COVID19-TB-04

Safety and Immunogenicity of a dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine in kidney transplant recipients with a persistently low SARS CoV-2 antibody titer

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Protocol Chair **Dorry Segev, MD, PhD** Professor of Surgery New York University [redacted]	**Co-Protocol Chair** **Peter Heeger, MD** Professor of Medicine Icahn School of Medicine at Mount Sinai Recanati Miller Transplant Institute [redacted]	**Co-Protocol Chair** **Christian Larsen, MD, DPhil** Professor of Surgery Emory University [redacted]
Co-Protocol Chair **William Werbel, MD** Johns Hopkins University [redacted]	**Grantee Principal Investigator** **Christine Durand, MD** Associate Professor Johns Hopkins University [redacted]	**Biostatistician** [redacted]
NIAID Medical Monitor [redacted]	**NIAID Regulatory Officer** [redacted]	**NIAID Project Manager** [redacted]

NIAID Pharmaceutical Specialist [redacted]		

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SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: COVID19-TB-04	**Version Number/Date: v3.0/April 19, 2023**
Protocol Title: Safety and Immunogenicity of a dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine in kidney transplant recipients with a persistently low SARS CoV-2 antibody titer	
IND Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
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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 Conference for Harmonisation (ICH) document entitled *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).]*

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Site Principal Investigator (Print)

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Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Safety and Immunogenicity of a dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine in kidney transplant recipients with a persistently low SARS CoV-2 antibody titer
Short Title	COVID Protection After Transplant - Sanofi GSK (CPAT-SG) Study
Clinical Phase	Phase II
Number of Sites	6
IND Sponsor/Number	NIAID/IND# 28523
Study Objectives	The primary objective is to determine whether a booster dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine will elicit an increased SARS-CoV-2 antibody response in participants who have failed to maintain an antibody titer >2500 U/mL (using the Roche Elecsys® anti-RBD assay) to a completed primary series and bivalent booster of mRNA based COVID-19 vaccine.
Study Design	An open label, non-randomized pilot study in kidney transplant recipients who received a completed primary series and bivalent booster of mRNA based COVID-19 vaccine and have ≤ 2500 U/mL SARS-CoV-2 S antibody concentration using the Roche Elecsys® anti-RBD assay. Up to 80 participants will be enrolled in this study. Eligible participants will receive a dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine candidate.
Primary Immunogenicity Endpoint	The primary endpoint is the proportion of participants who reach a SARS-CoV-2 S antibody level >5000 U/mL (using the Roche Elecsys® anti-RBD assay) at 30 days following a dose of the Sanofi-GSK COVID-19 vaccine.
Safety Endpoints	• Composite endpoint composed of any of the following events occurring within 30 days following the study dose of vaccine: death, graft loss, need for dialysis, and acute rejection • Components of the composite safety endpoint (death, graft loss, need for dialysis, acute rejection) within 30 days and 60 days of the study dose of vaccine • Solicited local and systemic vaccine reactogenicity (collected for 7 days following the study dose of vaccine) • Adverse Events (up to 30 days after the study dose of vaccine) • Serious adverse events during study participation • AESIs, including pIMDs, during study participation • Treated acute cell-mediated and/or antibody-mediated allograft rejection (clinical or biopsy-proven) within 60 days following the study dose of vaccine • Development of de novo donor-specific anti-HLA antibody within 90 days of the vaccine and up to 12-months post vaccine • Increase in pre-existing donor-specific anti-HLA antibody from study entry to 90 days post vaccine and up to 12-months post vaccine

Secondary, and Exploratory Endpoint(s)	**Secondary Endpoints** • Median and interquartile range of Roche Elecsys® anti-RBD antibody concentration at 30 days after the study dose of vaccine • Median and interquartile range of fold rise (FR) in Roche Elecsys® anti-RBD antibody concentration from baseline to 30 days after the study dose of vaccine • Median and interquartile range of Monogram pseudovirus antibody titers at 14 and 30 days after the study vaccine dose for selected variants of concern (prototype (Wuhan), beta, and omicron BA.1; additional alternative strains to be determined based on assay availability) • Median and interquartile range of fold rise (FR) in Monogram pseudovirus antibody titers from baseline to 14 and 30 days after the study vaccine dose for selected variants of concern (prototype (Wuhan), beta, and omicron BA.1; additional alternative strains to be determined based on assay availability) **Exploratory Mechanistic Immunogenicity Endpoints (up to 12-months post vaccine)** • Percentage of participants stratified by baseline antibody response (negative <0.8 U/mL, positive ≤500 U/mL, and >500-2500 U/mL) who reach an antibody concentration greater than 5000 U/mL (using the Roche Elecsys® anti-SARS-CoV-2 S assay) from before receiving the study dose of vaccine to 30 days after the study dose of vaccine • Longitudinal trajectory of antibody titers and measures of immunogenicity • NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay • SARS-CoV-2 virology, diagnostics, and sequencing (to classify viral strain) • Antigen specific B cell response assessed by flow cytometry, CyTOF, single cell multi-omics, and transcriptomics • Antigen-specific T cell response assessed by flow-cytometry, CyTOF, single cell multi-omics, and/or ELISPOT • B and T cell receptor VDJ repertoire analysis • Evidence of immune activation and metabolic profile by transcriptomics and cytokine signaling • Characterization and durability of de novo donor-specific anti-HLA antibody • A comparison of antibody levels attained (or percent neutralization) with matched historical control
Accrual Objective	The study will enroll a total of 80 evaluable kidney transplant recipients with an anti-RBD antibody concentration ≤ 2500 U/mL using the Roche Elecsys® anti-SARS-CoV-2 S assay after at least 2 doses of Moderna or Pfizer COVID-19 vaccine.
Study Duration	Accrual: 16 weeks Vaccination and Follow-up: 12 months Total Duration: 16 months
Treatment Description	A booster dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine, containing 5 µg protein antigen, consisting of a stabilized prefusion trimer of the SARS-CoV-2 B.1.351 variant S (spike) protein (referred to as the Sanofi-GSK COVID-19 vaccine).

Inclusion Criteria	Individuals must meet all the following criteria to be eligible: 1. Able to understand and provide informed consent. 2. Individual ≥ 18 years of age. 3. Recipient of kidney transplant ≥12 months prior to enrollment, without treated allograft rejection in the 6 months preceding enrollment. 4. Maintenance immunosuppressive regimen must include a calcineurin inhibitor (CNI), with or without low dose (≤5mg/day) prednisone or equivalent. 5. Received a completed primary series (3 doses) of mRNA vaccine (either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine) as specified in the respective package inserts. 6. Receipt a COVID-19 bivalent mRNA booster (Moderna or Pfizer-BioNTech) >30 days prior to enrollment. 7. Serum antibody concentration ≤ 2500 U/mL at ≥30 days from the last dose of mRNA COVID-19 vaccine and ≥30 days following receipt of a monoclonal antibody product or convalescent plasma for COVID-19, measured using the Roche Elecsys® anti-SARS-CoV-2 S assay. 8. Platelet count greater than 30,000/cu mm must be confirmed in participants with a known history of bleeding disorder or platelet count under 50,000/cu mm. 9. A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies: • Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile. **OR** • Is of childbearing potential and agrees to use an effective contraceptive method or abstinence for 12 weeks post vaccine and while taking mycophenolate mofetil/mycophenolic acid. *A participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 25 hours before any dose of study intervention.*
Exclusion Criteria	Individuals who meet any of the following criteria will not be eligible: 1. Recipient of any number of doses of any COVID vaccine product other than the Moderna COVID-19 vaccine or the Pfizer-BioNTech COVID-19 vaccine. 2. Recipient of any organ other than a kidney. 3. Known current or prior Donor Specific Antibody (DSA). 4. Any change in transplant immunosuppression regimen (drug or dose) in response to suspected or proven rejection within the last 6 months. 5. Known diagnosis of COVID-19 since last antibody test. 6. Receipt of a monoclonal antibody product or convalescent plasma within the last 30 days.

	7. Known history of hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to a vaccine containing any of the same substances. (components listed in Section 6, and the CoV2 and AS03 Investigator's Brochure). 8. Bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator's judgment. 9. Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided. 10. Receipt of any vaccine in the 30 days preceding the study vaccine or planned vaccines in the 30 days following the study vaccine. 11. Estimated Glomerular Filtration Rate <30mL/min/1.73m^2. 12. Receipt of any cellular depleting agent (e.g. ATG, Rituximab, Alemtuzumab, Cyclophosphamide) within 12 months preceding enrollment. 13. Receiving systemic immunomodulatory medication(s) for any condition other than transplant. 14. Any uncontrolled active infection. 15. Infection with HIV. 16. Maintenance immunosuppressive regimen that includes belatacept. 17. Recent (within one year) or ongoing treatment for malignancy, except for definitive surgical treatment of localized skin cancers. 18. Any known prior history of myocarditis or pericarditis, whether related to any vaccination or not. 19. Any unstable acute or chronic illness, treatments, or findings which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the candidate's ability to comply with study requirements or may impact the quality or interpretation of the data obtained from the study.
Pausing Rules	If the following occur, enrollment and study vaccination will be paused pending the results of an expedited DSMB review: • **Reactogenicity**: Any Grade 4 or higher reactogenic adverse event (AE) that is definitely or possibly related to the vaccine • **Allergy**: Two participants experiencing a Grade 3 or higher systemic allergic reaction that is definitely or possibly related to the vaccine • **Myocarditis and/or Pericarditis**: Any probable or confirmed case of either acute myocarditis or acute pericarditis that is at least possibly related to the vaccine. • **Acute Rejection:** Two participants with acute rejection (treated or biopsy proven AMR or ACR of any grade) occurring within 30 days of the study dose of vaccine • **Serious Adverse Reaction:** Any participants with a grade 4 or 5 serious adverse reaction that is definitely or possibly related to the vaccine. • **Death, Graft Loss or Need for Dialysis**: Any death, graft loss, or need for dialysis within 30 days of the study dose of vaccine

Study Contacts: Participating Centers

SITE PRINCIPAL INVESTIGATOR **JOHNS HOPKINS UNIVERSITY**	**SITE PRINCIPAL INVESTIGATOR** **EMORY UNIVERSITY**	**SITE PRINCIPAL INVESTIGATOR** **UNIVERSITY OF ILLINOIS-CHICAGO**
SITE PRINCIPAL INVESTIGATOR **UNIVERSITY OF WISCONSIN**	**SITE PRINCIPAL INVESTIGATOR** **UNIVERSITY OF CALIFORNIA, SAN FRANCISCO**	**SITE PRINCIPAL INVESTIGATOR** **UNIVERSITY OF CALIFORNIA, SAN DIEGO**

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Glossary of Abbreviations

CFR	Code of Federal Regulations
COP	Correlate of Protection
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
EUA	Emergency Use Authorization
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK	Glaxo Smith Kline
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
PI	Principal Investigator
pIMD	Potential Immune Mediated Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
SOT	Solid Organ Transplant
SUSAR	Serious Unexpected Suspected Adverse Reaction

Study Definitions Page

Acute Cellular-Mediated Rejection	A histologic event that meets the Banff 2017 criteria for acute cellular rejection.[58]
Acute Myocarditis / Acute Pericarditis	Myocarditis is inflammation of the heart muscle. Pericarditis is inflammation of the lining outside the heart. In this study, the definition of suspected or confirmed acute myocarditis or acute pericarditis is the Centers for Disease Control and Prevention (CDC) case definition criteria: https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm
Antibody-Mediated Rejection	A histologic event that meets the Banff 2017 criteria for antibody mediated rejection.[58]
Biopsy-Proven Rejection	Histologic evidence of rejection on biopsy meeting Banff 2017 criteria.[58]
Donor Specific Antibodies (DSA)	Antibodies directed donor human leukocyte antigens (HLA). Identification of DSA will be carried out at a central laboratory; see lab manual.
Estimated Glomerular Filtration Rate (eGFR)	eGFR will be calculated using the Chronic Kidney Disease Epidemiology equation (CKD-EPI): $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]
Evaluable Participant	Participant who has a baseline SARS-CoV-2 S antibody level ≤2500 U/mL performed by the central lab using the Roche Elecsys assay.
Graft Failure (Kidney)	Any of the following events: renal dialysis of more than 3 months duration; listing for re-transplantation; death with functioning graft.
Lost to Follow-up	Missing sequential visits including the final visit.
Medical Monitor	The physician who is responsible for Sponsor oversight of safety aspects of the trial. The medical monitor will determine the attribution of Serious Adverse Events after considering all investigator input.
Negative Antibody Response	A measurement of <0.8 U/mL using the Roche Elecsys® anti SARS-CoV-2 S assay.
NIAID Project Manager	NIAID assigned project manager who is responsible for all day to day protocol related issues, including version control, consent review, etc.
Principal Investigator	The physician responsible for supervising the conduct of the clinical investigation and to protecting the rights, safety, and welfare of participants consistent with 21 CFR Part 312.
Participant Premature Termination	Participants who are lost to follow up, withdraw consent, or die during the study. Data and specimens will no longer be expected from participants who are terminated from the study.
Program Officer	NIAID official who oversees the programmatic and budgetary aspects of the grant.
Low Antibody Response (entry criterion)	A measurement of ≤2500 U/mL using the Roche Elecsys® SARS-CoV-2 anti-SARS-CoV-2 S assay.

Protocol Mandated Procedures	A procedure or intervention that is a study requirement at the specified time point in the protocol.
Regulatory Affairs Officer	NIAID-assigned officer responsible for regulatory aspects of the study.
Sanofi-GSK COVID-19 vaccine	Monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine.
Significant Graft Dysfunction	Estimated Glomerular Filtration Rate less than 30mL/min/1.73m^2.
Site Principal Investigator	Lead investigator listed on the FDA Form 1572 at a particular clinical site who is responsible for the conduct of the study at that site.
Study Therapy	The investigational product is a booster dose of the Sanofi-GSK COVID-19 vaccine, containing 5 µg protein antigen, consisting of a stabilized prefusion trimer of the SARS-CoV-2 B.1.351 variant S (spike) protein.
Treated Rejection	Any clinical event, with or without supporting evidence from a biopsy, which the treating physician diagnosis as “rejection” AND for which the patient is treated with steroids, lytic therapy, or an increase in dose or number of immunosuppressive medications.

1. Background and Rationale

1.1 Background and Scientific Rationale

COVID-19 has a disproportionate impact on vulnerable populations, including those with impaired immune defenses. Organ transplant recipients are particularly at risk as a result of both the need for life-long immunosuppressive therapy to prevent rejection and a high prevalence of other risk factors for severe COVID-19 including cardiovascular disease, hypertension, and diabetes. The consequences of COVID-19 are severe in organ transplant recipients; in one study of a large (n=482) cohort of patients who had a confirmed diagnosis of COVID-19 by polymerase chain reaction, 78% were hospitalized, and of those, 39% required ICU care and 31% required mechanical ventilation. Mortality at 28 days from diagnosis was 17.8% overall and 20.5% among those who were hospitalized. Risk factors for mortality included age >65 years, congestive heart failure, chronic lung disease and obesity.[1-5]

Several, currently available, SARS-CoV-2 vaccines are highly immunogenic and effective in the general population.[6-8] Transplant recipients were largely excluded from landmark trials, but it has become evident during the post-EUA experience that the response to vaccination is substantially lower among organ transplant recipients as compared to the general population; in a cohort of 436 transplant recipients who had received two doses of either the Moderna COVID-19 vaccine or the Pfizer-BioNTech COVID-19 Vaccine, a positive anti-spike response was detectable in only 17% after the first dose and 30-60% after two doses in multiple studies.[9] Associations with suboptimal vaccine response include treatment with antimetabolite therapies such as mycophenolate or azathioprine, which are known to impair lymphocyte function and response to new antigens (such as influenza vaccination).[9-11]

The NIAID-sponsored COVID Protection After Transplant Pilot (CPAT-P) trial characterized the safety and immunogenicity of a third dose of mRNA COVID vaccine in clinically stable, SARS-CoV-2 kidney transplant recipients. These recipients were either seronegative (<0.8 U/ml) or a had a low (< 50 U/ml) seroresponse on the Roche Elecsys® anti-SARS-CoV-2 S immunoassay. Reactogenicity and safety including any potential alloimmune events were prospectively monitored; there were no vaccine-related serious adverse events, rejection episodes, nor episodes of de novo or increasing donor specific antibody.

Binding antibody responses after a third dose in the CPAT-P trial rose to a median (IQR) of 386 (8-2331) U/ml overall, with much more robust responses among those seropositive at baseline: median (IQR) 2331 (712-4390), while 46% of those seronegative at baseline remained seronegative, with overall 30 day median response of 10 (<0.4-132) U/ml. Day 30 anti-RBD antibody concentrations were negatively associated with mycophenolate use and proximity to transplant.

It is critical to better understand risk factors for vaccine failure given mounting reports of serious breakthrough infections in fully vaccinated SOT recipients.[13] Persistent knowledge gaps include full characterization of humoral vaccine responses (e.g., level and durability of neutralizing antibody, including versus novel variants), B cell memory responses, and antigen-specific T cell responses in transplant recipients.[14-16] Strategies to improve vaccine response to viral antigens in immunocompromised persons are largely based on experiences with influenza and hepatitis B vaccines; these include administration of additional vaccinations, higher antigen dosing, and mixing of vaccine platforms such as those containing immunostimulatory adjuvants.[17-20] Development of a strategy for eliciting an antibody response to COVID

vaccines in transplant recipients is complex as the pharmacologic immunosuppression that prevents response to the vaccine also prevents rejection of a life-sustaining allograft.[21] Potential interventions include alternate vaccine strategies including higher doses of vaccine or the use of adjuvanted vaccines. A decision algorithm for an individual patient must consider the likelihood of success of a low risk intervention (i.e. an additional dose of vaccine), the type of transplant (e.g. kidney, heart or lung), the likelihood and consequences of allograft rejection if the patient's immunosuppressive regimen is modified (e.g. the low likelihood of permanent injury after an episode of liver rejection versus the high likelihood of permanent injury after an episode of lung rejection), and the individual's risk for severe disease or death from COVID-19 if they have persistently low antibody responses to vaccination.

Compounding the issues with limited immunogenicity in transplant patients, new, highly transmissible SARS-CoV-2 variants of concern have emerged and are spreading globally.[22] The Alpha (B.1.1.7) variant first identified in the United Kingdom (UK) has been shown to be more transmissible and has since been detected in many other countries around the world.[23] Other variants of concern have emerged which were first identified in South Africa (Beta [B.1.351] variant, and later, the Omicron[B.1.1.529] variant), Brazil (Gamma [P.1] variant), and India (Delta [B.1.617.2] variant) have been detected in other countries.[22] A key question is whether currently authorized and available COVID-19 vaccines will be able to protect against infection or disease from these variants. Recent preliminary data using an adjuvanted protein sub-unit vaccine (Novavax) and the ChAdOx1 nCoV-19 vaccine (AZD1222 [Oxford University/AstraZeneca]) showed lower efficacy against mild to moderate COVID-19 in South Africa where the Beta (B.1.351) variant predominated, compared to the efficacy observed for these vaccines in studies conducted in the UK where Alpha (B.1.1.7) variant predominated.[24-27] However, data from the Ad26CoV2.S vaccine (Janssen) showed efficacy against symptomatic disease in South Africa suggestive of some evidence for the prototype vaccines to confer protection against the Beta (B.1.351) variant.[26,27] Sera from individuals immunized with prototype COVID-19 vaccines show an ability to neutralize the variants but to a lesser extent than the prototype strain.[28,29] This decrease in neutralization was considerable against the South African Beta (B.1.351) variant which has a characteristic E484K mutation in the receptor-binding domain along with other mutations in the N-terminal domain of the Spike (S) protein.[28-30] In late 2021, the initial new Omicron (B.1.1.529) variant emerged which is characterized by 15 mutations in the receptor-binding domain of the viral spike protein, and 15 additional mutations and 3 small deletions and a small insertion elsewhere in the spike protein. Accompanying these extensive mutations, there was an even more pronounced decrease in neutralization against the Omicron (B.1.1.529) variant in sera from COVID-19 vaccinees. These findings have led to development of variant strain vaccines and regulatory guidance for the development of vaccines against the variant strains for products that have already demonstrated efficacy with the prototype vaccines.[31-35] There has been particular emphasis on developing vaccines with the potential to induce broad cross-neutralizing antibody responses against multiple variants of concern. Real-world data from the UK has shown a modest decrease in vaccine effectiveness against symptomatic COVID-19 caused by the delta variant compared to the alpha variant in participants receiving two doses of the ChaAdOx-1 and BNT162b2 nCoV-19 vaccines which encode the parental D614 variant S protein sequence.[28,29] Preliminary data from Israel show a high level of vaccine effectiveness against hospitalization and severe disease at a time when the Delta (B.1.617.2) variant is prevalent in individuals who received 2 doses of the BNT-162b2 vaccine.[36] These data suggest that parental D614 vaccines provide significant, albeit lower magnitude of protection against the Delta (B.1.617.2) variant. Ongoing evolution of SARS-CoV-2 variants, especially in light of the

growing prevalence of vaccination and the selection pressure that this may exert, raises the strong public health requirement for SARS-CoV-2 vaccines, including those protective against emergent variants of concern.

To address the medical need caused by this pandemic, Sanofi Pasteur initiated development of a recombinant protein vaccine consisting of a stabilized prefusion trimer of the SARS-CoV-2 S protein based on the work by Wrapp and colleagues.[37] The recombinant protein vaccine is used in combination with GSK's adjuvant system, named AS03, to optimize the immune response.[33-35] A monovalent vaccine with the S protein sequence from the original variant (first identified in Wuhan) with D614 in the receptor-binding domain of the S protein was developed.[37] To combat the emergence of variant strains, Sanofi Pasteur has also been evaluating vaccine formulations containing recombinant prefusion delta TM proteins encoding the S protein sequence, including Beta (B.1.351) variant.[38]

In order to address the issues of poor immunogenicity in transplant patients and the emergence of new variants, this study will investigate the effect of a booster dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine in immunologically stable kidney transplant recipients who demonstrate a persistently low (≤ 2500 U/mL) immune response to the strains employed in the initial mRNA COVID-19 vaccines, following a minimum of two mRNA COVID-19 vaccine doses.

Rationale for Selection of Investigational Product or Intervention

Sanofi Pasteur's CoV2 preS dTM-AS03 vaccine is being developed in the setting of a pandemic for the active immunization and prevention of SARS-CoV-2 infection and COVID-19 disease. The initial intended use of the vaccine is for adults, 18 years of age and older.

The candidate antigen is a stabilized prefusion trimer of the SARS-CoV-2 S protein. The coronavirus S protein is the major viral envelope glycoprotein and mediates attachment and entry into host cells. The S protein precursor is cleaved to form non-covalently associated subunits, S1 and S2.[12] The S protein appears on the surface of the virus as a mushroom-like structure, containing a cap of three S1 subunits and a stem of three S2 subunits. The S1 subunit contains the receptor binding domain (RBD), which attaches to the host cellular receptor. In the case of SARS-CoV-2, the receptor is Angiotensin Converting Enzyme-Related Peptidase 2 (ACE2), a membrane-bound carboxypeptidase localized to vascular endothelial as well as epithelial surfaces.[43] The RBD is a major antigenic target for immune responses. The S2 domain contains the fusion peptide and transmembrane regions. Upon binding to the cellular receptor, S1 is cleaved from the virus and the S2 subunit undergoes a conformational change to mediate viral membrane fusion with the host cell membrane.

Prior research with Middle East Respiratory Syndrome (MERS)-CoV identified that the introduction of double proline substitutions (2P) at the beginning of the central helix of the S2 subunit could stabilize the structure and prevent conformational changes in the S trimer. When used to immunize mice, the MERS-CoV 2P construct was associated with improved breadth and potency of neutralizing responses compared to monomeric MERS-CoV S1 or wild-type S. This strategy was identified as being of general relevance to betacoronaviruses, which include HCoV-OC43, MERS-CoV, and SARS-CoV-1, and by extrapolation to SARS-CoV-2. The prefusion stabilized SARS-CoV-2 Spike construct to be evaluated in the current study is based on this research.[44]

The S1 subunit and RBD of the prefusion SARS-CoV-2 Spike antigen used in this vaccine is similar in sequence to the Spike antigens encoded by the mRNA vaccine constructs that have been shown to induce neutralizing antibody responses and confer robust efficacy against COVID-19[24,26], suggesting that other vaccines capable of inducing similar levels of neutralizing antibodies may also provide protection.

The antigen of the CoV2 preS dTM vaccine is manufactured using the same expression system technology as is used to manufacture a recombinant quadrivalent influenza vaccine (rQIV), licensed in the US and EU and commercialized as Flublok® and Supemtek®, respectively for the prevention of influenza in adults 18 years of age and older.[24] In this manufacturing platform, the gene of interest is cloned into a baculovirus transfer vector, which is used to form recombinant baculoviruses. The viral stock is used to infect an insect cell line (expresSF+). The recombinant protein is expressed in the infected insect cells. After incubation, the recombinant protein is purified by a series of filtration and chromatography steps. This process is adaptable to manufacture a variety of antigens. Millions of doses of recombinant influenza vaccine (trivalent and quadrivalent formulations) have been administered since its approval in the US for human use corresponding to hemagglutinins (HAs) of different influenza strains (H1, H3, and B) covering multiple influenza seasons. Additionally, the process has previously been applied to the development of candidate SARS-CoV-1 vaccines. Following the SARS outbreak, candidate S protein vaccines were developed, including a full-length S protein and a transmembrane-deleted ectodomain antigen. These were tested in a variety of preclinical models and found to induce neutralizing antibody responses in mice and ferrets and to be partially protective in a ferret challenge model.

The magnitude and quality of the immune response to the candidate antigen will be enhanced through delivery with an adjuvant. Previous clinical trials with rH5 HA and rH7 HA pandemic antigens in naïve individuals show that a 2-dose immunization regimen of antigen was poorly immunogenic in comparison to antigen delivered with an adjuvant.[45] This may allow for titration of the amount of antigen used and, thus, be antigen-sparing and potentially increase the available supply of antigen doses.

AS03 is an oil-in-water emulsion containing α-tocopherol and squalene. Safety of AS03-adjuvanted products has been extensively evaluated and found to be generally well tolerated with an acceptable safety profile.[46] AS03 has been approved as a component of Pandemrix and Arepanrix, two H1N1 pandemic influenza vaccines. AS03 was also evaluated with pandemic H7 rHA in humans, demonstrating robust neutralizing antibody responses and hemagglutination inhibition, together with an acceptable safety profile. As has been the case for several pandemic agents, unadjuvanted H7 HA-containing influenza vaccines were poorly immunogenic.[47,48] In addition to a Phase I/II study using the Sanofi-GSK CoV2 preS dTM antigen with AS03-adjuvanted system (NCT04537208),[49] AS03 has also been used in combination with other AS03-adjuvanted recombinant S proteins (Medicago [NCT04450004] and Clover Biopharmaceuticals [NCT04405908]).[50]

A potential theoretical safety issue with coronavirus vaccines is the ability to potentiate immunopathology in vaccinees upon exposure to wild-type virus,[51] called vaccine associated enhanced disease (VAED). The theoretical molecular mechanism for this phenomenon is not fully understood. In the context of coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with

functional characteristics such as binding to particular Fc receptors, and the nature of the Th cell response.[51-53] It is anticipated that the design of the candidate CoV2 preS dTM antigen selected for this study will promote generation of robust neutralizing antibodies over binding but non-neutralizing antibodies, based on data generated with other coronavirus vaccine antigens.[44] The inclusion of adjuvanted formulation is anticipated to further enhance the magnitude of neutralizing antibody responses and induce balanced Th1/Th2 cell responses.[45,54] Taken together, these strategies mitigate by design the theoretical risks of immune enhancement of viral infection. No evidence for Vaccine-Associated Enhanced Disease (VAED)/ Vaccine-Associated Enhanced Respiratory Disease (VAERD) has been observed with the Sanofi-GSK vaccine to date.[38,41]

This single-arm trial will administer a single dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine to kidney transplant recipients who demonstrate a persistently low (≤ 2500 u/mL) anti-spike antibody response after completion of at least two doses of either the Moderna COVID-19 Vaccine or the Pfizer-BioNTech Vaccine, as described in their respective Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs).

1.2 Preclinical Experience

Preclinical studies in mice and in non-human primates (NHP) were performed in order to provide an assessment of vaccine immunogenicity. The studies indicated that the CoV2 preS dTM vaccine formulated with AS03 induced high S-specific immunoglobulin G (IgG) and SARS-CoV-2 neutralizing responses in mice and NHPs, with evidence of a potent adjuvant-effect of AS03 as well as a robust recall response after the second injection. Humoral responses were generally similar or higher than levels observed in human convalescent sera. Cell-mediated immune (CMI) responses suggest a mixed Th1/Th2 profile, with no evidence of Th17 responses. These studies supported the first-in human Phase I/II study. There are no specific preclinical studies addressing whether and how these effects of immunization schedule on vaccine-induced immunity are affected by the immunosuppressant medications used in transplantation.[39,40]

1.3 Clinical Studies

A Phase I/II study in healthy adults 18 years of age and older to evaluate the safety and immunogenicity of the recombinant CoV2 prefusion Spike delta TM (CoV2 preS dTM) monovalent D614 vaccine adjuvanted with the AS03 or AF03 adjuvants was initiated in September 2020 and is currently ongoing. Interim results from this Phase I/II study showed lower than expected immunogenicity in combination with higher than expected reactogenicity.[38] The effective antigen dose levels administered in a 0.5 mL vaccine dose in this study were 1.3 µg (Low Dose) and 2.6 µg (High Dose) of functional SARS-CoV-2 preS protein with differences between the targeted and the effective antigen dose levels corresponding to an excess of Host Cell Protein (HCP) content in the clinical materials (recalculated HCP content, 3.7 µg and 12.4 µg). These data indicated that assessment of optimized antigen formulations (with higher antigen dose and lower HCP content) is necessary to select an antigen dose to progress to Phase III evaluation. Following the VAT00001 study, the manufacturing process had been further developed increasing the purity of the vaccine candidate to > 90% for the Phase II and Phase III clinical materials.[32]

In a Phase II study (VAT00002 [NCT04762680]) designed as a dose-finding, safety and immunogenicity study (hereafter referred to as the Original Cohort of VAT00002), the CoV2 preS dTM (D614) + AS03 vaccine candidate at three different antigen concentrations was administered as a two-dose primary series to a

total of 722 previously unvaccinated adults. Neutralizing antibody seroconversion was observed in 95% to 100% of participants following a second injection in all adult age groups (18 to 95 years old) across all formulations and doses (antigen dosages of 5, 10, and 15 µg).[41] These results served as the basis for selecting a 10 µg antigen formulation for a primary vaccination series in the Phase 3 trial VAT00008 (NCT04904549), which is being conducted in two stages, and for selecting a 5 µg antigen formulation for booster vaccination in a Phase III evaluation of prototype and modified protein vaccine boosters as part of an amendment to VAT00002. Stage One of the efficacy 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 year 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.

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 an externally sponsored, randomized, blinded clinical study evaluating the safety and immunogenicity of heterologous boosting with Sanofi-GSK monovalent CoV2 preS dTM (Beta) and monovalent (D614) following a 2-dose primary series of BNT162b2 compared to a homologous BNT162b2 third dose (NCT05124171), the Sanofi-GSK Beta vaccine elicited higher neutralizing antibody response against SARS-CoV-2 D614G, Beta, Delta and Omicron BA.1 variants compared with boosting with the BNT162b2 vaccine or the Sanofi-GSK D614 vaccine candidate. This study, which included 223 participants in the per-protocol population, also found that all three boosters were well tolerated and no safety concerns were identified during the conduct of the study.[42]

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 µg] 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.[43]

2. Study Hypotheses/Objectives

2.1 Hypotheses

Kidney transplant recipients who had a persistently low anti-SARS-CoV-2 S response (using the Roche Elecsys® assay) to a completed primary series and bivalent booster of prior mRNA COVID-19 vaccine will develop an increased SARS-CoV-2 antibody response after receiving a dose of the Sanofi-GSK COVID-19 vaccine, containing 5μg of recombinant protein antigen.

2.2 Primary Objective(s)

The primary objective is to determine whether a booster dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine will elicit an increased SARS-CoV-2 antibody response in participants who have failed to maintain an antibody titer >2500 U/mL (using the Roche Elecsys® anti-RBD assay) to a completed primary series and bivalent booster of mRNA based COVID-19 vaccine.

2.3 Safety Objectives

- To determine the incidence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs), including potential immune mediated diseases (pIMDs), following the study dose of vaccine.
- To determine the incidence of alloimmune events (e.g., kidney rejection and development of de novo DSA) following the study dose of vaccine.

2.4 Key Secondary Objectives

- To evaluate the proportion of participants who reach an antibody concentration greater than 5000 U/mL at 30 days following the study dose of vaccine.
- To assess the fold rise (FR) in antibody concentration (using the Roche Elecsys® anti-SARS-CoV-2 S assay) from baseline to 30 days after the study dose of vaccine.
- To assess the change in neutralizing antibody titers to the prototype and important diverse variants of concern using the Monogram pseudovirus assay from baseline to 14 and 30 days after the study dose of vaccine.

2.5 Exploratory Mechanistic Objectives

- To identify and evaluate candidate immunologic correlates of vaccine response.
- To evaluate immune activation in response to the vaccine.

3. Study Design

3.1 Description of Study Design

This is an open label, non-randomized pilot study in kidney transplant recipients who received a completed primary series and bivalent booster of mRNA based COVID-19 vaccine and have up to 2500 U/mL SARS-CoV-2 S antibody response using the Roche Elecsys® anti-RBD assay. Up to 80 participants will be enrolled and eligible participants will receive a dose of the Sanofi-GSK COVID-19 vaccine. Participants will be followed for 1-year post study vaccine per Appendix 1.

Recommendations to the public made by federal agencies, such as the Centers for Disease Control, are continually being updated based on the current state of the SARS-CoV-2 pandemic e.g., new variants. If meeting the current enrollment target is no longer feasible due to the dynamic state of the pandemic and available vaccines/therapies, enrollment will be halted and participants will be followed per protocol.

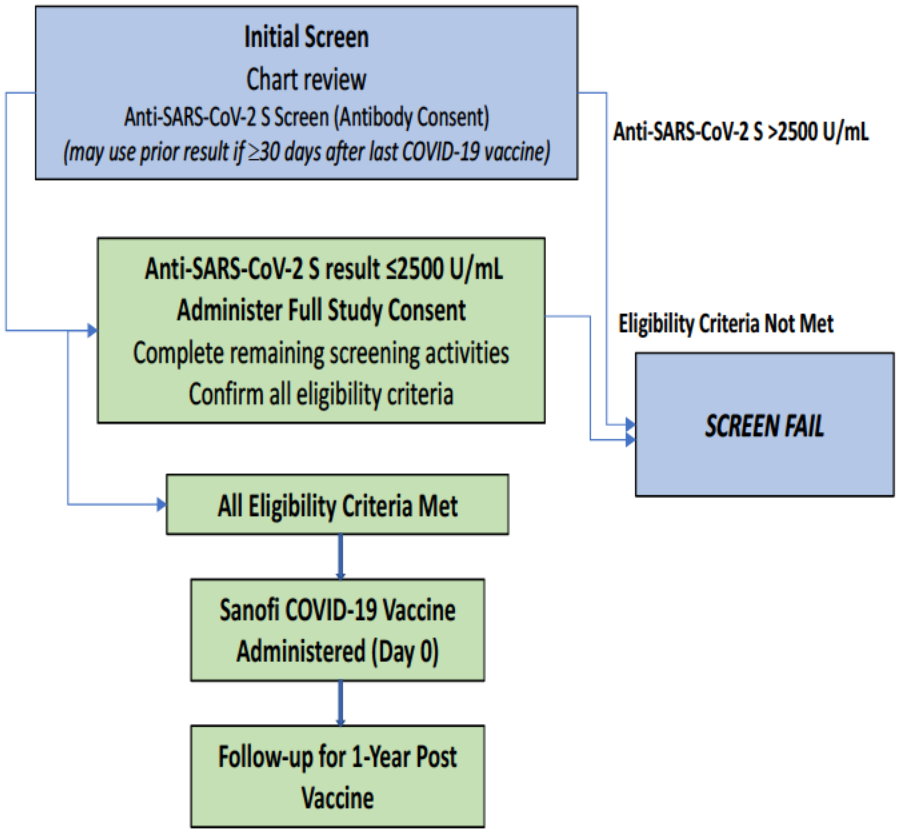


Figure 1. *Study Design Diagram*

3.2 Primary Immunogenicity Endpoint

The primary endpoint is the proportion of participants who reach a SARS-CoV-2 S antibody level >5000 U/mL (using the Roche Elecsys® anti-RBD assay) at 30 days following a dose of the Sanofi-GSK COVID-19 vaccine.

3.3 Safety Endpoints

- Composite endpoint composed of any of the following events occurring within 30 days following the study dose of vaccine: death, graft loss, need for dialysis, and acute rejection
- Components of the composite safety endpoint (death, graft loss, need for dialysis, acute rejection) within 30 days and 60 days of the study dose of vaccine
- Solicited local and systemic vaccine reactogenicity (collected for 7 days following the study dose of vaccine)
- Adverse Events (up to 30 days after the study dose of vaccine)
- Serious adverse events during study participation
- AESIs, including pIMDs, during study participation
- Treated acute cell-mediated and/or antibody-mediated allograft rejection (clinical or biopsy-proven) within 60 days following the study dose of vaccine
- Development of de novo donor-specific anti-HLA antibody within 90 days of the vaccine and up to 12-months post vaccine
- Increase in pre-existing donor-specific anti-HLA antibody from study entry to 90 days post vaccine and up to 12-months post vaccine

3.4 Secondary Endpoints

- Median and interquartile range of Roche Elecsys® anti-RBD antibody concentration at 30 days after the study dose of vaccine
- Median and interquartile range of fold rise (FR) in Roche Elecsys® anti-RBD antibody concentration from baseline to 30 days after the study dose of vaccine
- Median and interquartile range of Monogram pseudovirus antibody titers at 14 and 30 days after the study vaccine dose for selected variants of concern (prototype (Wuhan), beta, and omicron BA.1; additional alternative strains to be determined based on assay availability)
- Median and interquartile range of fold rise (FR) in Monogram pseudovirus antibody titers from baseline to 14 and 30 days after the study vaccine dose for selected variants of concern (prototype (Wuhan), beta, and omicron BA.1; additional alternative strains to be determined based on assay availability)

3.5 Exploratory Mechanistic Immunogenicity Endpoints (up to 12-months post vaccine)

Exploratory mechanistic immunogenicity endpoints may include:

- Percentage of participants stratified by baseline antibody response (negative <0.8 U/mL, positive ≤500 U/mL, and >500-2500 U/mL) who reach an antibody concentration greater than 5000 U/mL (using the Roche Elecsys® anti-SARS-CoV-2 S assay) from before receiving the study dose of vaccine to 30 days after the study dose of vaccine
- Longitudinal trajectory of antibody titers and measures of immunogenicity
- NIAID-VRC MSD 3 plex (Wu-1 full-length spike, RBD, and N proteins) assay
- SARS-CoV-2 virology, diagnostics, and sequencing (to classify viral strain)
- Antigen specific B cell response assessed by flow cytometry, CyTOF, single cell multi-omics, and transcriptomics

- Antigen-specific T cell response assessed by flow-cytometry, CyTOF, single cell multi-omics, and/or ELISPOT
- B and T cell receptor VDJ repertoire analysis
- Evidence of immune activation and metabolic profile by transcriptomics and cytokine signaling
- Characterization and durability of de novo donor-specific anti-HLA antibody
- A comparison of antibody levels attained (or percent neutralization) with matched historical control

4. Selection of Participants and Clinical Sites/Laboratories

4.1 Rationale for Study Population

Participants who received two or more doses of the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine and have SARS-CoV-2 S antibody concentration ≤2500 U/mL (using the Roche Elecsys® anti-RBD assay) will be enrolled in this study. This group of patients is at high risk for severe COVID-19 disease due to pharmacologic immunosuppression and a high prevalence of non-transplant risk factors such as obesity and diabetes.

The threshold of Roche Elecsys® anti-RBD assay ≤2500 U/ml SARS-CoV-2 S antibody concentration has been chosen to reflect the low prevalence of Omicron BA.1 neutralizing antibodies among vaccinated organ transplant candidates with anti-RBD ≤ 1000 U/ml[55] and estimates that the subsequent Omicron BA.4/5 neutralizing titers are still lower, perhaps by 1.5 to 5 fold.[56] Thus, the study population is anticipated to be enriched in participants with relatively weak or absent detectable neutralizing antibodies to the current or subsequent related strains.

4.2 Inclusion Criteria

Individuals who meet all the following criteria are eligible for enrollment as study participants:

1. Able to understand and provide informed consent.
2. Individual ≥ 18 years of age.
3. Recipient of kidney transplant ≥12 months prior to enrollment, without treated allograft rejection in the 6 months preceding enrollment.
4. Maintenance immunosuppressive regimen must include a calcineurin inhibitor (CNI), with or without ≤5mg/day prednisone or equivalent.
5. Received a completed primary series (3 doses) of mRNA vaccine (either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine) as specified in the respective package inserts.
6. Receipt a COVID-19 bivalent mRNA booster (Moderna or Pfizer-BioNTech) >30 days prior to enrollment.
7. Serum antibody titer up to 2500 U/mL at ≥30 days from the last dose of mRNA COVID-19 vaccine and ≥30 days following receipt of a monoclonal antibody product or convalescent plasma for COVID-19, measured using the Roche Elecsys® anti-SARS-CoV-2 S assay.
8. Platelet count greater than 30,000/cu mm must be confirmed in participants with a known history of bleeding disorder or thrombocytopenia (platelet count <50,000/cu mm).
9. A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:
    - Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile.

      OR
    - Is of childbearing potential and agrees to use an effective contraceptive method or abstinence for 12 weeks post vaccine and while taking mycophenolate mofetil/mycophenolic acid.

    A participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 25 hours before any dose of study intervention.

4.3 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Recipient of any number of doses of any COVID vaccine product other than the Moderna COVID-19 vaccine or the Pfizer-BioNTech COVID-19 vaccine.
2. Recipient of any organ other than a kidney.
3. Known current or prior Donor Specific Antibody (DSA).
4. Any change in transplant immunosuppression regimen (drug or dose) in response to suspected or proven rejection within the last 6 months.
5. Known diagnosis of COVID-19 since last antibody test.
6. Receipt of a monoclonal antibody product or convalescent plasma within the last 30 days.
7. Known history of hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to a vaccine containing any of the same substances. (components listed in Section 6, and the CoV2 and AS03 Investigator's Brochure).
8. Bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator's judgment.
9. Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided.
10. Receipt of any vaccine in the 30 days preceding the study vaccine or planned vaccines in the 30 days following the study vaccine.
11. Estimated Glomerular Filtration Rate <30mL/min/1.73m^2.
12. Receipt of any cellular depleting agent (e.g. ATG, Rituximab, Alemtuzumab, Cyclophosphamide) within 12 months preceding enrollment.
13. Receiving systemic immunomodulatory medication(s) for any condition other than transplant.
14. Any uncontrolled active infection.
15. Infection with HIV.
16. Maintenance immunosuppressive regimen that includes belatacept.
17. Recent (within one year) or ongoing treatment for malignancy, except for definitive surgical treatment of localized skin cancers.
18. Any known prior history of myocarditis or pericarditis, whether related to any vaccination or not.
19. Any unstable acute or chronic illness, treatments, or findings which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the candidate's ability to comply with study requirements or may impact the quality or interpretation of the data obtained from the study.

4.4 Selection of Clinical Sites

4.4.1 Selection of Clinical Site

This is a multicenter study utilizing clinical sites that have a cohort of potential study participants based on prior NIAID funded COVID-19 transplant studies.

5. Known and Potential Risks and Benefits to Participants

Information related to administration of a heterologous dose of vaccine to immunocompromised transplant recipients is scarce and anecdotal. The risks cited below reflect the experience in the prior studies utilizing the Sanofi-GSK monovalent (D614) CoV2 preS dTM-AS03 COVID-19 vaccine, bivalent CoV2 preS dTM-AS03 COVID-19 vaccine, and monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 vaccine.

5.1 Risks of the Investigational Products as cited in the Investigator Brochure

5.1.1 Risks of Sanofi-GSK COVID-19 vaccine

The most common side effects reported include injection site reactions (pain, redness and swelling), malaise, myalgia, headache, nausea, and diarrhea. Fever and chills were reported but less common. Most side effects occurred within 3 days of the vaccine and resolved within one week.

In general for all vaccines, there is a risk of anaphylactic reactions, vasovagal reactions or psychogenic reactions. Severe allergic reactions e.g., anaphylaxis were extremely rare in the Phase I-III studies conducted by Sanofi Pasteur.

Infrequent cases of myocarditis or pericarditis have been reported after the use of COVID-19 vaccines containing the SARS-CoV-2 S-antigen. Myocarditis and pericarditis have been reported in greatest numbers in males under the age of 40 years following a second dose of mRNA vaccines, but cases have been reported in older males and in females as well, and also following other doses, and other vaccine platforms, including after doses of an adjuvanted protein vaccine. The observed risk is highest in males 12 to 17 years of age. While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolve in most individuals with conservative management. Information is not yet available about potential long-term sequelae. The risk in children younger than 12 years old is currently being assessed, and both the size of the database and length of follow-up in this population are relatively smaller than that of those older than 12 years old. Therefore, the characterization of the risk in children younger than 12 years old is not as well-known as in adolescents and adults.

Because the Sanofi-GSK COVID-19 vaccine contains the SARS-CoV-2 Spike protein (S-antigen), there may be a risk of myocarditis or pericarditis following vaccination with the Sanofi GSK COVID-19 vaccine. According to the Sanofi IB, myocarditis and pericarditis are adverse events of special interest; no cases of myocarditis or pericarditis after Sanofi-GSK COVID-19 vaccination are noted in the Sanofi IB.

pIMDs : Based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, pIMDs are AESIs undergoing special safety monitoring for adjuvanted vaccines. pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology. pIMD is an AESI and will be collected over the duration of each participant’s study participation. No evidence for excess pIMD events have been observed in reported studies.

There is a theoretical concern for all COVID-19 vaccines for the vaccine to predispose to enhanced COVID-19 infection, sometimes also referred to as Vaccine Associated Enhanced Disease (VAED), in vaccine recipients, although this has not been seen in available data from the mRNA platforms, adenoviral vector , or in the experience with the Sanofi-GSK adjuvanted COVID-19 vaccine formations according to the Sanofi IB.

There is also a theoretical concern that adjuvanted vaccines may elicit or exacerbate autoimmune responses, leading to development or exacerbation of pre-existing immune-mediated diseases, although this has not been seen with the Sanofi-GSK adjuvanted COVID-19 vaccines formulations according to the Sanofi Investigator Brochure (IB).

During the informed consent process, the participants enrolling in the study will be informed of the potential risk of pIMD and other side effects and the need to attend the clinic if they are unwell.

There will be an observation period after vaccination and blood sample collection for early detection and treatment of any anaphylactic, vasovagal, or psychogenic reaction. Appropriate trained personnel, medical equipment and emergency medications, including epinephrine (1:1000), must be available at the study site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

5.1.2 Risks of Sanofi-GSK COVID-19 vaccine in Adults as Cited in Medical Literature

Based on Goepfert et al, an earlier version of the Sanofi-GSK (D614) was more reactogenic than expected; this was attributed to higher than intended levels of remnant host protein and prompted formulation revision.[38] In a dose-finding study, Sridhar et al found acceptable safety and reactogenicity.[41] No evidence for Enhanced COVID-19 (Vaccine Associated Enhanced Disease/Vaccine Associated Enhanced Respiratory Disease) was observed in either study.

5.1.3 Potential Risks to Study Population

Based on currently available information, the risk of serious allergic events is low, though the majority of participants in prior studies were immunocompetent.

5.2 Risks of Other Protocol Specified Medications

There are no other protocol specified medications.

5.3 Risks of Study Procedures

5.3.1 Risk of Blood Draw

Collection of blood may cause slight discomfort, pain, bleeding or bruising at the injection site. Rarely, fainting or infection may occur.

There is also a theoretical risk that a participant may be exposed to other SARS-CoV-2 infected individuals, which will be mitigated by appropriate local infection control measures e.g., minimize contact with other individuals in the clinic and appropriate personal protective equipment.

5.3.2 Risks Associated with Nasopharyngeal Swab Collection

Nasal swab collection may cause localized discomfort. Rarely, mild epistaxis may occur.

5.3.3 Risk of Internet Based Data Collection

Data from this study will be entered into a computerized database through a secured web site. All information will be saved and transmitted in a coded form. Only authorized personnel requiring a password will be permitted to enter data. There is risk, although minimal, of unauthorized persons obtaining confidential information.

5.4 Potential Benefits

There may be no benefit to participants in this study.

Study participation and study conduct are considered fundamental from the societal perspective towards the goal of finding vaccines to help control the pandemic and decrease both the individual and public health burdens of COVID-19 illness and SARS-CoV-2 infection.

In Stage 2 of the Phase 3 COVID-19 vaccine trial VAT00008 of more than 13,000 participants 18 and above years of age, the Sanofi-GSK Beta-containing vaccine candidate demonstrated an efficacy of 64.7% (95% confidence interval [CI, 46.6, 77.2]) against symptomatic COVID-19 and 72% efficacy (95% confidence interval [CI, 45.8, 86.6]) in Omicron-confirmed symptomatic cases (sequencing was performed for 71 cases out of 121 total cases to date).

In previously seropositive populations, the Sanofi-GSK COVID-19 vaccine candidate demonstrates an overall efficacy of 75.1% (95% confidence interval [CI, 56.3, 86.6]) against symptomatic infection, and 93.2% (95% confidence interval [CI, 73.2, 99.2]) in Omicron-confirmed symptomatic cases, according to the sequencing analysis performed to date. Throughout Stage 1 and Stage 2 of the VAT00008 trial (~23,000 participants in total), the Sanofi-GSK vaccine demonstrated a favorable safety and tolerability profile.

If a participant achieves a marked antibody response, particularly broadly cross-neutralizing antibodies, against diverse SARS-CoV-2 variants of concern as a result of participating in this study, there may be associated benefit, although whether this may be a correlate of protection remains uncertain. However, whether any participant will achieve a cross-neutralizing antibody response is unknown. The results of this study will inform larger scale studies designed to promote improved vaccine response in transplant recipients.

6. Investigational Agent

6.1 Sanofi-GSK COVID-19 vaccine

For this protocol, the name "Sanofi-GSK COVID-19 vaccine" refers to Sanofi Pasteur monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 Vaccine which is defined as the mixture of the Sanofi SARS-CoV-2 recombinant protein vaccine (CoV2 preS dTM vaccine) solution and the GSK Adjuvant AS03 emulsion that is prepared at each clinical research site.

6.1.1 Formulation, Packaging, and Storage

Each clinical site will be provided with kits prepared by NIAID's CPC and each 2-vial kit box contains one vial of Sanofi SARS-CoV-2 recombinant protein vaccine (CoV2 preS dTM vaccine) and one vial of GSK adjuvant AS03. The Kits must be stored at 2°C to 8°C (35°F to 46°F) and protected from light.

Sanofi SARS-CoV-2 recombinant protein vaccine (CoV2 preS dTM vaccine) Solution Vial

As described in Sanofi's IB for CoV2 preS dTM-AS03 adjuvanted vaccine, Sanofi SARS-CoV-2 recombinant protein vaccine (CoV2 preS dTM vaccine) solution is a sterile, clear, colorless solution (with possible presence of endogenous particles) of SARS-CoV-2 prefusion S proteins for intramuscular injection. Each 0.5 mL dose of the Sanofi-GSK COVID-19 vaccine will contain the following: preS-delta TM B.1.351: prefusion S delta TM B.1.351 COVID-19 antigen, (5 µg). If present, these light-colored particles are slow sinking and suspended in solution. 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).

Excipients of CoV2 preS dTM Antigen Solution:

- Sodium phosphate monobasic monohydrate
- Sodium phosphate dibasic dodecahydrate
- Sodium chloride
- Polysorbate 20
- Water for injection

GSK Adjuvant AS03 Emulsion

As described in GSK's IB for Adjuvant AS03, GSK adjuvant AS03 is an oil-in-water emulsion. The family of AS03 Adjuvant systems consists of the oil-in-water emulsion, presented in a glass container. AS03 contains a surfactant polysorbate 80 (Tween 80) and 2 biodegradable oils, squalene and α-tocopherol (Vitamin E), in phosphate buffered saline (PBS) as the aqueous carrier.[57] It is a preservative free, whitish to yellowish homogenous milky liquid emulsion.

Excipients of AS03 Adjuvant Emulsion:

- Sodium chloride
- Disodium hydrogen phosphate
- Potassium dihydrogen phosphate
- Potassium chloride
- Water for injection

The Sanofi-GSK COVID-19 vaccine should be stored between 2 to 8°C (35°F to 46°F) and protected from light. After mixing, the combined final product can be held for up to 12 hours post preparation at 2 to 8°C or at controlled room temperatures (up to 27°C) and must be protected from light. Once the 12-hour mark has been reached the product must be discarded. The product should never be frozen and should be discarded if it has been frozen.

6.1.2 Dosage, Preparation, and Administration

The vaccine is a solution and emulsion and must be mixed pre-injection according to the dose preparation steps in the Pharmacy Manual that are based on Sanofi's instruction. Once mixed, the solution (antigen) and emulsion (AS03 adjuvant) will form a multiple-dose (maximum of 10 doses) vaccine in a single vial. Each 0.5 mL dose of the Sanofi-GSK COVID-19 vaccine will contain the following: preS-delta TM B.1.351: prefusion S delta TM B.1.351 COVID-19 antigen, (5 µg).

AS described in Sanofi's IB, after mixing, the Sanofi Pasteur monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 Vaccine is a whitish to yellowish homogeneous milky liquid emulsion. The mixture can be held for up to 12 hours post preparation at 2 to 8 °C or at controlled room temperatures (up to 27 °C) and must be protected from light.

The Sanofi-GSK COVID-19 Vaccine will be administered intramuscularly in the deltoid muscle of the upper arm.

6.2 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 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.

6.3 Assessment of Participant Compliance with Investigational Agent

Not Applicable; one time dose administration of COVID-19 vaccine.

6.4 Toxicity Prevention and Management

The vaccine will be administered by qualified personnel in dedicated observation rooms. Participants will be monitored for allergic reactions or other intolerance for 30 minutes following vaccine administration. Appropriate medications to address allergic reactions will be supplied by the investigational pharmacy (i.e.,

epinephrine, anti-histaminergic medications) and there is access to local rapid response team support in case of serious adverse events.

6.5 Premature Discontinuation of Investigational Agent

Not Applicable

7. Other Medications

7.1 Concomitant Medications

7.1.1 Protocol-mandated

None

7.1.2 Other permitted concomitant medications

Transplant immunosuppression as determined by the treating transplant physician may include tacrolimus or cyclosporine, corticosteroids, MMF/mycophenolic acid, azathioprine and sirolimus.

7.2 Prophylactic Medications

None.

7.3 Prohibited Medications

Participants should not receive any vaccines, including COVID-19 vaccines or boosters, for 30 days following the study dose of vaccine.

After that point, receipt of other COVID-19 boosters are no longer a prohibited medication. Section 8.3.4 specifies study procedures for participants who subsequently receive an updated COVID-19 booster, when these boosters become available and recommended.

7.4 Pre-Exposure Prophylaxis and Treatment of COVID-19 Infection

Participants in this study should not receive any pre-exposure prophylaxis (PrEP) e.g. tixagevimab plus cilgavimab (Evusheld™, AstraZeneca) during the 2-week period following any dose of COVID-19 vaccine. From a study perspective, it would be best to delay administration of any PrEP until after the Day 30 post-vaccine visit, when the primary endpoint is collected. If the participant or his/her treating physician feels it is in the patient's best interest to administer PrEP before Day 30 following the study dose of vaccine, we ask that the study team be informed since this will impact subsequent study evaluations, in particular antibody testing.

If a participant has a known exposure to COVID-19 and/or develops COVID-19 infection, treatment should be prescribed as clinically indicated by the participant's primary provider. Participants may receive antiviral medications directed at treatment or post exposure prophylaxis of SARS-CoV-2 as directed by the participant's primary provider. There will be active surveillance for COVID-19 cases at select visits during study participation; in addition, participants will be asked to report any COVID-19 infections diagnosed during the study period.

Administration of PrEP or any treatment of COVID-19 will be captured in the clinical database.

7.5 Rescue Medications

Appropriate trained personnel, medical equipment and emergency medications, including epinephrine (1:1000), must be available at the study site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

8. Study Procedures

8.1 Enrollment

Potential study participants may be identified by medical chart review and initially contacted by a member of the study team in person or over the phone. During this initial contact, the potential participant will be provided information regarding the study and asked about their interest in study participation. If they elect to continue, they will be appropriately consented and move to the screening portion of the study.

During the consent process, potential participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures.

8.2 Screening Visit

The purpose of the screening period is to confirm eligibility prior to the study intervention. During the screening period for study eligibility, the study personnel will review the participant's medical record for previous and current medical history.

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

- Review medical history and immunosuppression to confirm eligibility.
- Blood drawn locally for SARS-CoV-2 S antibody (using Roche Elecsys® assay). A prior result may be used for eligibility if it was obtained at least 30 days following the last dose of COVID-19 vaccine.

8.3 Study Visits or Study Assessments

8.3.1 Vaccination Visit (Day 0)

Participants who meet inclusion and do not meet any exclusion criteria will be scheduled for a vaccination visit. Baseline blood, nasopharyngeal, and urine samples will be collected per the Schedule of Events in Appendix 1.

Following sample collection, the participant will proceed to the administration location and receive the dose of the Sanofi-GSK COVID-19 vaccine (see Section 6.1 for vaccine details). Participants will be observed for 30 minutes post vaccine administration.

8.3.2 Follow-up Visits

Follow-up will occur on Days 7, 14, 30 (month 1), 90 (month 3), 180 (month 6), and 365 (year 1) following vaccine administration. The Day 30 visit is the primary endpoint visit. During these visits, participants will be asked about their general health, any new events, immunosuppression medication changes and their transplanted kidney. All incidences of allograft rejection will be reported on a case report form for the duration of study participation.

In addition, blood will be collected for assessments to be run in the clinical and research laboratories per the Schedule of Events in Appendix 1. Nasal swabs for local SARS-CoV-2 PCR testing will be collected at baseline and Day 30 following vaccine administration and in any case of

suspected COVID-19 infection. Participants will be instructed to contact the study team if they receive any COVID-19 testing at an outside lab during the course of the study. All instances of COVID-19 infection will be reported on a case report form.

8.3.3 Suspected or Confirmed Cases of COVID-19 Infection

If participants suspect they have contracted COVID-19 infection, they will be directed to follow-up with their local transplant physician or primary care provider to obtain the appropriate clinical care. Information related to their illness will be collected for the study and reported in the clinical database. All cases of COVID-19 are reported for the duration study participation.

8.3.4 Receipt of a Non-Study COVID-19 Booster Vaccine

Participants should consult with the study team regarding non-study COVID-19 booster doses in order to maintain compliance with current CDC recommendations, while not compromising participation in the research study. Current CDC recommendations can be found at the following link: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised. Current recommendations may change over the course of the study.

8.4 Unscheduled Visits

If there is a change in immunosuppressive medications, new medical events or a diagnosis of rejection between regularly scheduled visits, participants will be instructed to contact study personnel and may be asked to return to the study site for an “unscheduled” visit.

Participants will be instructed to seek prompt medical attention if they develop symptoms of myocarditis or pericarditis, such as including chest pain, shortness of breath, or palpitations. Participants will also be instructed to notify the study site team. Participants diagnosed with acute myocarditis or acute pericarditis within 6 weeks of any COVID-19 vaccine will be referred to a cardiologist for evaluation and management. Cases of study-defined probable or definite acute myocarditis or acute pericarditis will be followed until resolution of symptoms and abnormal test findings.

8.5 Visit Windows

Study visits should take place within the time limits specified below: the designated visit windows *(i.e. +/- n days)* for each scheduled visit are also indicated on the Table of Events.

Visits 1 (Day 7)	+/- 1 day
Visits 2-3 (Day 14, Day 30)	+/- 3 days
Visits 4-6 (Month 3, Month 6, Month 12)	+/- 2 weeks

9. Mechanistic Assays

9.1 Introduction

Effective vaccinations induce potent protective humoral and cellular immunity and promote development of robust T and B cell memory, together preventing infection and accelerating viral clearance following pathogen exposure. Current concepts are that vaccination results in activation of both T cells and B cells. Vaccine antigen-activated B cells can differentiate into low affinity IgG- or IgM-secreting plasma cells (PCs). Alternatively, vaccine antigen-activated B cells can interact with antigen-activated CD40+ CD4+ (Th1) helper T cells to undergo an isotype switch and enter germinal center (GC) reactions wherein they undergo affinity maturation. Positive selection of the highest affinity B cells in the GC requires cognate interactions with antigen specific IL-21-producing follicular helper CD4+ T cells (Tfh). The positively selected high affinity B cells then can differentiate into long lived antibody-secreting PCs, can become memory B cells (Bmem), or can reenter the GC to undergo further affinity maturation. Crucial features of the antibody repertoire relevant to pathogen clearance include antibody specificity, affinity, titer, isotype class, and glycosylation patterns, among others. Antigen-reactive CD4+ and CD8+ T cells that expand and differentiate following vaccination are also crucial mediators of pathogen clearance independent of their functions as helper cells for effective humoral immune responses. Important characteristics of these induced T cell responses include epitope specificity, cytokine secretion patterns, and cytotoxic function, among others. Effective anti-pathogen immunity also involves activation of innate immune cells, including dendritic cells, macrophages, and natural killer cells that can interact with an enhance the adaptive immune responses and have been recently shown to exhibit cellular and molecular features consistent with memory.

As noted in the background section, emerging evidence indicates that the overwhelming majority of transplant recipients taking immunosuppressant medications do not produce effective antibody responses to SARS-CoV-2 spike protein mRNA vaccinations. Whether these patients develop and maintain protective T cell responses after an adjuvanted vaccine is not known. A detailed kinetic analysis of innate and adaptive immunity following the Sanofi-GSK vaccination, particularly comparing differing levels of antibody at enrollment, is thus essential in order to interpret the clinical trial outcome and to guide design of follow up studies aimed at overcoming identified defects. Moreover, if it were possible to identify an early post vaccine molecular signature that correlates with vaccine success vs failure, such a biomarker could be used to guide subsequent strategies aimed at enhancing induction protective immunity in each transplant patient.

Thus, the overall goals of the proposed mechanistic studies are to a) characterize the vaccine-induced innate and adaptive immune responses in each study subject, b) provide insight into immune mechanisms that prevent formation and/or durability of the induced responses, c) identify molecular markers of successful vaccination.

To this end we will serially collect serum, plasma and PBMC samples over the entire study period. Using these samples we will a) provide a detailed kinetic characterization of the vaccine induced antibody repertoire (specificity, isotype, titer, neutralization capacity), b) perform a kinetic phenotypic and functional analysis of antigen specific Bmem (frequency, antigen specificity, surface markers, metabolomics, gene expression patterns, single cell sequencing) and PC, c) perform a kinetic, analysis of antigen specific CD4+ and CD8+ T cells (frequency, epitope specificity, surface markers, metabolomics, gene expression patterns

single cell sequencing), d) assess phenotypic, functional and gene expression patterns of innate immune DC, monocyte/macrophage and NK cell subsets in peripheral blood, and e) perform genomic profiling of peripheral blood cells that will provide a biomarker for an effective response.

9.2 Objective 1: To provide a detailed kinetic characterization of the vaccine induced antibody repertoire (specificity, isotype, titer, neutralization capacity).

While relative contributions of vaccine induced humoral and T cell immunity in the protection from severe SARS-CoV-2 disease are not fully understood, the development of neutralizing titers against SARS-CoV-2 strainsare emerging as a candidate correlate of protection. A detailed understanding of the profile of Ab responses in transplant recipients after vaccination is crucial step toward understanding what population benefits from additional doses of vaccine. Another exploratory endpoint of this study focuses on the candidate correlate of protection MSD 3-plex (S-2P, RBD and N protein +BSA) assay. This objective will provide a deeper mechanistic characterization to support hypothesis generating observations to understand the mechanisms underlying vaccine failure and to identify candidate humoral biomarkers to predict vaccine response. This includes surrogate and live virus neutralization titers including novel variants of concern, including the prototype strain, beta, and omicron B.1.1.529 strains.

9.3 Objective 2: To perform a kinetic phenotypic and functional analysis of antigen specific Bmem (frequency, antigen specificity, surface markers, metabolomics, gene expression patterns, single cell sequencing) and PC.

To identify and characterize SARS-CoV-2 memory B cells we will use fluorescently labeled multimerized probes for targets of the beta spike vaccine (spike receptor-binding and ectodomain) and as well as non-vaccine expressed SARS-CoV-2 antigens (e.g. Nucleocapsid). The magnitude and differentiation of antigen-specific IgM+ and IgG+ memory B cells will be assessed at each time point. We will use flow cytometry, CyTOF, single B cell multi-omics (cell surface CITE-seq profiling using tagged antibody and multimerized probes for vaccine targets), transcriptomics, and B cell receptor VDJ repertoire analysis to characterize antigen specific B cells. We will perform in vitro ELISPOT assays to determine frequencies of antigen specific PCs in peripheral blood.

9.4 Objective 3: To perform a kinetic, analysis of antigen specific CD4+ and CD8+ T cells (frequency, epitope specificity, surface markers, metabolomics, gene expression patterns single cell sequencing).

While the requirements for sustained protection against SARS-CoV-2 are not yet known, effective control of viral pathogens often depends on the development of both humoral and cellular immunity.

We will assess the strength, breadth and other characteristics of the anti-spike T cell response in study participants using flow-cytometry based, ELISPOT, and single cell-multi-omics assays. Antigen-specific cells will be interrogated using a rapidly evolving set of peptide and MHC multimer reagents using flow-cytometry, CyTOF, and or ELISPOT readouts. For flow-based analysis we will utilize 1) antigen specific functional assays (activation-induced marker (AIM), intracellular cytokine secretion assays and novel T cell metabolic profiling assays and, 2) phenotypic characterization of spike-specific T cells MHC-peptide multimer staining. We will use single T cell multi-omics (cell surface CITE-seq profiling using tagged antibody and tetramers, transcriptomics, and T cell receptor VDJ repertoire analysis.

Exploratory analysis of associated of these deep immune profiling assessments with candidate correlates of protective immunity will be performed.

9.5 Objective 4: To assess phenotypic, functional and gene expression patterns of innate immune DC, monocyte/macrophage and NK cell subsets in peripheral blood.

We will characterize the kinetics of peripheral blood immune landscape of mononuclear leukocyte lineage and phenotypic markers to broadly assess the immunological cellular profile of transplant recipients before and after vaccination, focusing on the absolute and relative frequency of T, B, NK and APC subsets.

We will characterize these cells types in peripheral blood using flow cytometry and or CyTOF assays. We will test function using in vitro assays that include in vitro stimulation of DC subsets with TLR ligands (cytokine and surface marker readouts as measures of activation), in vitro stimulation of macrophages with LPS (cytokine readouts as a measure of trained immunity, which would then be followed up with epigenetic analyses), in vitro functional analyses of NK cells.

9.6 Objective 5: Exploration of molecular biomarkers of early responders to vaccination

We will collect serial blood samples for RNA profiling (RNAseq) and/or proteomics in addition to characterization of cytokine signaling at early (14 day and/or 30 day) sample collection timepoints after vaccine intervention.

10. Biospecimen Storage

Biological specimens obtained under this protocol may be used in future assays to reevaluate biological responses as additional research tests are developed over time. These may include, but are not limited to, tests examining aspects of host immunology, cell biology, or human genetics as it relates to any of these aspects. The consent for the study will also include appropriate informed consent for the collection and storage of samples. The specimens from these evaluations will be labeled with a coded ID and may be stored beyond the funding period.

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

11.1 Participant Completion

All participants will be followed for 12 months post vaccine administration (see Appendix 1).

11.2 Participant Withdrawal Criteria

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

1. The participant 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.

11.3 Participant Replacement

Evaluable participants who withdraw or are withdrawn will not be replaced.

11.4 Follow-up after Early Study Withdrawal

If a participant is withdrawn from the study for any reason, the participant may be asked to complete a final visit and/or final assessments.

11.5 Study Pausing Rules

The study vaccine doses will be administered over a very short period at the beginning of the study, and there are no further interventions. There will therefore be a very brief window for the implementation of pausing rules. Pausing rules will only remain in effect until all study participants have received the study booster dose of vaccine.

If the following occur, enrollment will be temporarily halted and an expedited DSMB review will take place:

- **Reactogenicity**: Any Grade 4 or higher reactogenic adverse event (AE) that is definitely or possibly related to the vaccine
- **Allergy**: Two participants experiencing a Grade 3 or higher systemic allergic reaction that is definitely or possibly related to the vaccine
- **Myocarditis and/or Pericarditis**: Any probable or confirmed case of either acute myocarditis or acute pericarditis that is at least possibly related to the vaccine.
- **Acute Rejection:** Two participants with acute rejection (treated or biopsy proven AMR or ACR of any grade) occurring within 30 days of the study dose of vaccine
- **Serious Adverse Reaction:** Any participants with a grade 4 or 5 serious adverse reaction that is definitely or possibly related to the vaccine
- **Death, Graft Loss or Need for Dialysis**: Any death, graft loss, or need for dialysis within 30 days of the study dose of vaccine

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 12.5.1, Reporting of Serious Adverse Events and Adverse Events) to the sponsor, DAIT/NIAID. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 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: http://ctep.cancer.gov/reporting/ctc.html.

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, an adverse event will include the following, temporally associated with the study dose of vaccine and study mandated procedures.

COVID-19 vaccine administration:

- Unsolicited AEs occurring within 30 days following vaccine administration
- All SAEs for the duration of the study
- All AESIs, including pIMDs diagnosed post vaccine, for the duration of the study

Study mandated procedures:

- Any AE occurring within 24 hours of a protocol mandated blood draw
- Any AE occurring within 24 hours of a protocol mandated nasal swab

12.2.2 Solicited Adverse Events

For the purposes of this study, the following specific local and systemic adverse events, will be solicited from the participant through a remote contact on Day 7 post-vaccination. These solicited adverse events will be considered as 'related' to the vaccination. Any other adverse events reported during the course of this remote contact will be reported on the AE eCRF. Study clinicians will follow all adverse events to resolution.

- Local reactions at the injection site including erythema/redness, swelling, and pain.

- Systemic reactions including fever, headache, malaise, myalgia, arthralgia, and chills.

12.2.3 Unsolicited Adverse Events

Participants will be instructed to contact the study site and report any unsolicited adverse events up to 30 days post vaccine administration. This will include any delayed onset local reactions occurring after the 7 day collection period of solicited adverse events.

12.2.4 Adverse Events of Special Interest (AESI)

Adverse Events considered potentially related to the COVID-19 vaccine will be reported as AESIs on the appropriate case report form. These include:

- Anaphylactic reactions
- Generalized convulsion
- Thrombocytopenia
- Thrombosis with thrombocytopenia syndrome
- Myocarditis
- Pericarditis
- Potential immune-mediated diseases (pIMDs) (see Section 12.2.5)

For myocarditis and pericarditis events, any relevant laboratory information, imaging (echocardiography, cardiac MRI) and/or pathology (cardiac biopsy) results will be reported on the appropriate case report forms. The NIAID medical monitor may require that appropriately deidentified copies of assessments, including but not limited to EKG, imaging, cardiac biopsies digital images, or other follow-up results (stress tests results) be made available for medical monitor or ad hoc DSMB review.

12.2.5 Potential immune-mediated diseases (pIMDs)

Potential immune-mediated diseases (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. New onset PIMDs that need to be recorded and reported include those listed in Appendix 2. 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 2, 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. In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of PTs and PT codes corresponding to the above diagnoses will be available to Investigators at study start. Once a pIMD is diagnosed (serious or non-serious) in a study participant, this will be reported as a SAE in the clinical database to ensure prompt reporting to the Study Sponsor.

12.2.5.1 Suspected Adverse Reaction (SAR)

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the SARS-CoV-2 vaccine caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.6 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or Package Insert or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the IND.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)*]*

12.2.7 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction 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 subject 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 subject 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

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse

Events (CTCAE) Version 5.0. 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 adverse events. The NCI-CTCAE has been reviewed by the NIAID medical monitor and protocol chair and has been deemed appropriate for the subject population to be studied in this protocol.

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; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ADL: Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)
Grade 4 = Life-threatening consequences; urgent intervention indicated.
Grade 5 = Death related to AE.

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 adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events 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 adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

12.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE/SAE eCRF. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.3.2.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 12.3.2 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

- Adverse Events temporally associated (24 hours) with the research blood draws and nasopharyngeal swabs will be collected from the time of the screening visit until a subject completes study participation.
- Adverse Events as defined in Section 12.2.1 will be collected for 30 days following COVID-19 vaccine administration.
- Serious Adverse Events will be collected for the study duration.
- AESIs (including pIMDs) will be collected for the study duration.

12.4.2 Collecting Adverse Events

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

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

12.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events and AESIs as described previously (Section 12.2, *Definitions)* on the appropriate source document and then on the electronic case report form regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 Reporting of Serious Adverse Events to DAIT/NIAID

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via the AE/SAE eCRF. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all serious adverse events (see Section 12.2.7, *Serious Adverse Event)*, regardless of relationship or expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information will be entered on the AE/SAE eCRF. 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 to the Statistical and Clinical Coordinating Center (SACCC). Initial SAE eCRFs should include as much information as possible, but at a minimum:

- AE term
- Relationship to study vaccination
- Relationship to study procedure
- Reason why the event is serious
- Supplementary eCRF pages that are current at the time of the SAE reporting e.g. medical history and vaccine administration

12.5.2 Reporting to Health Authority

After an adverse event requiring 24 hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to Sponsor*) is submitted by the site investigator and assessed by DAIT/NIAID, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities:

12.5.2.1 Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.5.1, Suspected Adverse Reaction, and Section 12.2.6, Unexpected Adverse Event).
- Serious and not a suspected adverse reaction (see Section 12.2.5.1, Suspected Adverse Reaction).
- Pregnancies.

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

12.5.2.2 Expedited Safety Reporting

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

Category 1: **Serious and unexpected suspected adverse reaction** [**SUSAR]** (see Section 12.2.5.1, *Suspected Adverse Reaction* and Section 12.2.6, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

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

1. 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);
2. 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);
3. 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 suggests a significant human risk**
The sponsor shall report any findings from other epidemiological studies, analyses of adverse events 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, 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.

12.5.3 Reporting of Adverse Events to IRBs/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All Safety Reports to the FDA shall be distributed by DAIT/NIAID or designee to all participating institutions for site IRB/IEC submission.

12.5.4 Mandatory reporting to Vaccine Adverse Event Reporting System

The site investigator, or designee, is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):

- vaccine administration errors whether or not associated with an adverse event,
- serious adverse events (irrespective of attribution to vaccination),

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

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 Pregnancy

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

The investigator shall report to the SACCC all pregnancies within 1 business day of becoming aware of the event using the SAE eCRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The SAE eCRF shall be updated and submitted to the SACCC when details about the outcome are available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study subject.

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.

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion - an SAE shall be submitted to the SACCC using the SAE reporting procedures described above.

12.6 Reporting of Other Safety Information

An investigator shall promptly notify the site IRB as well as the SACCC when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

12.7 Review of Safety Information

12.7.1 Medical Monitor Review

The NIAID medical monitor shall receive reports from the SACCC compiling new and accumulating information on AEs and SAEs recorded by the study site(s) on appropriate eCRFs.

In addition, the NIAID medical monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the SACCC (See Sections 12.5.1, Reporting of Serious Adverse Events to Sponsor, and Section 12.5.5, Pregnancy Reporting).

12.7.2 DSMB Review

12.7.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data one month after all study participants have received study vaccine, unless a safety event requires earlier review. They will review the study again when the database is locked after the last patient's last visit. Interim DSMB reviews may occur at any time at the discretion of the medical monitor or the protocol chair. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of any Expedited Safety Reports within one week of submitting such reports to the FDA.

12.7.2.2 Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the sponsor (NIAID DAIT) may call upon the DSMB for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review if a Pausing Rule (see Section 11.5) is met.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.7.2.2.1 Temporary Suspension of enrollment for ad hoc DSMB Safety Review

See Section 11.2 for Participant Stopping Rules and Withdrawal Criteria.

13. Statistical Considerations and Analytical Plan

13.1 Overview

The goal of the study is to assess antibody response to a dose of the Sanofi-GSK monovalent (B.1.351) CoV2 preS dTM-AS03 COVID-19 kidney transplant recipients who have failed to respond to a minimum of two doses of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine. The study population will consist of kidney transplant recipients who have received at least two doses of the Moderna or Pfizer-BioNTech vaccine and subsequently shown an antibody concentration ≤2500 U/mL. The study is a single-arm, non-randomized intervention study in which all participants receive a dose of the Sanofi-GSK COVID-19 vaccine.

13.2 Endpoints

The primary endpoint is the proportion of participants who reach a SARS-CoV-2 S antibody level >5000 U/mL (using the Roche Elecsys anti-RBD assay) at 30 days following a dose of the Sanofi-GSK COVID-19 vaccine.

13.3 Measures to Minimize Bias

This is an unrandomized, unblinded, single-arm study. To minimize measurement bias, baseline exposures will be measured before the study dose is received. To minimize bias in ascertainment of outcomes, all outcome definitions will be standardized and all assays will be processed in a centralized laboratory.

13.4 Analysis Plan

13.4.1 Analysis Populations

The safety analysis will include all participants who receive the vaccine.

The per-protocol analysis of the primary outcome includes all evaluable participants, i.e., those who receive the intervention, have a baseline antibody ≤2500 U/mL, and have an antibody response measured at 30 days after the intervention.

For secondary and exploratory outcomes, all individuals who receive the intervention and have that outcome measured will be included.

13.4.2 Primary Analysis of Primary Endpoint

The primary endpoint is the proportion of participants who reach a SARS-CoV-2 S antibody level >5000 U/mL (using the Roche Elecsys anti-RBD assay) at 30 days following a dose of the Sanofi-GSK COVID-19 vaccine. The primary outcome is binary: whether or not titer measured 30 days after the intervention exceeds 5000 U/mL. We will calculate an exact binomial confidence interval around this proportion.

13.4.3 Supportive Analyses of the Primary Endpoint

We will characterize risk factors associated with the primary outcome using logistic regression. Risk factors (age, sex, race/ethnicity, years since transplant, antimetabolite usage, vaccine type) will analyzed individually using univariable logistic regression. Additionally, we will analyze all risk factors in a single multivariable logistic regression model.

13.4.4 Analyses of Secondary and Other Endpoints

Secondary endpoints will be analyzed using exact binomial confidence intervals and logistic regression as per the methods described in 13.4.2 and 13.4.3. We will analyze exploratory mechanistic and other endpoints by reporting proportion with binomial exact confidence interval for binary variables, proportions for categorical variables, and median (IQR) for continuous variables. We will also report these outcomes stratified by the primary outcome, with Fisher exact tests for binary and categorical variables and ranksum tests for continuous variables.

13.4.5 Descriptive Analyses

We will describe demographics and other baseline (pre-intervention) characteristics (medication use, time since transplant, type of vaccine) in the study population by reporting proportion for binary and categorical variables, and median (IQR) for continuous variables. We will report these overall and stratified by the primary outcome.

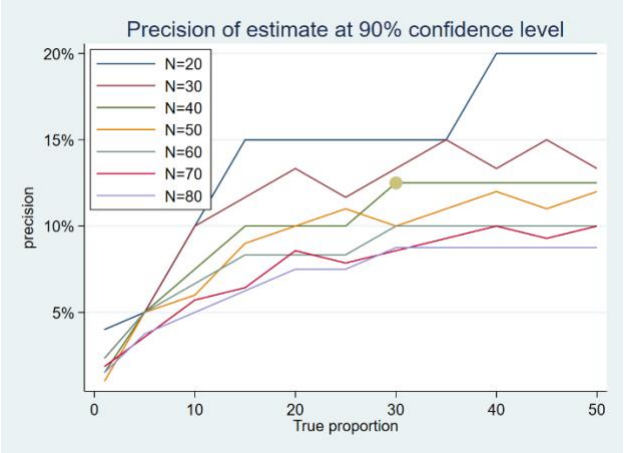
13.5 Interim Analyses

No interim analyses are planned prior to the primary endpoint analysis.

13.6 Statistical Hypotheses

This is a single-arm pilot study to estimate the proportion of individuals with a positive antibody response to an additional dose of an investigational adjuvanted protein vaccine. For the primary endpoint, we do not test any specific hypothesis. Rather, our goal is to estimate the proportion of individuals with a titer exceeding 5000 U/mL. We will estimate this proportion, with 95% confidence interval, using an exact binomial confidence interval.

13.7 Sample Size Considerations



In the context of estimating a single proportion, the relevant consideration for sample size is the difference between the true proportion (what proportion of all individuals would have a positive response if our sample size was infinite) and the observed proportion (what proportion in the actual study have a positive response). For a range of true proportions (5%-50%) and Ns (20-80), we ran 5,000 simulations of the study, and calculated the absolute value of the difference between the true proportion and the proportion observed in the study. We denoted the 90th percentile of this value the "precision of the estimate at a 90% confidence level". Depending on the true proportion, the precision of the estimate ranged from 1.5% to 8.75% overall (N=80. Our sample size, therefore, will be sufficient to provide an accurate estimate of the true proportion.

14. Identification and Access to Source Data

14.1 Source Data

Source documents and source data are the original documentation where subject information, visits 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.

14.2 Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID and their representatives as well as to relevant health authorities (Food and Drug Administration). 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

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

16. Protocol Deviations

16.1 Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance with the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection 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 subject'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 principal investigator 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.

17. Ethical Considerations and Compliance with Good Clinical Practice

17.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, 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 Institutional Review Board (IRB). 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 principal investigator or designee listed on the FDA Form 1572 will review the consent and answer questions. The prospective participant 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 will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in the participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing, and new safety information that becomes available will be communicated to the participants. 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 (PHI) to the study sponsor or their representatives.

18. Publication Policy

The publication guidelines and policies stipulated in the grant will apply to this protocol.

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Appendix 1: Schedule of Events

Study Schedule	Day					Month			
Time points	**Screen**	**0**	**7**	**14**	**30**	**3**	**6**	**12**	**For Cause[1]**
Visit #	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**FC**
Visit Windows (+/-)		**-**	**1d**	**3d**	**3d**	**2w**	**2w**	**2w**	**-**
General Assessments									
Informed Consent	X	X[2]							
Medical History[3] (including vaccine history)	X								
Remote Contact	X		X		X	X	X	X	X
Immunosuppressive Medications[4,5]	X	X	X	X	X	X	X	X	X
Adverse Event/Serious Adverse Event Assessment	X	X	X	X	X	X	X	X	X
Local Clinical Laboratory Assessments									
Complete Blood Count		X			X	X	X	X	
Metabolic Panel[6]		X			X	X	X	X	
Quantitative Immunoglobulins		X					X		
SARS-CoV-2 S Antibody (Roche Elecsys®)	X[7]								
SARS-CoV-2 PCR nasal swab (surveillance)		X			X				
Serum or Urine Pregnancy Test[8]		X[9]							
Investigational Intervention									
COVID-19 vaccine administration		X							
Central Laboratory Assessments									
Antibody/Neutralization assays[10]	X[11]	X		X	X	X	X	X	X
SARS-CoV-2 PCR nasal swab (COVID-19 infection)									X
Proteomics		X			X				
Transcriptomics		X			X				
T and B Cell Assays		X		X	X	X	X	X	X
Donor Specific Antibodies (DSA)		X			X	X	X	X	

[1] Unscheduled "for cause" visit for breakthrough infection or rejection . If the participant reports breakthrough COVID-19 infection, a nasal swab will be collected by the participant remotely.
[2] Reconfirm eligibility by history at the time of the main study consent.
[3] Review medical history to confirm eligibility. A thorough COVID-19 vaccine history will be collected.
[4] Ensure the participant has not received any medications since the time of transplant that make them ineligible.
[5] Immunosuppressive medications will be collected for 90 days post vaccine. Following 90 days, immunosuppressive medications will be collected in cases of allograft rejection and SAEs.
[6] Comprehensive metabolic panel at baseline, basic metabolic panel all other timepoints.
[7] Performed locally for eligibility. Must be within last 4 months.
[8] Results are required prior to vaccination.
[9] Must be within 25 hours of the study vaccine administration.
[10] This includes both the SARS-CoV-2 Spike and Nucleocapsid antibody using the Roche Elecsys®. Not all assays will be done at each timepoint. Please refer to the lab manual for specific details.
[11] A confirmatory SARS-CoV-2 S blood sample will be sent to the central lab for eligibility.

Appendix 2. 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:
  ○ Warm antibody hemolytic anemia
  ○ Cold antibody hemolytic anemia
- Autoimmune lymphoproliferative syndrome (ALPS)
- Autoimmune neutropenia
- Autoimmune pancytopenia
- Autoimmune thrombocytopenia*
  ○ Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”.
- Evans syndrome
- Pernicious anemia
- Thrombosis with thrombocytopenia syndrome (TTS)
- Thrombotic thrombocytopenic purpura
  ○ Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”
	- Idiopathic Myocarditis/Pericarditis, including:
	  ○ Autoimmune / Immune-mediated myocarditis
	  ○ Autoimmune / Immune-mediated pericarditis
	  ○ Giant cell myocarditis
	- Idiopathic pulmonary fibrosis, including:
	  ○ Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune-mediated pneumonitis)
	  ○ Pleuroparenchymal fibroelastosis (PPFE)
	- Pulmonary alveolar proteinosis (PAP)
	  ○ Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”
		- Addison’s disease
		- Autoimmune / Immune-mediated thyroiditis, including:
		  ○ Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)
		  ○ Atrophic thyroiditis
		  ○ Silent thyroiditis
		  ○ Thyrotoxicosis
		- Autoimmune diseases of the testis and ovary, including:
		  ○ Autoimmune oophoritis
		  ○ Autoimmune ovarian failure
		  ○ Autoimmune orchitis
		- Autoimmune hyperlipidemia
		- Autoimmune hypophysitis
		- Diabetes mellitus type I
		- Grave's or Basedow’s disease, including:
		  ○ Marine Lenhart syndrome
		  ○ Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
		- Insulin autoimmune syndrome
		- Polyglandular autoimmune syndrome, including:
		  ○ Polyglandular autoimmune syndrome type I, II and III

Eye disorders	**Gastrointestinal disorders**	**Hepatobiliary disorders**

- Ocular Autoimmune / Immune-mediated disorders, including:
  ○ Acute macular neuroretinopathy (also known as acute macular outer retinopathy)
  ○ Autoimmune / Immune-mediated retinopathy
	- Autoimmune / Immune-mediated pancreatitis
	- Celiac disease
	- Inflammatory Bowel disease, including:
	  ○ Crohn’s disease
	  ○ Microscopic colitis
	  ○ Terminal ileitis
	  ○ Ulcerative colitis
		- Autoimmune cholangitis
		- Autoimmune hepatitis
		- Primary biliary cirrhosis
		- Primary sclerosing cholangitis

○ Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia ○ Cogan's syndrome: an oculo-audiovestibular disease ○ Ocular pemphigoid ○ Ulcerative keratitis ○ Vogt-Koyanagi-Harada disease	○ Ulcerative proctitis	
Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**
- Gout, including: ○ Gouty arthritis - Idiopathic inflammatory myopathies, including: ○ Dermatomyositis ○ Inclusion body myositis ○ Immune-mediated necrotizing myopathy ○ Polymyositis - Mixed connective tissue disorder - Polymyalgia rheumatica (PMR) - Psoriatic arthritis (PsA) - Relapsing polychondritis - Rheumatoid arthritis, including: ○ Rheumatoid arthritis associated conditions ○ Juvenile idiopathic arthritis ○ Palindromic rheumatism ○ Still's disease ○ Felty's syndrome - Sjögren's syndrome - Spondyloarthritis, including: ○ Ankylosing spondylitis ○ Juvenile spondyloarthritis ○ Keratoderma blenorrhagica ○ Psoriatic spondylitis ○ Reactive Arthritis (Reiter's Syndrome) ○ Undifferentiated spondyloarthritis - Systemic Lupus Erythematosus, including:	- Acute disseminated encephalomyelitis (ADEM)* and other inflammatory-demyelinating variants, including: ○ Acute necrotising myelitis ○ Bickerstaff's brainstem encephalitis ○ Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) ○ Myelin oligodendrocyte glycoprotein antibody-associated disease ○ Neuromyelitis optica (also known as Devic's disease) ○ Noninfective encephalitis / encephalomyelitis / myelitis ○ Postimmunization encephalomyelitis - Guillain-Barré syndrome (GBS)*, including: ○ Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN) - Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including: ○ Cranial nerve neuritis (e.g. Optic neuritis) ○ Idiopathic nerve palsies/paresis (e.g. Bell's palsy) ○ Melkersson-Rosenthal syndrome ○ Multiple cranial nerve palsies/paresis - Multiple Sclerosis (MS), including: ○ Clinically isolated syndrome (CIS)	- Autoimmune / Immune-mediated glomerulonephritis, including: ○ IgA nephropathy ○ IgM nephropathy ○ C1q nephropathy ○ Fibrillary glomerulonephritis ○ Glomerulonephritis rapidly progressive ○ Membranoproliferative glomerulonephritis ○ Membranous glomerulonephritis ○ Mesangioproliferative glomerulonephritis ○ Tubulointerstitial nephritis and uveitis syndrome

○ Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) ○ Complications such as shrinking lung syndrome (SLS) - Systemic Scleroderma (Systemic Sclerosis), including: ○ Reynolds syndrome (RS) ○ Systemic sclerosis with diffuse scleroderma ○ Systemic sclerosis with limited scleroderma (also known as CREST syndrome)	○ Malignant MS (the Marburg type of MS) ○ Primary-progressive MS (PPMS) ○ Radiologically isolated syndrome (RIS) ○ Relapsing-remitting MS (RRMS) ○ Secondary-progressive MS (SPMS) ○ Uhthoff's phenomenon - Myasthenia gravis, including: ○ Ocular myasthenia ○ Lambert-Eaton myasthenic syndrome - Narcolepsy* (with or without presence of unambiguous cataplexy) - Peripheral inflammatory demyelinating neuropathies and plexopathies, including ○ Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) ○ Antibody-mediated demyelinating neuropathy ○ Chronic idiopathic axonal polyneuropathy (CIAP) ○ Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) ○ Multifocal motor neuropathy (MMN) - Transverse myelitis (TM), including: ○ Acute partial transverse myelitis (APTM) ○ Acute complete transverse myelitis (ACTM)	
Skin and subcutaneous tissue disorders	**Vasculitis**	**Other (including multisystemic)**
- Alopecia areata - Autoimmune / Immune-mediated blistering dermatoses, including: ○ Bullous Dermatitis ○ Bullous Pemphigoid ○ Dermatitis herpetiformis ○ Epidermolysis bullosa acquisita (EBA)	- Large vessels vasculitis*, including: ○ Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) ○ Giant cell arteritis (also called temporal arteritis) ○ Takayasu's arteritis - Medium sized and/or small vessels vasculitis*, including:	- Anti-synthetase syndrome - Capillary leak syndrome ○ Frequently used related terms include : “systemic capillary leak syndrome (SCLS)” or “Clarkson's Syndrome” - Goodpasture syndrome

○ Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease ○ Pemphigus - Erythema multiforme - Erythema nodosum - Lichen planus, including: ○ Liquen planopilaris - Localised Scleroderma (Morphoea) ○ Eosinophilic fasciitis (also called Shulman syndrome) - Psoriasis - Pyoderma gangrenosum - Reactive granulomatous dermatitis, including : ○ Interstitial granulomatous dermatitis ○ Palisaded neutrophilic granulomatous dermatitis - Stevens-Johnson Syndrome (SJS), including: ○ Toxic Epidermal Necrolysis (TEN) ○ SJS-TEN overlap - Sweet's syndrome, including: ○ Acute febrile neutrophilic dermatosis - Vitiligo	○ Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) ○ Behcet's syndrome ○ Buerger's disease (thromboangiitis obliterans) ○ Churg–Strauss syndrome (allergic granulomatous angiitis) ○ Erythema induratum (also known as nodular vasculitis) ○ Henoch-Schonlein purpura (also known as IgA vasculitis) ○ Microscopic polyangiitis ○ Necrotizing vasculitis ○ Polyarteritis nodosa ○ Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) ○ Wegener's granulomatosis	○ Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)" - Immune-mediated enhancement of disease, including: ○ Vaccine associated enhanced disease (VAED and VAERD). 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: ○ Kawasaki's disease ○ Multisystem inflammatory syndrome in adults (MIS-A) ○ Multisystem inflammatory syndrome in children (MIS-C) - Overlap syndrome - Raynaud's phenomenon - Sarcoidosis, including: ○ 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.

Appendix 3: Solicited AR Intensity Grading Scale

Adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".

Solicited injection site reactions: terminology, definitions, and intensity scales – Adults

CRF term (MedDRA lowest level term [LLT])	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
Patient Reported Outcome Term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling

Intensity scale*	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Patient Reported Outcome scale:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

MedDRA: Medical Dictionary for Regulatory Activities

* For pain, the scale will be provided in the CRF and the intensity will be transcribed based on patient interview (phone or in-person). For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Solicited systemic reactions: terminology, definitions, and intensity scales –Adults

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Arthralgia**	**Chills**
Patient Reported Outcome Term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Joint pain	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Pain in a joint or joints	Sensation of cold

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Arthralgia**	**Chills**
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of adverse event (AE) that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Arthralgia	Chills
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, or ≥ 101.2°F to ≤ 102.0°F	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Arthralgia**	**Chills**
	Grade 3: ≥ 39.0°C or ≥ 102.1°F	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Patient Reported Outcome:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Patient Reported Outcome:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Patient Reported Outcome:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Patient Reported Outcome:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Patient Reported Outcome:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions, the scale will be provided in the CRF and the intensity will be recorded based on patient interview (phone or in-person).