in arm							
Swelling in leg							

ACV01 Pediatric Diary Card (3 - 4 year old) Participant ID: _____

ADDITIONAL SYMPTOMS: Has your child experienced any other symptoms (including an increase in symptoms in their underlying autoimmune disease) not listed above? ☐ Yes ☐ No

If Yes, record the symptoms they experienced. If you need more space, record symptoms on a separate piece of paper and keep it with your diary.

Symptom Experienced	Highest Rating Experienced*	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)

Use the Symptom Rating Scale on page 3 and record only the highest rating experienced for that symptom between the start and stop dates (i.e., a headache rated 2 on Day 1 that increases to a 3 on Day 2 would be marked as a 3).

20.6 Pediatric Vaccine Reaction Diary (5 – 17 year old)

ACV01 Pediatric Diary Card (5-17 year old) Participant ID: _____

Study Doctor: _____ Phone Number: _____

Call the Study Doctor listed above:

- If you or your child has a temperature equal to or greater than 102.4 °F
- If you or your child has any severe symptom that prevents daily activity or requires medical care
- If injection site symptoms are noted larger than ring B on the measuring tool
- If you or your child has any concerns or questions about completing the Pediatric Diary Card or about any symptoms you or your child is experiencing

PLEASE HAVE THIS DIARY CARD WITH YOU DURING EACH SCHEDULED CALL WITH STUDY STAFF

YOUR CALL IS SCHEDULED ON: _____ **AT:** _____ **AM / PM**

TEMPERATURE RECORDING: Take and record your or your child's oral temperature daily. Aim to take your or your child's temperature at the same time each day. Record all temperatures in degrees Fahrenheit (°F).

Directions:

1. Wipe the thermometer clean with rubbing alcohol and rinse with cold tap water before and after each use.
2. You or your child should not eat, drink any liquids, exercise, bathe, or smoke for at least 15 minutes before taking your temperature.
3. Press the On/Off button. You will see the last recorded temperature briefly. The thermometer is ready to use when it reads "Lo" and a blinking "°F" is visible.
4. Place the thermometer under your or your child's tongue as far back as you can comfortably put it. Keep your or your child's mouth closed and hold the thermometer in the same spot until the thermometer beeps.
5. Record the date, time (using a 12-hour clock with AM or PM), and temperature reading in the table below.
6. If you take your or your child's temperature more than once in a day, record the highest temperature.

	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_	__ __ / __ __ __ / 202_
Time (HH:MM)	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM
Temperature (°F)	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F	__ __ __ . __ °F

ACV01 Pediatric Diary Card (5-17 year old) Participant ID: _____

INJECTION SITE SYMPTOM RECORD: The site coordinator will provide you with the appropriate measuring tool based upon participant age (5-17 year old measuring tool). Using the measuring tool provided at the time of your or your child's injection, rate the symptoms you experience in the table below. For each injection site symptom listed, mark either *Not Present* or circle the appropriate letter. Every day you must select either *Not Present* or record a rating for each symptom listed.

Directions:

1. Center the measuring tool over the injection site.
2. Note the letter (A, B, C or D) of the ring that holds the widest point of redness and/or swelling / hardness.
3. Circle the letter corresponding to each symptom in the table below. **Please select only one answer per box.**

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_
Injection Site Redness	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D
Injection Site Swelling / Hardness	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D	◻ Not Present A B C D

MEDICATION CHANGES: Have you or your child changed or added any new medications this week (prescription and/or over-the-counter)? ◻ Yes ◻ No

If yes, record each new or updated medication below. If you need more space, record medications on a separate piece of paper and keep it with your diary.

Medication Name	Dose	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Reason

ACV01 Pediatric Diary Card (5-17 year old) Participant ID: _____

SYMPTOMS EXPERIENCED: Using the symptom rating scale provided, rate the symptoms you or your child experiences in the table below. If you or your child has no symptoms, place an "X" in the *No Symptoms* box and leave all other boxes for that day blank. If you or your child hasone or more of the listed symptoms, use the rating scale to rate each symptom. Every day you must check either *No Symptoms* or record a rating (at minimum the applicable number: 0, 1, 2, 3; you may also write none, mild, moderate, or severe) for all of the symptoms listed. **CALL THE STUDY DOCTOR IF YOU OR YOUR CHILD EXPERIENCES ANY SEVERE (RATING #3) SYMPTOMS.**

GENERAL SYMPTOM RATING SCALE:

0 No symptoms
1 Mild (present, but did not require over-the-counter or prescription medications; did not interfere with daily activities)
2 Moderate (required over-the-counter or prescription medications; caused some interference with daily activities)
3 Severe (required over-the-counter or prescription medications; significant, incapacitating discomfort preventing daily activities)

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (DD/MMM/YYYY)	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202_	__ __/__ __ __/202	__ __/__ __ __/202
No Symptoms							
Injection Site Reactions:							
Pain at Injection Site							
Redness at Injection Site							
Swelling / Hardness at Injection Site							
Papules							
Ulceration							

Instructions for Other Symptoms: Grade the other symptoms noted below using the General Symptom Rating Scale above, with the following exceptions:

SYMPTOM-SPECIFIC RATING SCALE: [b] NAUSEA / VOMITING		SYMPTOM-SPECIFIC RATING SCALE: [c] DIARRHEA	
0	No symptoms	0	No symptoms
1	Mild: 1 to 2 times in 24 hours	1	Mild: 2 to 3 loose stools in 24 hours
2	Moderate: >2 times in 24 hours	2	Moderate: 4 to 5 loose stools in 24 hours
3	Severe: Prevents daily activity	3	Severe: 6 or more loose stools in 24 hours

ACV01 Pediatric Diary Card (5-17 year old) Participant ID: _____

Days After Vaccination	Day 1 (Vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Other:							
Lymph Node – Arm pit							
Chills							
Muscle Aches/Pain							
Joint Pain							
Tiredness / Fatigue							
Headache							
Nausea [b]							
Vomiting [b]							
Hives							
Diarrhea [c]							
Shortness of Breath							
Chest Pain							
Pain in arm							
Pain in leg							
Swelling in arm							
Swelling in leg							

ACV01 Pediatric Diary Card (5-17 year old) Participant ID: _____

ADDITIONAL SYMPTOMS: Have you or your child experienced any other symptoms (including an increase in symptoms in your underlying autoimmune disease) not listed above? ☐ Yes ☐ No

If Yes, record the symptoms experienced. If you need more space, record symptoms on a separate piece of paper and keep it with your diary.

Symptom Experienced	Highest Rating Experienced*	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)

Use the Symptom Rating Scale on page 3 and record only the highest rating experienced for that symptom between the start and stop dates (i.e., a headache rated 2 on Day 1 that increases to a 3 on Day 2 would be marked as a 3).

20.7 List of potential immune-mediated diseases (version: January-2022)

Blood Disorders and coagulopathies	Cardio-pulmonary inflammatory disorders	Endocrine disorders

• Antiphospholipid syndrome
• Autoimmune aplastic anemia
• Autoimmune hemolytic anemia, including:
  o Warm antibody hemolytic anemia
  o Cold antibody hemolytic anemia
• Autoimmune lymphoproliferative syndrome (ALPS)
• Autoimmune neutropenia
• Autoimmune pancytopenia
• Autoimmune thrombocytopenia*
  o Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)", "idiopathic immune thrombocytopenia", and "primary immune thrombocytopenia".
• Evans syndrome
• Pernicious anemia
• Thrombosis with thrombocytopenia syndrome (TTS)
• Thrombotic thrombocytopenic purpura
  o Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"
	• Idiopathic Myocarditis/Pericarditis, including:
	  o Autoimmune / Immune-mediated myocarditis
	  o Autoimmune / Immune-mediated pericarditis
	  o Giant cell myocarditis
	• Idiopathic pulmonary fibrosis, including:
	  o Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune mediated pneumonitis)
	  o Pleuroparenchymal fibroelastosis (PPFE)
	• Pulmonary alveolar proteinosis (PAP)
	  o Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"
		• Addison's disease
		• Autoimmune / Immune-mediated thyroiditis, including:
		  o Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)
		  o Atrophic thyroiditis
		  o Silent thyroiditis
		  o Thyrotoxicosis
		• Autoimmune diseases of the testis and ovary, including:
		  o Autoimmune oophoritis
		  o Autoimmune ovarian failure
		  o Autoimmune orchitis
		• Autoimmune hyperlipidemia
		• Autoimmune hypophysitis
		• Diabetes mellitus type I
		• Grave's or Basedow's disease,
		• including:
		  o Marine Lenhart syndrome
		  o Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
		• Insulin autoimmune syndrome
		• Polyglandular autoimmune syndrome, including:
		  o Polyglandular autoimmune syndrome type I, II and III

Eye disorders	**Gastrointestinal disorders**	**Hepatobiliary disorders**

• Ocular Autoimmune / Immune mediated disorders, including:
  o Acute macular neuroretinopathy (also known as acute macular outer retinopathy)
  o Autoimmune / Immune mediated retinopathy
  o Autoimmune / Immune mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia
  o Cogan's syndrome: an oculoaudiovestibular disease
  o Ocular pemphigoid
  o Ulcerative keratitis
  o Vogt-Koyanagi-Harada disease
	• Autoimmune / Immune-mediated pancreatitis
	• Celiac disease
	• Inflammatory Bowel disease, including:
	  o Crohn's disease
	  o Microscopic colitis
	  o Terminal ileitis
	  o Ulcerative colitis
	  o Ulcerative proctitis
		• Autoimmune cholangitis
		• Autoimmune hepatitis
		• Primary biliary cirrhosis
		• Primary sclerosing cholangitis

Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**

• Gout, including:
  o Gouty arthritis
• Idiopathic inflammatory myopathies, including:
  o Dermatomyositis
  o Inclusion body myositis
  o Immune-mediated necrotizing myopathy
  o Polymyositis
• Mixed connective tissue disorder
• Polymyalgia rheumatica (PMR)
• Psoriatic arthritis (PsA)
• Relapsing polychondritis
	• Acute disseminated encephalomyelitis (ADEM)* and other inflammatory-demyelinating variants, including:
	  o Acute necrotising myelitis
	  o Bickerstaff's brainstem encephalitis
	  o Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis)
	  o Myelin oligodendrocyte glycoprotein antibody-associated disease
	  o Neuromyelitis optica (also known
		• Autoimmune / Immune-mediated glomerulonephritis, including:
		  o IgA nephropathy
		  o IgM nephropathy
		  o C1q nephropathy
		  o Fibrillary glomerulonephritis
		  o Glomerulonephritis rapidly progressive
		  o Membranoproliferative glomerulonephritis
		  o Membranous glomerulonephritis
		  o Mesangioproliferative glomerulonephritis

• Rheumatoid arthritis, including: o Rheumatoid arthritis o associated conditions o Juvenile idiopathic arthritis o Palindromic rheumatism o Still's disease o Felty's syndrome • Sjögren's syndrome • Spondyloarthritis, including: o Ankylosing spondylitis o Juvenile spondyloarthritis o Keratoderma blenorrhagica o Psoriatic spondylitis o Reactive Arthritis (Reiter's Syndrome) o Undifferentiated spondyloarthritis • Systemic Lupus Erythematosus, including: o Lupus associated conditions (e.g., Cutaneous lupus erythematosus, Lupus nephritis, etc.) o Complications such as shrinking lung syndrome (SLS) • Systemic Scleroderma (Systemic Sclerosis), including: o Reynolds syndrome (RS) o Systemic sclerosis with diffuse scleroderma o Systemic sclerosis with limited scleroderma (also known as CREST syndrome)	as Devic's disease) o Noninfective encephalitis / encephalomyelitis / myelitis o Postimmunization encephalomyelitis • Guillain-Barré syndrome (GBS)*, including: o Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN) • Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including: o Cranial nerve neuritis (e.g., Optic neuritis) o Idiopathic nerve palsies/paresis (e.g., Bell's palsy) o Melkersson-Rosenthal syndrome o Multiple cranial nerve palsies/paresis • Multiple Sclerosis (MS), including: o Clinically isolated syndrome (CIS) o Malignant MS (the Marburg type of MS) o Primary-progressive MS (PPMS) o Radiologically isolated syndrome (RIS) o Relapsing-remitting MS (RRMS) o Secondary-progressive MS (SPMS) o Uhthoff's phenomenon • Myasthenia gravis, including: o Ocular myasthenia o Lambert-Eaton myasthenic syndrome • Narcolepsy* (with or without presence of unambiguous cataplexy) • Peripheral inflammatory demyelinating neuropathies and plexopathies, including o Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) o Antibody-mediated demyelinating neuropathy o Chronic idiopathic axonal polyneuropathy (CIAP) o Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g., multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) o Multifocal motor neuropathy (MMN) • Transverse myelitis (TM), including: o Acute partial transverse myelitis (APTM) o Acute complete transverse myelitis (ACTM)	o Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	**Vasculitis**	**Other disorders (including multisystemic)**

• Alopecia areata • Autoimmune / Immune mediated blistering dermatoses, including: o Bullous Dermatitis o Bullous Pemphigoid o Dermatitis herpetiformis o Epidermolysis bullosa acquisita (EBA) o Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease o Pemphigus • Erythema multiforme • Erythema nodosum • Lichen planus, including: o Liquen planopilaris • Localized Scleroderma (Morphoea) o Eosinophilic fasciitis (also called Shulman syndrome) • Psoriasis • Pyoderma gangrenosum • Reactive granulomatous dermatitis, including : o Interstitial granulomatous dermatitis o Palisaded neutrophilic granulomatous dermatitis • Stevens-Johnson Syndrome (SJS), including: o Toxic Epidermal Necrolysis (TEN) o SJS-TEN overlap • Sweet's syndrome, including: o Acute febrile neutrophilic dermatosis • Vitiligo	• Large vessels vasculitis*, including: o Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) o Giant cell arteritis (also called temporal arteritis) o Takayasu's arteritis • Medium sized and/or small vessels vasculitis*, including: o Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) o Behcet's syndrome o Buerger's disease (thromboangiitis obliterans) o Churg–Strauss syndrome (allergic granulomatous angiitis) o Erythema induratum (also known as nodular vasculitis) o Henoch-Schonlein purpura (also known as IgA vasculitis) o Microscopic polyangiitis o Necrotizing vasculitis o Polyarteritis nodosa o Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) o Wegener's granulomatosis	• Anti-synthetase syndrome • Capillary leak syndrome o Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome" • Goodpasture syndrome o Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)" • Immune-mediated enhancement of disease, including: o Vaccine associated enhanced disease (VAED and VAERD). o Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE) • Immunoglobulin G4 related disease • Langerhans' cell histiocytosis • Multisystem inflammatory syndromes, including: o Kawasaki's disease o Multisystem inflammatory syndrome in adults (MIS-A) o Multisystem inflammatory syndrome in children (MIS-C) • Overlap syndrome • Raynaud's phenomenon • Sarcoidosis, including: o Loefgren syndrome • Susac's syndrome
*Adverse events of special interest (AESI) considered potentially applicable to COVID-19 vaccines as defined by the Safety Platform for Emergency Vaccines (SPEAC), based on known association with vaccination in general (see https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf). SPEAC list extended with additional potential immune-mediated diseases.		

20.8 Case definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥1 new or worsening of the following clinical symptoms:*	Presence of ≥1 new or worsening of the following clinical symptoms:*
	• chest pain, pressure, or discomfort	• chest pain, pressure, or discomfort
	• dyspnea, shortness of breath, or pain with breathing	• dyspnea, shortness of breath, or pain with breathing
	• palpitations	• palpitations
	• syncope	• syncope
	OR, infants and children aged <12 years might instead have ≥2 of the following symptoms:	OR, infants and children aged <12 years might instead have ≥2 of the following symptoms:
	• irritability	• irritability
	• vomiting	• vomiting
	• poor feeding	• poor feeding
	• tachypnea	• tachypnea
	• lethargy	• lethargy
	AND	AND
	≥1 new finding of	≥1 new finding of
	• troponin level above upper limit of normal (any type of troponin)	• Histopathologic confirmation of myocarditis[†]
	• abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis[§]	
	• abnormal cardiac function or wall motion abnormalities on echocardiogram	• cMRI findings consistent with myocarditis[¶] in the presence of troponin level above upper limit of normal (any type of troponin)
	• cMRI findings consistent with myocarditis[¶]	
	AND	AND
	• No other identifiable cause of the symptoms and findings	• No other identifiable cause of the symptoms and findings
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features:	
	• acute chest pain[††]	
	• pericardial rub on exam	

Condition	Definition
	• new ST-elevation or PR-depression on EKG
	• new or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram.

* Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

† Using the Dallas criteria (Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol 1987; 1:3–14). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.

¶ Using either the original or the revised Lake Louise criteria. https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon

** https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon

†† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.