Additional Recombinant COVID-19 Humoral and Cell-Mediated Immunogenicity in Immunosuppressed Populations. (ARMOR-COVID)

October 5, 2024

NCT06027229

Additional Recombinant COVID-19 Humoral and Cell-Mediated Immunogenicity in Immunosuppressed Populations. (ARMOR-COVID)

Sponsor- Investigator: Freddy Caldera, DO, MS

Protocol Number: Oncore Protocol number: 235058
IRB Protocol number: 2023-1208

IND Number: 29913

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Source of Funding Novavax

Version Date: October 5, 2024

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1.0 STATEMENT OF COMPLIANCE

I confirm that I have read this protocol. I will comply with the IRB-approved protocol, and applicable regulations, guidelines, laws, and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

Name	**Signature**	**Date**
_____	_____	_____
Sponsor-Investigator		

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event
CMS	Centralized Monitoring Service
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data & Safety Monitoring Plan
eCRF	Electronic Case Report Forms
EHR	Electronic Health Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IND	Investigational New Drug Application
IRB	Institutional Review Board
OnCore	Online Collaborative Research Environment
PHI	Protected Health Information
PI	Principal Investigator
pIMDs	Potential Immune-Mediated Diseases
PRC	Pharmaceutical Research Center
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMP	Study Monitoring Plan
UP	Unanticipated Problem

3.0 SYNOPSIS

Full Title	Additional Recombinant COVID-19 Humoral and Cell-Mediated Immunogenicity in Immunosuppressed Populations
Short Title	ARMOR-COVID
Protocol Number	Oncore Protocol number: 235058 IRB Protocol number: 2023-1208
ClinicalTrials.gov Identifier & Summary	NCT06027229 To determine whether providing a 2023/2024 (monovalent, XBB containing) Novavax COVID-19 vaccine, the Omicron XBB.1.5 vaccine is named BV2601, with the drug product as NVX-CoV2601, improves sustained humoral and cell-mediated immunogenicity against SARS-CoV-2 in immunosuppressed patients with IBD and/or solid organ transplant recipients. The study will be extended to 2024/2025 season which will determine whether providing a 2024/2025 (monovalent, XBB containing) *Novavax COVID-19 vaccine, the Omicron XBB.1.5* vaccine is named BV2601, with the drug product as *NVX-CoV2024-2025,* improves sustained humoral and cell-mediated immunogenicity against SARS-CoV-2 in immunosuppressed patients with IBD and/or solid organ transplant recipients.
Number of Site(s)	One clinical site in the United States.
Phase	Phase II
Main Inclusion Criteria	• Patient is between the ages of 18-85 years. • Patients has a history of ulcerative colitis (UC), Crohn's disease, or pouchitis diagnosed by standard clinical, radiographic, endoscopic, and histopathologic criteria or solid organ transplant recipient. • Have received at least three doses of a COVID-19 vaccine. • On systemic immunosuppressive therapy for inflammatory bowel disease or for solid organ transplant
Main Exclusion Criteria	• Allergy to recombinant COVID-19 vaccine or any component of it • Patient cannot or will not provide written informed consent. • Unable to provide appropriate informed consent because of illiteracy or impairment in decision-making capacity. • Active antibody-mediated or cellular rejection. • Recent IBD flare requiring initiation of systemic corticosteroids within the past month.
Objective(s)	<u>2023-2024 season</u> <u>Primary Objective</u> • Humoral Immunogenicity of a *NVX-CoV2601* <u>Secondary Objectives</u> • Sustained antibody concentrations of the *NVX-CoV2601* booster dose. • Seroconversion. • Cell-mediated immunity to *NVX-CoV2601* booster vaccine • Sustained cell-mediated immunity to the NVX-CoV2601booster vaccine. • Describe the safety of the NVX-CoV2601.

	• Evaluate the disease activity following administration of the booster dose up to 30 days post-last vaccination and during the whole post-vaccination follow-up period. • Evaluate for solid organ transplant rejection following administration of booster dose, up to 30 days post-vaccination and during the whole post-vaccination follow-up period 2024-2025 season (The 2024-2025 season activities will not proceed as originally planned due to the withdrawal of financial support from our sponsor). <u>Primary Objective</u> • Humoral Immunogenicity of a *NVX-CoV2024-2025 booster* <u>Secondary Objectives</u> • Sustained antibody concentrations of the *NVX-CoV2024-2025 booster*. • Seroconversion. • Cell-mediated immunity to *NVX-CoV2024-2025 booster* • Sustained cell-mediated immunity to the *NVX-CoV2024-2025 booster* • Describe the safety of the *NVX-CoV2024-2025 booster* • Evaluate the disease activity following administration of the booster dose up to 30 days post-last vaccination and during the whole post-vaccination follow-up period. • Evaluate for solid organ transplant rejection following administration of booster dose, up to 30 days post-vaccination and during the whole post-vaccination follow-up period
Endpoints	<u>2023-2024 Season</u> <u>Primary Endpoint</u> • Antibody concentrations at V2 are statistically significantly higher than at V1. <u>Secondary Endpoints</u> • Seropositivity rate at V2 and V3 in all participants. • Individuals who achieve seroconversion at V2 • Interferon gamma responses at V2 compared to V1. • Interferon gamma responses at V3 compared to V1. • The number and percentage of subjects reporting solicited and unsolicited AEs, pIMDs, and SAEs. • Number and percentage of participants reporting disease flares of IBD. • Number and percentage of participants reporting acute rejection of their transplant. 2024-2025 Season <u>Primary Endpoint</u> • Antibody concentrations at V2 are statistically significantly higher than at V1. <u>Secondary Endpoints</u>

	• Seropositivity rate at V2 and V3 in all participants. • Individuals who achieve seroconversion at V2 • Interferon gamma responses at V2 compared to V1. • Interferon gamma responses at V3 compared to V1. • The number and percentage of subjects reporting solicited and unsolicited AEs, pIMDs, and SAEs. • Number and percentage of participants reporting disease flares of IBD. • Number and percentage of participants reporting acute rejection of their transplant.
Study Design	2023-2024 season This will be a single-center, prospective, unblinded, non-randomized study of 120 immunosuppressed patients who are planning to receive a NVX-CoV2601 COVID-19 vaccine booster dose. 2024-2025 season This will be a single-center, prospective, unblinded, non-randomized study of 120 immunosuppressed patients who are planning to receive a *NVX-CoV2024-2025 COVID-19 booster*
FDA Regulatory Overview	The protocol uses an investigational product, NVX-CoV2601, and is being conducted under IND NUMBER 29913 that is held by Dr. Freddy Caldera.
Study Intervention	NVX-CoV26012023/2024 (monovalent, XBB containing) Novavax COVID-19 vaccine, the Omicron XBB.1.5 vaccine is named BV2601 *NVX-CoV2024-2025 booster* Novavax COVID-19 vaccine, the Omicron XBB.1.5 vaccine is named BV2601
Total Number of Subjects	2023-2024 season - 21 patients were enrolled in this season 2024-2025 season (none will be recruited anymore) (The 2024-2025 season activities will not proceed as originally planned due to the withdrawal of financial support from our sponsor). - A total 120 subjects will be enrolled. A total of 141 subjects will be enrolled for this study for both seasons.
Study Population	Male and females aged 18 to 85 with IBD and/or who are solid organ transplant recipients.
Statistical Methodology	In analyzing the primary endpoint, a paired t-test will be utilized to test whether, on average, there is a change of at least 15% antibody blood concentration between the first and second

	blood draws. A test statistics and degrees of freedom, including the 95% confidence intervals will be reported. In addition, we will model the post measurement blood draw concentrations (i.e., V2 and V3) as the response variable using an ANOVA (i.e., ANOVA-POST), while adjusting for the initial responses (V1) and other baseline covariates.
Estimated Subject Duration	The duration of the study for each subject is approximately 6 months.
Estimated Enrollment Period & Study Duration	Study enrollment and follow-up will occur over 6 months with the total expected duration of the trial to be 24 months.

4.0 KEY ROLES

The following is a list of all key personnel and roles:

Sponsor-Investigator	**Freddy Caldera, DO, MS** University of Wisconsin School of Medicine & Public Health Department of Medicine, Division of Gastroenterology & Hepatology 1685 Highland Avenue Madison, WI 53705 **608-628-8201**
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Study Monitoring Contact	Centralized Monitoring Service 1685 Highland Avenue Madison, WI 53705
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5.0 INTRODUCTION

5.1 Background and Scientific Rationale

Immunosuppressed populations, which include patients with inflammatory bowel disease (IBD) and those with solid organ transplant (such as liver transplant recipients), account for approximately 3% of the population in the United States (US).[1] They are commonly treated with immunosuppressive medications that can increase their risk of respiratory infections such as influenza, invasive pneumococcal disease and SARS-CoV-2 all which are potentially vaccine preventable diseases.[2] Coronavirus disease 2019 (COVID-19) has resulted in a global pandemic with greater than 500 million infections and more than 6 million deaths worldwide. Immunosuppressed populations are at an increased risk for severe COVID-19 outcomes. Three safe and highly efficacious SARS-CoV-2 vaccines are authorized by the Food and Drug Administration (FDA) in response to the COVID-19 pandemic.[1] Immunosuppressed patients were excluded from the original Phase III clinical trials; therefore, the efficacy in this population is unknown. These vaccines have been found to be safe in patients with IBD, with similar rates of localized and systemic adverse events as found in the general population, with low rates of IBD flares following vaccination (2%). [3, 4] Additionally these vaccines are associated with similar rates of reactogenicity in solid organ transplant recipients and low rates of acute rejection following immunization. [5, 6]

Patients with solid organ transplant are less likely to seroconvert after the two-dose series.[7, 8] The humoral response to COVID-19 vaccines in patients with solid organ transplant has been reported to be approximately 50-70%.[7, 8] In contrast, it appears that most patients with IBD are able to mount an antibody response post immunization.[9] In our study HERCULES we found that patients with IBD had lower antibody concentrations than healthy controls.[9] These studies have raised concerns that immunosuppressed patients may be susceptible to breakthrough COVID-19 infections and potential complications from COVID-19 disease despite being immunized. Our study HERCULES showed robust antibody responses after three doses of COVID-19 vaccines in patients with IBD, with antibody concentrations being higher after the third dose than after the two doses primary series.[10] In contrast, among immunosuppressed solid organ transplant recipients, a third dose improves humoral immune response but they are still suboptimal when compared to the general population.[11]

There is evidence of waning humoral immunity in the general population following vaccination, especially in those who are immunosuppressed or greater than 65 years.[12] A high incidence of breakthrough infection among vaccinated healthcare workers has also been described.[13] As such, the Advisory Committee on Immunization Practice (ACIP) recommended a booster mRNA vaccine dose five months after completion of the original two-dose vaccine series for all adults. Booster doses have reduced the incidence of infection and severity of illness.[14] For those who completed a three-dose mRNA vaccine primary series, as recommended by the ACIP for those who are moderately to severely immunosuppressed, are now eligible for up to two additional booster doses.

Homologous booster strategies have improved vaccine response in the general population and immunosuppressed populations. Heterologous prime boost strategies may offer immunological advantages to optimize the breadth and longevity of protection achieved with the currently available vaccines. A recent study showed that both homologous and heterologous boosting strategies resulted in improved humoral immunogenicity in adults.[15] Furthermore a large population based study showed that heterologous boosting achieved higher vaccines effectiveness for many clinical outcomes compared to homologous boosting.[16] [17]

A new COVID-19 vaccine, NVX-CoV2372 (Novavax), made up of a full-length stabilized recombinant spike protein, has been found to be safe and effective in preventing COVID-19.[18] It recently received approval from the FDA for emergency use authorization (EUA). The ACIP also recommended the use of this vaccine as a primary series. This recombinant COVID-19 vaccine may be an ideal agent to boost, given that it has a different mechanism and has the full length of the spike protein compared to mRNA vaccines. Thus, there is a critical need to evaluate whether a recombinant COVID-19 vaccine can improve the immune response to COVID-19 vaccines in immunosuppressed populations. The goal of this study to evaluate the immunogenicity of a 2023/2024 and 2024/2025 (monovalent, XBB containing) Novavax COVID-19 vaccine, the Omicron XBB.1.5 vaccine is named BV2601 with the drug product as NVX-CoV2601 and not to evaluate the impact of a heterologous boosting strategy. This critical need will be addressed via a collaborative study with investigators in expertise in inflammatory bowel disease and vaccinology (Freddy Caldera, DO, MS), vaccinology (Mary Hayney, PharmD, MPH), and immunology (Keith Knutson, PhD). Whether antibody concentrations will continue to wane after booster doses of mRNA vaccines and increase the risk of breakthrough infections in immunosuppressed patients remains unknown. Thus, there is a *critical need* to continue investigating ways to improve sustained protection in these populations. We will help answer this critical question with the following aims.

5.2 Study Aim and Hypotheses.

Aim 1: To determine whether providing a NVX-CoV2601 booster COVID-19 vaccine improves sustained humoral and cell-mediated immunogenicity against SARS-CoV-2 in immunosuppressed patients with IBD and/or solid organ transplant recipients.
We hypothesize that solid organ transplant recipients receiving a combination of immunosuppressive regimens will have lower antibody concentrations than patients with IBD because our previous work has shown that patients with IBD have higher rates of seroconversion than solid organ transplant recipients.

6.0 STUDY OBJECTIVES & ENDPOINTS

The vaccine will be evaluated for two seasons separately: 2023/2024 and 2024/2025. Thus, we will have two co primary objectives.

- 2023-2024 season

  The primary objective of this study is to evaluate the immunogenicity of a 2023/2024 (monovalent, XBB containing) Novavax COVID-19 vaccine, the Omicron XBB.1.5 NVX-CoV2601 in immunosuppressed populations.

- 2024-2025 season (The 2024-2025 season activities will not proceed as originally planned due to the withdrawal of financial support from our sponsor).

  The primary objective of this study is to evaluate the immunogenicity of a 2024/2025 (*monovalent, XBB containing)* Novavax COVID-19 vaccine, the *Omicron XBB.1.5* **NVX-CoV2601** in immunosuppressed populations.

6.1 Primary Objective

The following objective will be evaluated separately based on the season 2023-2024 and 2024-2025.

Humoral Immunogenicity of a NVX-CoV2601/(2024/2025 COVID booster).
We will evaluate antibody concentrations 1 month after the recombinant vaccine booster (V2) in patients with IBD and solid organ transplant recipients compared to their baseline visit (V1). We measured antibody concentrations in patients with IBD one-month post-booster and found robust responses.[10] We will measure anti-receptor binding domain (RBD) antibody levels and nucleocapsid antibodies in all participants at baseline and post-immunization.

Success Criterion: The objective of our primary endpoint will be achieved if the antibody concentration at V2 is at least 15% higher than at V1.

6.2 Secondary objectives

The vaccine will be evaluated for two seasons, separately: 2023/2024 and 2024/2025. Thus, we will have two co-secondary objectives.

6.2.1 Sustained antibody concentrations of NVX-CoV2601 booster dose/(2024/2025 COVID booster).

We will evaluate sustained antibody concentrations using a quantitative assay from LabCorp, which is currently being used by the Centers for Disease Control and Prevention (CDC) to evaluate seroprevalence and study immunity at six months after completion of the booster dose (V3).

Endpoint:
We will evaluate individuals who are seropositive at V2 and V3 in both groups.

Seropositivity rate at V2 and V3 in all participants.
Seropositive will be defined by positive anti-receptor binding domain (RBD) IgG antibodies specific to SARS-CoV-2 performed by Labcorp (greater than 1.0 in µg/mL).

Success Criterion: Descriptive

6.2.2 Seroconversion.

Percentages (and 2-sided 95% Cis) of participants who were seronegative (less than 1.0 in µg/mL) at baseline and became seropositive (greater than 1.0 in µg/mL) after immunization will be evaluated for before and after measures. For initially seropositive subjects at V1, antibody concentration at post-vaccination (V2) ≥ 4 fold the pre-vaccination antibody concentration.

Endpoint:
Individuals who achieve seroconversion at V2.

Success Criterion: Descriptive

6.2.3 Cell-mediated immunity to NVX-CoV2601/(2024/2025 COVID booster). COVID-19 booster vaccine.

We will evaluate cell-mediated immunity to a booster dose vaccine at baseline (V1) and one month after a booster dose (V2) in patients with IBD and solid organ transplant recipients. IFN-Ɣ ELISpot, which detects both CD4 and CD8 T cell effectors, will be used to detect T-cell immunity to the Covid-spike protein or peptides.

Endpoint:
We will evaluate the interferon gamma responses at V2 compared to V1.

An interferon gamma response will be considered any measurable response.

Success Criterion: Descriptive

6.2.4 Sustained cell-mediated immunity to NVX-CoV2601/(2024/2025 COVID booster). COVID-19 booster vaccine.

We will evaluate sustained cell-mediated immunity against Covid-spike proteins approximately six months following V1 (V1 + 180 days, +/-30 days) (V3)

Endpoint:
We will evaluate the interferon gamma responses at V3 compared to V1.

Success Criterion: Descriptive

The safety of the vaccine boosters will be assessed for both seasons separately. This includes section 6.3-6.5.

6.3 Describe the safety of NVX-CoV2601/(2024/2025 COVID booster). COVID-19 vaccine.

Participants will be asked to fill out their vaccine diary daily for 7 days post immunization. They will record the information daily for 7 days post immunization.
Participants will be provided a paper vaccine diary on visit 1 to enter their answers.

At follow up visit 1 the research coordinator will remind patients to complete their diary. If they have lost the diary the coordinator will fill out the diary with participant.

At follow up visit 1 they will be asked about any unsolicited or solicited adverse events occurred following immunization. The call will involve standardized list of potential adverse effects, including fever, injection site reaction, fatigue, myalgia, and other reactions not listed.[18]
Participants who do not fill out their vaccine diary or unable to be contacted at FU1 will be considered to have missing post immunization data. This data will be considered non-reported data.

Participants will be asked about unsolicited and solicited adverse events at all study visits V1, V2, and V3.

Safety and reactogenicity up to 30 days post-last vaccination and during the whole post-vaccination follow-up period

Endpoints:
Solicited Adverse Events (AEs)
The number and percentage of participants reporting each solicited local AE and each solicited systemic AE within seven days (Days 1-7) after the booster dose and overall will be summarized for both study groups.

- Solicited local AEs included injection site pain, redness, and swelling.
- Solicited systemic AEs included fatigue, myalgia, arthralgia, headache, shivering/chills, fever, and gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain).

Success Criterion: Descriptive

Unsolicited Adverse Events
The number and percentage of participants reporting unsolicited AEs within 30 days (Days 1-30) after the booster dose and overall will be summarized for both the study groups.

Success Criterion: Descriptive

Potential Immune-Mediated Diseases (pIMDs)
The number and percentage of participants reporting pIMDs from the booster dose to the study end will be summarized for both study groups. Please refer to the full list of pIMD's in Appendix 3.

Success Criterion: Descriptive

Serious Adverse Events (SAEs)
The number and percentage of participants reporting SAEs and fatal SAEs from the booster dose administration to the study end will be summarized for both the study groups.

Success Criterion: Descriptive

6.4 Evaluate the disease activity following administration of the booster dose up to 30 days post-vaccination and during the whole post-vaccination follow-up period.

Disease activity will be assessed by monitoring disease activity using the Short Crohn's Activity Index (SCAI)[19] for patients with Crohn's disease or the Simple Clinical Colitis Activity Index (SCCAI) questionnaire for patients with Ulcerative colitis at the baseline visit (V1), V2, and V3 visits. For patients with pouchitis we will use the simplified pouchitis disease activity index (PDAI). The incidence of IBD flares will be evaluated in all patients receiving recombinant boosters. This will be quantified by patients who were in clinical remission who develop a disease flare after receiving a recombinant COVID-19 booster.

Endpoint:
The number and percentage of participants reporting disease flares of IBD.

Success Criterion: Descriptive

6.5 Evaluate for solid organ transplant rejection following administration of booster dose, up to 30 days post- vaccination and during the whole post-vaccination follow-up period.

Participants will be asked if they have been diagnosed with acute rejection after their baseline visit (V1). Episodes of acute rejection will be collected by searching electronic medical records and asking patients at each clinic visit (V2 and V3). Acute rejection will be defined as a notation of a new episode of acute rejection (cellular or antibody-mediated), a steroid bolus and taper in the absence of another indication, or administration of a T or B cell depleting agent or immune globulin.[20]

This will be quantified by patients who develop acute rejection of their transplant after receiving a recombinant COVID-19 booster.

Endpoint:
The number and percentage of participants reporting acute rejection of their transplant.

Success Criterion: Descriptive

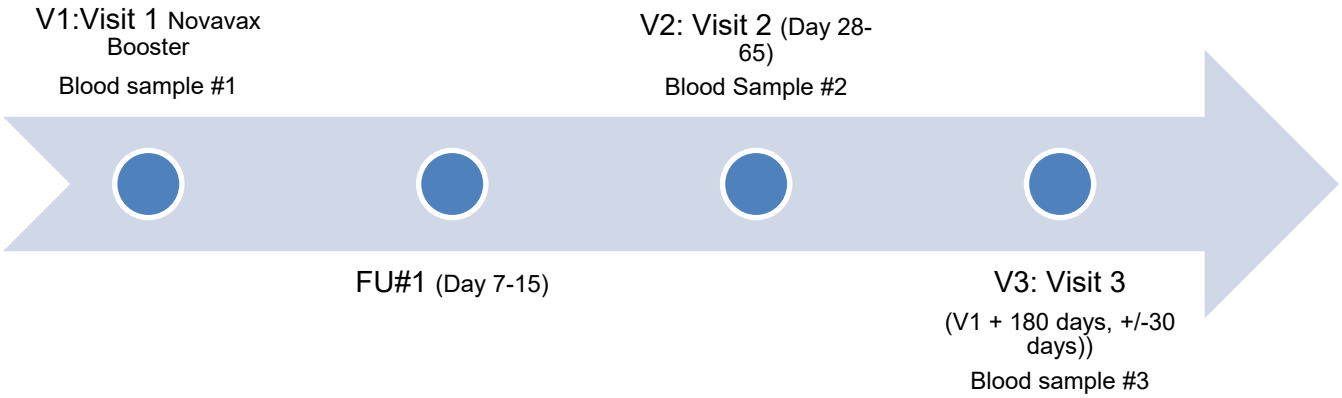
7.0 STUDY DESIGN

7.1 Program Type / Scope of Study / Clinical Design / Sites

This will be a single-center, prospective, unblinded, non-randomized study of 141 immunosuppressed patients who are planning to receive a NVX-CoV2601 COVID-19 vaccine booster dose as standard of care and are willing to participate in the study. We have paused recruitment in 2023-2024 season due to low recruitment. We are extending the study to enroll an additional 120 immunosuppressed patients who are planning to receive a *2024/2025* COVID-19 vaccine booster dose as standard of care and are willing to participate in the study.

During the 2024/2025 season at least 35 patients will have inflammatory bowel disease and at least 35 patients will be a solid organ transplant recipient. After obtaining informed consent, individuals who meet the inclusion criteria and none of the exclusion criteria will be invited to participate in the study. Blood samples will be collected from each participant at the baseline visit (V1), at 1M post–booster (V2 visit), and 6M post–booster (V3).

Figure 1. Schematic of Visits:



7.2 Site Responsibilities Overview

The University of Wisconsin Hospital and Clinics will be the site of the study and will be responsible for coordinating activities, receiving and analyzing samples and data, and developing and updating the study protocol as needed. The UNC-developed data/web platform will be used to collect subject data and subject data will be stored on UNC platforms. A Data Transfer Use Agreement between UW and UNC will be executed before the sharing of data with UNC begins. UNC will obtain their own IRB approval.

Communication plan: Monthly conferences led by Freddy Caldera, PI, with research staff at UW. In this teleconference, the following will be discussed: recruitment, barriers to recruitment, and potential future protocol changes.

Adverse events/SAE/Unanticipated problems: All events, including adverse events to vaccines, IBD flares, transplant rejection, noncompliance, unanticipated events, protocol deviations, protocol violations, or serious adverse events will be reported to the regulatory bodies, including the IRB, as appropriate and per posted guidelines. The UW PI will be responsible for reporting any adverse events, as described in the Safety Reporting section.

Compliance with protocol: To ensure that no deviations from the protocol occur, the PI will review random cases every two months. Any deviations in the protocol will be investigated to evaluate the root cause for deviation. Noncompliance, unanticipated events, protocol deviations, protocol violations, or serious adverse events will be reported to the IRB per the posted guidelines.

7.3 Study Population Overview

Adults with established IBD on immunosuppression age 18-85 years and/or solid organ transplant recipients on systemic immunosuppressive therapy.

Inclusion criteria

- Have received at least three doses of a COVID-19 vaccine.
- On systemic immunosuppressive therapy for inflammatory bowel disease
    - Immunomodulator (e.g. azathioprine, methotrexate)
    - Anti-TNF inhibitor
    - Il 12/23 blocker
    - IL 23 blocker
    - Janus Kinase inhibitor
    - S1P inhibitor

- On systemic immunosuppressive therapy for solid organ transplant
    - Mycophenolate
    - Tacrolimus or cyclosporine
    - Sirolimus or everolimus
    - Azathioprine
    - Corticosteroids
    - Belatacept

7.4 Study Duration

Major Study Periods

First Patient In (FPI) to Last Patient In (LPI):	6 months
LPI to Last Patient Out (LPO):	6 months
LPO to manuscript	4 months

We will publish the first manuscript based on the vaccine response baseline compared to 1 month post immunization 4 months after LPI.
The second manuscript will be published after completion of the study.

7.5 Ethical and Regulatory Considerations

Prior to initiating the study, IRB approval will be sought from the University of Wisconsin School of Medicine and Public Health.

Once approval is obtained, we will start recruitment. UW research staff (such as the PI and research coordinator) will hold monthly research conferences to ensure that there are no deviations in the protocol.

Compliance with protocol*:* To assure no deviations from protocol occur, random cases from the single-UW enrolling site will be reviewed by the PI to assure no deviations from protocol every 2 months. Any deviations in the protocol will be investigated to evaluate the root cause of the deviation.

The investigation will be conducted in compliance with the requirements for review by the IRB.

8.0 SELECTION AND WITHDRAL OF SUBJECTS

Patients with IBD (at least 35 subjects) and solid organ transplant recipients (at least 35 subjects)

8.1 Inclusion criteria

- Patient is between the ages of 18-85 years.
- Patient has a history of ulcerative colitis (UC), Crohn's disease, pouchitis, or indeterminate colitis diagnosed by standard clinical, radiographic, endoscopic, and histopathologic criteria.
  And/or patient is a solid organ transplant recipient (e.g. lung, kidney, liver)
- Have received at least three doses of a COVID-19 vaccine.
  - Three mRNA vaccines
    Or
  - One or two viral vector vaccine and one or two mRNA vaccines.

- Female participant of non-childbearing potential (pre-menarche, current tubal ligation, hysterectomy, oophorectomy or post-menopause) and childbearing potential (if they had: practiced adequate contraception (include -IUD or equivalent, hormonal contraceptive (e.g. pill, patch, ring, implant or an injection used consistently and that has reached full effect prior to the first dose of vaccine), hysterectomy and/or a bilateral tubal ligation or bilateral oophorectomy) for 1 month prior to vaccination and agreement to use such for an additional 8 weeks after administration of the Novavax COVID-19 vaccine). Non-pregnant females with a negative pregnancy test who are willing to practice adequate contraception 8 weeks after administration of the Novavax COVID-19 vaccine.

- On one of the following treatment regimens
  - IBD
    - Thiopurine Therapy Group: on azathioprine at least 2.0mg/kg or 6MP 1.0mg/kg
    - Anti-TNF Therapy Group: on maintenance therapy infliximab (at least every 8 weeks), golimumab (at least monthly), adalimumab (at least every 2 weeks), or certolizumab (at least monthly)
    - Anti-TNF Combination Therapy Group: on anti-TNF therapy as described above along with either 15mg of methotrexate or azathioprine at least 1.0mg/kg or 6MP 0.5mg/kg.
    - Vedolizumab Therapy Group: either vedolizumab monotherapy at least every 8 week dosing or combination therapy Group: on vedolizumab therapy at with azathioprine or methotrexate
    - Ustekinumab Therapy Group: either ustekinumab monotherapy or combination therapy with methotrexate or azathioprine.
    - Tofacitinib Therapy Group: on tofacitinib at least 5mg PO twice daily
    - Risankizumab Therapy: 360mg at least every 8 weeks
    - Mirikizumab: 200mg at least every 4 weeks
    - Upadacitinib Therapy Group: on upadacitinib at least 15mg PO daily
    - Ozanimod: at least 0.92mg once daily
    - Etrasimod: at least 2mg once daily

- Solid organ transplant recipient (on any dose of the following regimens: patients can be on more than one of the regimens below)
  - Mycophenolate
  - Tacrolimus or cyclosporine
  - Sirolimus or everolimus
  - Azathioprine
  - Corticosteroids
  - Belatacept

8.2 Exclusion criteria

A patient will not be eligible for inclusion in this study if they meet any of the following criteria.

- Allergy to recombinant COVID-19 vaccine or any component of it
- Patient cannot or will not provide written informed consent.
- Unable to provide appropriate informed consent because of illiteracy or impairment in decision-making capacity.
- Active antibody-mediated or cellular rejection within the past six months
- Recent IBD flare requiring initiation of systemic corticosteroids within the past month.
- Previous history of myocarditis or pericarditis ever.
- Patients who are pregnant
- Patients who are lactating
- Patients with an active COVID-19 infection
- Patients with a COVID-19 infection within the past two months

8.3 Subject Identification and Recruitment

Patients will be recruited from the University of Wisconsin Hospital and Clinics if they meet the inclusion criteria (see Section 8.0). Patients will be recruited in the following manner. Clinical research coordinators will prescreen provider clinic schedules (e.g. Clinics at the Digestive Health Center, Transplant Surgery, and etc.) and review medical records to evaluate potential study subjects that meet all inclusion criteria. The clinical research coordinator will review potential patients with the subspecialist who sees that patient. Any patient planning to receive a recombinant COVID-19 vaccine booster as standard of care will be invited to participate. Patients will be invited to participate after having any type of clinical contact with their provider or any member of their healthcare team. A member of the health team will provide patients with information about the study. The research coordinator will further review the information, invite participants to participate in the study, and obtain consent either in person or via remote consent.

If study team members are available, subjects would undergo an in-person consent discussion and be asked to sign a paper copy of the consent form. Alternatively, a member of the care team would obtain subject permission to allow study team members to contact the subject by phone for a follow-up discussion, and/or set up a virtual meeting using a HIPAA-compliant virtual platform, with subjects providing signed consent using an FDA part 11 compliant electronic signature (i.e., DocuSign).

Advertising (study flyers) will be posted throughout UW health entities such as the UW Digestive Health Center (DHC), 1 South Park, UW Hospital Ambulatory Center, Transplant Clinic, and other clinics throughout UW Health. These flyers will be used on TV screens in waiting room locations.

The study flyer will be shared through social media such as Twitter and tweeted by the PI, inviting patients to participate.

We will recruit participants via MyChart, UW Health's patient portal. Participants will be identified via a chart review by the Clinical Research Data Service (CRDS). We will obtain all needed approvals from UW Health and CRDS and follow the required workflows. We will/have create(d) an OnCore study record that is interfaced with Health Link and will track individual level recruitment in OnCore. Once approvals are in place, the IRB-approved invitation will be posted to invited participants' Research Studies page in MyChart and patients will initiate contact with study team if interested.

The patient-facing MyChart invitation is included with the IRB application for review and approval.

Patients will be recruited from the University of Wisconsin Hospital and Clinics if they meet the inclusion criteria (see Section 8.0). Patients will be recruited in the following manner. Clinical research coordinators will prescreen **using Research Elecetronic Data Capture (REDCap) database system from** provider clinics (e.g. Clinics at the Digestive Health Center, Transplant Surgery, etc.) and review medical records to evaluate potential study subjects that meet all inclusion criteria. The clinical research coordinator will review potential patients with the subspecialist who sees that patient. Any patient planning to receive a recombinant COVID-19 vaccine booster as standard of care will be invited to participate. Patients will be invited to participate after having any type of clinical contact with their provider or any member of their healthcare team. A member of the health team will provide patients with information about the study. The research coordinator will further review the information, invite participants to participate in the study, and obtain consent either in person or via remote consent.

A phone screening script will be used when contacting potential subjects by phone for recruitment or in person to the study flyer.

8.4 Remuneration for participation

Participants will be paid $75 for each completed in-person study visit for a total up to $75, $150, and $225, depending on the number of study visits. Payments will be made at the end of the study. If subjects choose to leave or are taken off the study before they complete it, they will receive payment for the visits completed.

8.5 Premature Subject Discontinuation

Patients will be encouraged to complete the study; however, they may voluntarily withdraw at any time.

The Principal Investigator may discontinue or withdraw a subject from the study for the following reasons at his/her discretion:

- Subject non-compliance with study requirements (e.g., study intervention non-compliance, do not complete scheduled visits)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject

Subjects who sign the informed consent form but do not receive the study intervention will be replaced and will not be counted against the enrollment total. A one-to-one replacement will occur. Every patient who does not receive the study intervention will be replaced with another participant.

9.0 STUDY AGENT - NOVAVAX COVID-19 VACCINE, ADJUVANTED

The U.S. Food & Drug Administration (FDA) required an investigational new drug (IND) for the use of the Novavax Covid-19 Vaccine, Adjuvanted currently available under an Emergency Use Authorization (EUA).

9.1 Source

Study drug will be provided free of charge by the manufacturer, Novavax, for the study. Novavax will distribute the study drug to the study site. The University of Wisconsin Madison's Pharmaceutical Research Center (PRC) will be responsible for receipt of the product from the manufacturer.

Each shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit, as well as a packing slip. On delivery of the product to the site, the person in charge of product receipt will follow standard PRC instructions for receipt of product, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature indicator). The contents of the shipment will then be reviewed and verified against the packing slip, and will be documented as instructed at the initiation visit.

If the temperature-monitoring indicator reflects that the cold chain has been broken, the entire shipment must be immediately quarantined and further processed consistent with PRC operating procedures.

9.2 Packaging and Labeling

The Novavax COVID-19 Vaccine, Adjuvanted will be obtained from the manufacturer in a multidose vial containing 5 or 10 doses of 0.5 mL each. Packages will be labeled with the statement ""Caution: New Drug—Limited by Federal (or United States) law to investigational use."

9.3 Preparation

The PRC will prepare the suspension for intramuscular injection as follows:

<u>Inspection of the vial</u>

- The Novavax COVID-19 Vaccine, Adjuvanted (Omicron XBB.1.5) NVX-CoV2601 is a colorless to slightly yellow, clear to mildly opalescent suspension, free from visible particles.
- The multi-dose vial will be gently swirled before each dose withdrawal. Do not shake.
- Each vial will be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The vaccine will not be administered if either of these conditions exist.

<u>Handling of Multidose Vial</u>

- The date and time of the first puncture will be recorded on the vial label.
- After the first needle puncture, the vial will be held between 2 to 25°C (36 to 77°F) for up to 12 hours.
- The vial will be discarded 12 hours after the first puncture.

<u>Handling of filled syringe</u>

- The date and time that the syringe was prepared will be recorded on the syringe label along with subject ID
- Syringes will be labeled with the statement ““Caution: New Drug—Limited by Federal (or United States) law to investigational use.”
- The syringe will be held between 2 to 25°C (36 to 77°F) for up to 12 hours.

9.4 Storage and Stability

Investigational product must be stored separately from normal hospital stocks and must be stored in a securely locked area accessible only to authorized trial personnel until dispensed. The temperature must be monitored and documented on the appropriate form for the entire time that the investigational product is at the trial site. If the storage temperature deviates from the permitted range, the investigational product must not be administered, and the sponsor-investigator should be contacted for additional instruction.

Novavax COVID-19 Vaccine, Adjuvanted unpunctured multi-dose vials may be stored in refrigeration between 2 to 8°C (36 to 46°F). Vaccine must not be frozen and must be protected from light. After the first needle puncture, the vial may be held between 2 to 25°C (36 to 77°F) for up to 12 hours. Discard the vial 12 hours after the first puncture.

9.5 Accountability

The PRC will maintain records of product delivery, site inventory, and product disposal or return. The data coordinating center will verify each site’s product accountability records against the record of administered doses in the electronic case report forms (eCRFs), the source documents, and the communication from the online randomization program.

9.6 Dosing and Administration

Study product will be supplied by the PRC as 0.5 mL single-dose, pre-filled syringes. Administer as follows:

- Visually inspect the syringe for particulate matter and/or discoloration prior to administration. If either of these conditions exist, do not administer.
- Gently shake the prefilled syringe.
- Identify the deltoid muscle (upper arm) and cleanse the injection site with alcohol.
- Insert needle (22 to 25 -gauge 1-inch needle recommended; 1 ½ inch needle recommended for those with BMI ≥ 30) at a 90-degree angle to the skin and inject entire contents of the syringe intramuscularly. Do not inject the vaccine subcutaneously or intravenously. Care should be taken to avoid administering the injection into or near blood vessels and nerves.
- Monitor the subject for at least 15 minutes post administration. Monitor for 30 minutes if allergy-related contraindication to another type of COVID-19 vaccine, non-severe immediate (onset within 4 hours) allergic reaction after a previous dose of COVID-19 vaccine or anaphylaxis after non-COVID-19 vaccines or injectable therapies.

10.0 STUDY ASSESSMENT SCHEDULE AND PROCEDURES

10.1 Study Calendar

Procedure (Visit Window)	**Visit 1 (V1)** (Day 0)	**F/U 1[5]** (Day 7-15)	**Visit 2 (V2)** (Day 28-65)	**Visit 3 (V3)** (V1 + 180 days +/- 30 days)
Informed Consent	X			
Demographics	X			
Concomitant Medications	X		X	X
Medical History[1]	X			
Inclusion/Exclusion Criteria	X			
Blood draw (Serum & CMI)	X		X	X
Standard of Care Recombinant COVID-19 Vaccine Booster	X			
7-Day Vaccine Diary[2]	- - - - - - - -X - - - - - - -			
SCAI, PDAI, or SCCAI Questionnaire[3]	X		X	X
Adverse Event Monitoring	X	X	X	X
Telephone Contact[4]		X		

Notes:

1. Baseline medical history included all IBD diagnoses or solid organ transplant diagnoses, medication history, and information in the source documents.
2. Dispense the 7-day Vaccine Diary at Visit 1 for subjects to complete at home.
3. SCAI, PDAI, or SCCAI will be administered based on IBD diagnosis at visits 1, 2, and 3.
4. Between Visit 1 and Visit 2, the study staff will attempt two phone contacts to assess AEs and remind them to complete vaccine diaries as well as to assist with subject retention.
5. Visits can be conducted via telephone calls. Patients who don't respond to survey will be emailed and receive a phone call reminding them to fill out diary.

10.2 Study Assessments by Visit

Visit #1 (V1) Baseline/Enrollment Visit (Day 0)

- Obtain written informed consent or remote consent.
- Review the inclusion and exclusion criteria to confirm eligibility.
- Assign Subject ID number.
- Record demographics (gender, age, race and ethnicity)

- Collect medical history, including vaccination history and medications (ongoing and any medications taken during the last 30 days)
- If patient has IBD complete Short Crohn's Activity Index (SCAI), Simplified Pouchitis Disease Activity Index (PDAI), or Simple Clinical Colitis Activity Index (SCCAI)
- Collect a baseline blood sample #1 of approximately 60ml (12 teaspoons)
- Provide study intervention, recombinant NVX-CoV2601 COVID-19 booster.
- If the patient is receiving the standard-of-care blood tests, these additional research samples will be collected at the same time as the standard-of-care tests.
- Subjects will be instructed to contact the study team with any concerns or development of fever, chills, rash, or other concerning symptoms.
- A paper version of the vaccine diary chart is also provided.
- A paper ruler will be provided to measure any swelling or redness.

Follow up Phone Call (Day 7-15)

- 7-15 days after the patient receives the COVID-19 vaccine booster, the patient will be contacted by clinical research coordinator
- Collect information to identify any adverse events including fevers or chills, rash and any unplanned visits to the emergency room or to their primary care physicians.
- Collect vaccine diary (phone) remind patient to fill out if not already filled out.

Visit #2 (V2) Month 1 (Day 28-65) post COVID-19 booster.

- Collect blood sample #2 of approximately 60ml (12 teaspoons)
- Collect SCAI, PDAI, or SCCAI for patients with IBD.
- Ask solid organ transplant recipients if they have been diagnosed with transplant rejection.
- Collect information to identify any adverse effects, including, fever, chills, rash, and any unplanned visits to the emergency room or to their primary care provider.

Visit #3 (V3) (V1 + 180 days +/- 30 days)

- Collect blood sample #3 of approximately 60ml (12 teaspoons)
- Collect SCAI, PDAI, or SCCAI for patients with IBD.
- Ask solid organ transplant recipients if they have been diagnosed with transplant rejection.
- Collect information to identify any adverse effects, including, fever, chills, rash, and any unplanned visits to the emergency room or to their primary care provider.

10.3 Informed Consent Procedures

The informed consent process will be conducted following all federal and institutional regulations relating to informed consent. Informed consent will be obtained prior to conducting any study-related activities.

The informed consent process will be performed as follows:

- Delegated study staff will review the informed consent form and discuss the study in detail with the potential research subject.
- Delegated study staff will explain the study, its risks and benefits, what would be required of the research subject, and alternatives to participation.
- The research subject will be given the opportunity to take the informed consent form home so that they may discuss it with family members, friends, clergy or others when possible.

- The subject will have the opportunity to ask questions and have all questions answered by the delegated study staff and/or PI.
- The informed consent document must be signed and dated by the research subject.
- Delegated study staff will review the informed consent document to ensure that all fields that require a response are complete (i.e., checkbox marked yes or no, etc.) as applicable.
- The research subject will be given a copy of the signed and dated informed consent form. The original signed informed consent form is kept with the subject records.

A research subject will be defined as "enrolled" in the study when they meet the following criteria:

- The subject has been consented by study staff and received the study intervention.

10.4 Clinical assessments

10.4.1 Blood Samples

All subjects participating in the study will have blood specimens collected at three in-person visits. All of these blood specimen collections will be for evaluation of humoral and cell mediated immunity to COVID-19 vaccine. To evaluate humoral immunity we will send samples to LabCorp. They will use a quantitative assay to determine COVID-19 antibodies. We have used these assays in our previous studies evaluating humoral immunogenicity to COVID-19 vaccines. [10, 21]

Cell-mediated immunity to COVID-19 will be evaluated at UW. Specimens at UW will be labeled with the subject's study ID number and date of collection so that the data collected for this protocol can be linked to the sample. Samples will be stored in Rennebohm Hall at the University of Wisconsin. Only investigators and key personnel assigned to the laboratory have access to the lab. Samples will be coded (labeled with subject ID and date of collection) before they arrive at the laboratory. All computers used for data storage and analysis are password protected and used exclusively by key personnel.

Blood samples will be stored for future unspecified studies. Participants may withdraw their samples by contacting Dr. Caldera at any time. Any future studies that will utilize these specimens will be done by UW researchers and will be submitted for a separate IRB approval. Only coded samples and data will be released for future research. Information linking the samples and data to individual participants will not be released.

COVID-19 antibody concentration analysis: These samples will be shipped to LabCorp. They will use LabCorp's Cov2Quant IgG™ assay which uses immunoassay that uses electrochemiluminescent technology (ECL) for quantitative determination of anti-receptor binding domain (RBD) IgG antibodies specific to SARS-CoV-2. The RDB of the spike protein is the moiety that interacts directly with the ACE2 receptor on a host cell to enable viral entry. In addition to RBD being a critical player, it is also poorly conserved among other coronaviruses. Therefore, RBD represents a promising antigen for detecting SARS- antibodies in humans. There is also a strong correlation between levels of RBD-binding antibodies and SARS-COV-2 neutralizing antibodies in patient sera. The results of this assay will be shared with patients as positive or negative rather than the amount of antibody detected. Patients will be asked to follow up with their gastroenterologist or transplant surgeon if they have any questions regarding the test results. We will also use LabCorp Qualitative detection of high affinity antibodies to SARS-CoV-2 nucleocapsid (N) protein, the virus that causes COVID-19, to aid in identifying individuals with an

adaptive immune response to SARS-CoV-2, indicating recent or prior infection. This will be done at every time point.

Cell Mediated Immunity to COVID-19
For each patient, peripheral blood mononuclear cells (PBMCs) will be isolated from green tubes or CPT tubes per study visit, and stored in liquid nitrogen. IFN-Ɣ ELISpot, which detects both CD4 and CD8 T cell effectors, will be used to detect T-cell immunity to the Covid-spike protein or peptides. The plates will be read on an AID ELISpot reader (Cell Technology, Inc., Columbia MD, reader software v.3.1.1.). A positive response to antigen will be defined as a frequency that was significantly ($p < 0.05$, two-tailed t test) greater than the mean of control no-antigen wells and detectable (i.e., >1:100,000). T cell responses will be correlated to Covid-19 neutralizing antibody responses. We have previously evaluated cell-mediated immunogenicity to COVID-19 vaccine in patients with IBD. [22]

10.4.2 Disease Activity Assessment

The Short Crohn's Activity Index (SCAI), the Simplified Pouchitis Disease Activity Index (PDAI), or the Simple Clinical Colitis Activity Index (SCCAI) questionnaire will be used to assess CD, Pouchitis, or UC disease activity, respectively (**Appendices 1 and 2**). These assessments include questions about patient overall well-being as well as specific symptoms and complications of CD or UC, such as stool frequency and abdominal pain.

Subjects will be questioned at each visit, V1, V2, and V3, regarding their clinical symptoms and subsequently scored accordingly.

Transplant Rejection
Episodes of acute rejection will be collected by searching electronic medical records and asking patients at each clinic visit V1, V2, and V3. Acute rejection will be defined as a notation of a new episode of acute rejection (cellular or antibody-mediated), a steroid bolus and taper in the absence of another indication, or administration of a T or B cell depleting agent or immune globulin.

10.4.3 Adverse Events Assessments

Adverse events data collection for this study begins at the time the subject signs the informed consent. Adverse event assessments included questioning subjects both at the follow-up phone call and at the follow-up visit regarding Adverse Events and SAEs.

Participants who do not fill out their vaccine diary or unable to be contacted at FU1 will be considered to have missing post immunization data. This data will be considered non-reported data.

10.4.4 Other Measurements

Medical history, including medications used to treat IBD or solid organ transplant, will be obtained from the subjects' medical records and entered into the research records. Medical history included all diagnoses and other diseases.

Medication history must be present in the subject's medical records and recorded in the subject's research records, including all prescription medications and nonprescription therapies taken within 30 days prior to the initial visit.

Data Handling and Record Keeping The only identifiers UNC will have access to are Subject ID numbers and dates of service and vaccination. They will not have access to linking coded data. The link to the subject ID will be maintained by UW research staff.

11.0 DATA HANDLING AND RECORD KEEPING

Data will be stored on a web-based platform to collect all patient-related information, disease activity, and other study questionnaires. This web-based platform will be developed by University of North Carolina. They will not be the data safety monitor for the study.

The University of North Carolina will serve as a Data Management Center (DMC) for this study. The work will be conducted in the Bioinformatics and Biostatistics Core of the Center for Gastrointestinal Biology and Disease (CGIBD). Dr. Millie Long, will lead the DMC for this study. The Core has served as the Data Management Center for the Crohn's and Colitis Foundation Clinical Alliance. In that capacity the DMC has conducted a number of randomized trials and observational studies of IBD. They have also served as the Data Management Center for the Sinai Helmsley Alliance for Research Excellence which is a multicenter study of patients with IBD. The DMC will be charged with creating, managing, and housing the data management system.

The DMC will be responsible for all of the data management needs of the study. These activities will include, but not be limited to the following. They will build applications to collect baseline and follow-up data as specified in the protocol, generate reports about recruitment, enrollment, compliance, and dropouts, provide barcodes for biological specimens and build tracking programs for the specimens, provide data sets for analysis, and participate in data analysis and reporting. The only identifiers UNC will have access to are Subject ID numbers and dates of service. They will not have access to linking coded data. The link to the subject ID will be maintained by UW research staff.

Site Coordinators will collect data on source documents and will complete double data entry onto electronic CRFs in the data management system created by the DMC. Participants will collect data via direct data capture. All of the data will be maintained, archived, retrieved and distributed (except for the source documents completed by the Site Coordinators), by a computer system. The use of electronic records will increase the speed of data collection and exchange. Electronic records permit economical storage of study data and ease of accessibility and analysis. Data management and data quality systems will be built into the system. The DMC will have password-required access to the data management system where they can export data. UW will have password-required access to the data management system as well but they will only have access to their site's data and they will not be permitted to export the data.

The DMC at the CGIBD at the University of North Carolina will track the data collection, provide data security, control for confidentiality of study data, maintain computer backups to protect data until study closure and archive study data. Electronic signatures will be linked to each entry.

All computer systems and programs will be password protected, and all electronic communications of study and other confidential information will be encrypted. Personnel at the CGIBD have extensive training and experience using electronic data systems. Good computer security practice (restricting physical access to machines, prohibition of password sharing, and logging off computers after work hours or when away from the machine) will be required of all study personnel.

Standard Operating Procedures exist for users of the DMC. The DMC will be housed on an https secure website in order to protect the study participants' information. Only authorized persons are authorized for data entry and access. Data security systems require password protected identification codes for data entry and provide protection against data manipulation. The database is located on a server protected by firewalls. Access to the database server will not be allowed by

users on computers outside of the firewall-protected zone. Virus protection software is installed on each study machine. System access to computer systems will be audited. Redundant backups and off-site backup storage will allow for quick restoration of data in the unlikely event that a hardware failure, disaster, or security breach should occur. Servers and backups will be located in a secured location with access limited to authorized personnel.

Standardized study management reports will be generated monthly during the recruitment phase of the study. These reports will be used to track study progress including patient enrollment, randomization, compliance, patient status changes, and study events. The data will be reported for each Study Center individually and summarized for the study as a whole. Every six months, a standardized report will also be generated for meeting with University of Wisconsin team. This report will include additional information on clinical events and adverse events that is coded by treatment group. Other than the UW, the study statistician and statistical analyst, no study personnel will see this report.

Patient data from in-person visits will also be recorded in the electronic medical records. Any original subject files and protocol paperwork will be kept in the secured Office of Clinical Trials. We will keep these files within the Office of Clinical Trials until 2 years after the study completion at that time they will be archived to the State Record Center.

Transfer of data: LabCorp will perform quantitative COVID-19 antibody levels, they will transfer final data to UW for final analysis in files that will be password protect by LabCorp IT service.

Specimens at UW will be labeled with the subject's study ID number and date of collection so that the data collected for this protocol can be linked to the sample. Samples will be stored in Rennebohm Hall at the University of Wisconsin. Only investigators and key personnel assigned to the laboratory have access to the lab. Samples will be coded (labeled with subject ID and date of collection) before they arrive at the laboratory. All computers used for data storage and analysis are password protected and used exclusively by key personnel.

Any future studies that will use these specimens will be conducted by UW researchers and submitted for separate IRB approval. Only coded samples and data will be released for future research. Information linking the samples and data to individual participants will not be released.

All data will be labeled with the subject's study ID number and stored at the University of Wisconsin. Data will be stored in an Excel spreadsheet on secured servers and will only be accessible to those with a valid UW username and password with the right to see those files. The link connecting the subject ID number and study data will be stored separately from the study data. The servers are housed in locked cabinets inside locked, climate-controlled rooms. Access to UW servers is restricted by UW firewalls. Any connections to UW servers from outside the UW network must travel over UW Madison's virtual private network (VPN). This ensures that all communications between the UW and remote user are encrypted.

The samples shipped to LabCorp will be destroyed by them. Cell-mediated immunity will be analyzed, and the samples will be banked. Banked data may be used in future research to study the clinical outcomes of the COVID-19 vaccination and the sustained protection provided by the vaccine. These data may also be utilized to study the safety of vaccination and its long-term protection against COVID-19.

12.0 STUDY ANALYSIS

12.1 Number of Subjects (Statistical Justification)

We used results from our previous COVID-19 vaccine study to calculate our sample size needed for this study.We anticipate that antibody concentrations wane but with infection and multiple doses of vaccine, we estimated that the trough antibody concentration will be somewhat higher than it was after two doses of vaccine. The sample size 20 patients for this study was chosen based on feasibility and practicality of enrolling such patient populations. Therefore, a formal sample size estimation was not calculated, as the results would be deem descriptive and exploratory in nature. However, this sample size is sufficient to provide accuracy in estimating adverse event rates.

12.2. Statistical Analysis

In general, simple descriptive statistics will be provided to summarize demographics and baseline characteristics parameters. Categorical data will be summarized as frequency and its corresponding percentage. For continuous data, frequency (n), mean, standard deviation, median (as appropriate), minimum, and maximum will be provided for each of the parameters. A formal statistical analysis plan (SAP) will be developed before the database lock. It will include a detailed description of summaries and mock-ups of tables, listings, and figures to be included in the clinical study report.

In analyzing the primary endpoint, frequencies and percentages of antibody concentrations will be summarized in table formats. For exploratory purposes, a paired t-test will be utilized to test whether, on average, there is a change of at least 15% antibody blood concentration between the first and second blood draws. A test statistics and degrees of freedom, including the 95% confidence intervals will be reported

For the secondary endpoints, we will use descriptive statistics and formal tests (for exploratory purposes) to analyze the data, as described above, when appropriate and informative.

13.0 SAFETY REPORTING

13.1 Definitions:

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure*.
* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

Adverse Events will be reported in accordance with all 21 CFR 312.32 requirements" (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32)

Medically attended AEs

MAEs will be collected during the 6 months after vaccination. Medically attended AEs are defined as AEs leading to a visit to or from medical personnel for any reason. A phone call with a healthcare professional was not considered medically attended.

Participants will be asked about any AE at FU1, V2, and V3. Research coordinators will interview all participants at these visits and ask them about any AE since immunization.

Serious adverse Event.

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, meets any of the following criteria:

- Results in death
- Are life-threatening (Refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically, might have caused death if it were more severe.)
- Requires an inpatient hospitalization or prolongation of an existing hospitalization

- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.)
- Results in a congenital anomaly/birth defect, constitute, based upon appropriate medical judgment, an event that may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.
- Important medical events that may not result in death, be life-threatening, or require hospitalization and that may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse")

13.11 Relationship of Adverse Event to Study Vaccine

The relationship or association of the study vaccine in causing or contributing to the AE will be characterized by the investigator as "Related" or "Not Related". All AE, SAE, Adverse of Special interest will be presented in a summary table. If the relationship information is missing, the AE will be considered "Related" in the summary but will be presented as missing in the data listings.

We will use a binary scale related versus not related. We will use the following definitions:

- **Not related**: There is not a reasonable possibility of relationship to study vaccine. The AE does not follow a reasonable temporal sequence from administration of study vaccine or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).
- **Related:** There is a reasonable possibility of relationship to study vaccine. The AE follows a reasonable temporal sequence from administration of study vaccine and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications), represents a known reaction to study vaccine or other vaccines in its class, is consistent with the known pharmacological properties of the study vaccine, and/or resolves with discontinuation of the study vaccine(and/or recurs with re-challenge, if applicable).

13.2 Severity of Event

All AEs will be assessed by the principal investigator using the Table below.

The intensity of the following solicited AEs will be assessed as described:

Table Intensity scales for AEs

Event	Intensity grade	Parameter
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
	4	Potentially life threating: Emergency room (ER) visit or hospitalization
Redness at administration site		Greatest surface diameter in mm (see below)
Swelling at administration site		Greatest surface diameter in mm (see below)
Temperature*		Temperature in °F (see below)
Pruritis at administration site	0	None
	1	Mild: Itchy sensation that neither interferes with nor prevents normal everyday activities.
	2	Moderate: Itchy sensation that interferes with normal everyday activities.
	3	Severe: Itchy sensation that prevents normal everyday activities.
	4	Potentially life threating: ER visit or hospitalization
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
	4	Potentially life threating: ER visit or hospitalization
Fatigue	0	None
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
	4	Potentially life threating: ER visit or hospitalization
Myalgia	0	None
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity

Event	Intensity grade	Parameter
	4	Potentially life threating: ER visit or hospitalization
Arthralgia	0	None
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity
	4	Potentially life threating: ER visit or hospitalization
Gastrointestinal symptoms	0	None
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
	4	Potentially life threating: ER visit or hospitalization
Shivering/chills	0	None
	1	Mild: Shivering that is easily tolerated
	2	Moderate: Shivering that interferes with normal activity
	3	Severe: Shivering that prevents normal activity
	4	Potentially life threating: ER visit or hospitalization
Acute allergic event	0	none
	1	Transient flushing or rash; drug fever <38°C (<100.4°F)
	2	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)
	3	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension
	4	Anaphylaxis/Death
Syncope	0	None
	1	Pre-syncopal symptoms light headness.
	2	Symptoms without loss of consciousness
	3	Symptoms with loss of consciousness
	4	Life threatening consequences
Paresthesia	0	None

Event	Intensity grade	Parameter
	1	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function
	2	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL
	3	Sensory alteration or paresthesia interfering with ADL
	4	Disabling
Hypoesthesia	0	None
	1	Asymptomatic; altered sensory response (e.g touch, virbtation or cold temperature) but not interfering with function
	2	Sensory alteration, interfering with function, but not interfering with ADL
	3	Sensory alteration interfering with ADL
	4	Disabling

*Fever is defined as temperature ≥ 38.0°C (100.4°F) by any route. The preferred location for measuring temperature will be the oral route.

The maximum intensity of injection administration site redness/swelling and fever will be graded as follows:

	Redness/swelling	Fever
0:	≤20 mm	<38.0°C (100.4°F)
1:	>20 - ≤50 mm	≥38.0°C (100.4°F) - ≤38.5°C (101.3°F)
2:	>50 - ≤100 mm	>38.5°C (101.3°F) - ≤39.0°C (102.2°F)
3:	>100 mm	>39.0°C (102.2°F)
4	Necrosis or exfoliative dermatitis	Fever resulting in hospitalization

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to 1 of the following categories:

Grade	
1 (mild)	An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe)	An AE which prevents normal, everyday activities. Such an AE would, for example, prevent attendance at work/school and would cause the participant to seek medical advice.
4 (potentially life threating)	An AE which results in an emergency room visit or hospitalization

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in the section above.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4) because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; however, the event itself may be of relatively minor medical significance (such as a Grade 3 headache). This is different from serious, which is based on the patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. Severe AE (grade 3 or 4) do not necessarily need to be considered as serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

13.21 Adverse Events of Special Interest

Myocarditis and pericarditis will be adverse events of special interest. All patients will be counseled on the potential risk of myocarditis or pericarditis from COVID-19 vaccination.

1) Potential myocarditis and pericarditis events

a. Participants reporting acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis within 4 to 6 weeks after vaccination must be referred to a cardiologist for evaluation and management.

b. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings.

Myocarditis and pericarditis cases will be defined by based on the Centers for Disease Control and Prevention (CDC) care definition. [23] (Appendix 5)

2) IBD flares will be evaluated based on SCAI, PDAI, and SCCAI based on follow-up at V1, V2, & V3,.

3) Solid organ transplant rejection will be reviewed based on follow-up at V1, V2, & V3. Episodes of acute rejection will be documented by chart review.

13.22 Expectedness to Study Intervention

The PI will be responsible for determining whether an AE is expected or unexpected in relation to the study procedures and intervention(s) (as applicable).

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the clinical protocol, device manual, investigator's brochure, the package insert(s), the IRB application, or the informed consent document. Expectedness is recorded for both study procedures and interventions.

13.23 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after the administration of the study drug through the 6 month follow-up visit. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution, stabilization, or completion of study participation.

13.24 Reporting AEs and SAEs

Institution/Investigator is solely responsible for reporting all Adverse Events and Serious Adverse Events to regulatory authorities, investigators, IRBs or IECs, and Novavax, as applicable, in accordance with national regulations in the countries where the study is conducted.

13.24.1 Reporting AEs

- AEs will be recorded from the initiation of study treatment until the 6 month follow-up visit.
- AEs will be recorded regardless of whether they are considered related to the study drug(s).
- All AEs will be recorded on the appropriate study specific eCRF form within <the clinical trial management system>.
- All AEs considered related to the vaccine will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or study completion.

13.24.2 Reporting of SAEs

The sponsor-investigator will immediately review all SAEs, whether or not considered study intervention-related, including those listed in the protocol or package insert and will provide an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All SAEs will be followed until satisfactory resolution or until the sponsor-investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC) should be provided as soon as possible.

The sponsor-investigator will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor-investigator must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

13.24.3 Additional Reporting Requirements

Regardless of expectedness or causality, all must also be reported in English by a facsimile to Novavax or a designee:

> **Adverse Event Reporting.** Investigator shall report all Adverse Events (“AEs”), including follow-up information, as defined below, concerning a Novavax Product directly to Novavax by emailing PostmarketingPVOps@Novavax.com in the form of a CIOMS I Form or electronic AE Data Capture Form:
>
> - within one (1) Business Day of receipt/awareness of a Serious Adverse Event (SAE), as defined below;
>
> - within three (3) Business Days of receipt/awareness of an AEs.

> On a monthly basis, Investigator will provide a listing of all AEs sent to Novavax PostmarketingPVOps@Novavax.com for the previous month. The reconciliation list should be provided no later than the 15th of the month for the previous month. Any discrepancy identified during reconciliation shall be investigated, clarified, and agreed upon by both parties.

Novavax shall be solely responsible for reporting of Adverse Event information to regulatory authorities, which shall include reporting of individual Adverse Events and periodic safety reports.

"**Adverse Event**" means any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes other safety information such as:

- Overdose, abuse, or misuse of the product;
- An adverse event occurring from the withdrawal of the product;
- Lack of product effect/efficacy;
- Accidental exposure;
- Medication error (i.e., administration of expired product)
- Pregnancy or exposure during breast feeding;
- Suspected transmission of infectious agents;
- An unexpected therapeutic or clinical benefit;
- Off label use.

"**Serious Adverse Event**" means any untoward medical occurrence that, at any dose,

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of an existing hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

Fatal and Life-Threatening SAEs within 1 business day of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non-life threatening) events within 3 business days of the sponsor-investigator's observation or awareness of the event

All reported adverse drug reactions and safety issues related to Novavax will be included in the final study report.

13.25 Unanticipated Problems

An unanticipated problem (UP), as defined by the DHHS Office for Human Research Protection (OHRP), is any incident, experience, or outcome that meets all of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the informed consent documents, the Investigator's Drug Brochure) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.
- The incidence, experience, or outcome is related or probably related to participation in the research study. "Probably related" means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

The investigator will report UPs to the reviewing IRB and to the Data Coordinating Center (DCC). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol, informed consent documents, or other corrective actions that have been taken or are proposed in response to the UP.

Report UPs within the timeframe specified by the IRB of record.

13.26 Safety Oversight and Stopping Rules

To evaluate whether the vaccine results in SAE, IBD flares, transplant rejection, or myocarditis/pericarditis these will be monitored with the following DSMP. For every 40 patients enrolled in the study, the rate of SAE and IBD flares or episodes of acute rejection will be reviewed. SAE will be reviewed based on follow-up at V1, V2, V3, and vaccine diaries. IBD flares will be evaluated based on SCAI, PDAI, and SCCAI, and episodes of acute rejection will be documented by chart review. Episodes of potential myocarditis or pericarditis will be reviewed after evaluation by a cardiologist and defined based on CDC case definition (appendix 5).A The Principal Investigator (PI) will be responsible for reviewing these data will be reviewed continuously and pause the study if any stopping rules are met. He will have the SMC review the AE and determine if study should be stopped.

The study will be halted if any of the following criteria are met:

- Any serious AE occurs, including death, that is assessed as related to the product and occurring within the entire length of the study.
- Three or more participants experience the same or similar grade 3 or greater AEs, including laboratory abnormalities, that are assessed as related to the product, and occurring within the entire length of the study.
- More than 5 participants have an IBD flare of at least moderate activity (defined by the Short Crohn's Disease Activity Index [sCDAI], Simplified Pouchitis Disease Activity Index [PDAI], or the Simple Clinical Colitis Activity Index [SCCAI]) without a known cause.
- More than 4 participants have allograft rejection that requires treatment without a known cause. [24]
- More than 2 participants have an episode of myocarditis or pericarditis.

In the event that study stopping rules are met, enrollment and vaccine administration in the study will be paused while an assessment by the Sponsor-Investigator takes place.

Progress reports and notifications of unanticipated problems, adverse events, protocol deviations, and protocol violations will be reported to the IRB per the posted guidance.

13.27 Study Monitoring

We will use an internal safety monitoring committee (SMC) comprised of experienced clinical researchers representing a diversity of backgrounds, skills and knowledge. The SMC helps investigators ensure subject safety, research integrity, and compliance with federal regulations and local policies. The SMC also makes recommendations to the PI that could include actions of continuation, modification, suspension, or termination.

The SMC will be able to meet on an adhoc basis to review any number of AE, SAE, or AE of special interest that may have met the stopping rules. They will determine if these events have met the criteria for halting the study. Recruiting will halt until the SMC has determine whether the stopping rules have been met. If the SMC determines the stopping rules have not been met then resumption of enrollment will continue.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements.

- Monitoring for this study will be performed by the University of Wisconsin – Madison's Central Monitoring Service.
- On site monitoring will be conducted for this study which will include a site initiation visit, interim monitoring visits, and close out visit as outlined in the clinical monitoring plan. Monitoring will include review of regulatory files, investigational product, and up to 20% of subject records and data. Additional records may be reviewed, as needed, to ensure compliance with applicable regulatory requirements.

- The sponsor-investigator will be provided copies of monitoring reports within 30 days of visit.

14.0 RISK-BENEFIT

14.1 Risks of Study

The risks to subjects in this trial will be minimized by compliance with the eligibility criteria, clinical monitoring, adherence to protocol requirements, and investigator guidance regarding specific safety areas.

Appropriate medical treatment will be available to manage immediate allergic reactions in the event an acute anaphylactic reaction occurs following administration of the Novavax COVID-19 Vaccine, Adjuvanted.

Adverse reactions reported in clinical trials following administration of the Novavax COVID-19 Vaccine, Adjuvanted include injection site pain/tenderness, fatigue/malaise, muscle pain, headache, joint pain, nausea/vomiting, injection site redness, injection site swelling, fever, chills, injection site pruritus, hypersensitivity reactions, lymphadenopathy-related reactions, myocarditis, and pericarditis.

Myocarditis, pericarditis, anaphylaxis, paresthesia, and hypoesthesia have been reported following administration of the Novavax COVID-19 Vaccine, Adjuvanted outside of clinical trials.

The rate of IBD flares or solid organ transplant rejections will be evaluated in the study populations following the administration of the Novavax COVID-19 vaccine.

To ensure subject privacy, the study procedures will be performed in a private room. The study team members will be in a private space when conducting study phone/video calls with potential participants.

The specific safety areas that will be closely monitored in this subject population are the risk of flares post-immunization and the rates of transplant rejection.

Loss of confidentiality: There is a risk that the subject information could become known to someone not involved in this study.

Phlebotomy: Blood draws can cause bruising in the skin at the injection site and, rarely, infection in the skin. Rarely, dizziness or fainting occurs after blood is drawn.

14.2 Potential Benefits of Study

Beyond any protection from COVID-19 infection conferred by this vaccine booster dose, this study may benefit other people in the future by helping us learn more about immune responses to the recombinant COVID-19 vaccine in immunosuppressed populations, especially a mix and match strategy. This study will help determine whether patients with IBD on certain immunosuppressive regimens will require booster doses of COVID-19 vaccines.

15.0 STUDY FEASBILITY

Currently greater than 1500 patients are seen at UW health for the treatment of their inflammatory bowel disease and at least 800 transplants are performed annually. The majority of patients with IBD and solid organ transplant recipients who are seen at UW health facilities will be eligible to participate in our study. We have 6 providers that focus exclusively seen patients with IBD and the transplant surgery group consist of 13 faculty. We anticipate that we will be able to recruit 35 patients per month to participate in our study.

The primary outcome will be 1 month post-immunization, so we anticipate that we could submit this information as a late-breaking abstract to Digestive Disease Week 2025 in February 2025.

The study duration will be approximately 2 years. Each subject will be involved in the study for approximately 6 months.

The strengths of conducting studies at the University of Wisconsin include a collaborative team with research expertise, and access to the Wisconsin Immunization Registry (WIR), a state-wide computerized internet database that was developed to record and track immunization records of Wisconsin residents. The WIR captures 97% of vaccines administered in the state,[25] including data from both public and private providers, and 98.5% of Wisconsin residents have an active WIR record.[26] We recently used the WIR to show high COVID-19 vaccine uptake among patients with IBD. [27]

16.0 APPENDICES

16.1 Appendix 1: Short Crohn's Disease Activity Index (sCDAI)

The sCDAI uses the same scale as the full CDAI, such that scores <150 define remission, 150–219 mild activity, 220–450 moderate activity, and >450 severe activity. Computation is straightforward: [19]

$$sCDAI = 44 + \left(2 * \sum_{n=1}^{7} L\right) + \left(5 * \sum_{n=1}^{7} A\right) + \left(7 * \sum_{n=1}^{7} W\right)$$

Where *L* is the number of liquid stools, *A* is the rating of abdominal pain (0–3, none to severe), *W* is the rating of general wellbeing (0–4, generally well to terrible), and *n* is the day of follow-up. In study 1, we estimated sCDAI scores from only 1 day of data by multiplying the individual component scores by 7.

16.2 Appendix 2: Simple Clinical Colitis Activity Index

Simple Clinical Colitis Activity Index (SCCAI)

Sub score Category	Scores				
	0	1	2	3	4
Bowel Frequency (day)	1-3	4-6	7-9	>9	
Bowel Frequency (night)	0	1-3	4-6		
Urgency of defecation	None	Hurry	Immediately	Incontinence	
Blood in stool	None	Trace	Occasionally frank	Usually frank	
General well-being	Very Well	Slightly below par	Poor	Very poor	Terrible
Extra-intestinal manifestations (arthritis, pyoderma gangrenosum, erythema nodosum, uveitis)		1 per manifestation			

A maximum score of 19 points:

1) Remission = Score of 0 to 4 points
2) Mild Activity = Score of 5 to 7 points
3) Moderate Activity = Score of 8 to 16 points
4) Severe Activity = Score of > 16 points

Appendix 2b: Pouchitis Disease Activity Index (PDAI)

Criteria		Score
Clinical	**Stool frequency**	
	Usual post-operative stool frequency	0
	1-2 stools/day > post-operative usual	1
	3 or more stools/day > post-operative usual	2
	Rectal bleeding	
	None or rare	0
	Present daily	1
	Fecal urgency or abdominal cramps	
	None	0
	Occasional	1
	Usual	2
	Fever (body temperature >37.8°C)	
	Absent	0
	Present	1

Score ≥6 pouchitis.

Score < 6 remission

16.3 Appendix 3: List of potential Immune-mediated Diseases (pIMDs)

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and 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)	

Medical Concept	Additional Notes
Thrombotic thrombocytopenic purpura	• Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	Including but not limited to: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include “Interstitial lung disease”, “Pulmonary fibrosis”, “Immune-mediated pneumonitis”) • Pleuroparenchymal fibroelastosis (PPFE)
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”
Endocrine disorders	
Addison’s disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow’s disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • 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
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	

Medical Concept	Additional Notes
Celiac disease	
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (Systemic Sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	Includes the following: • 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)

Medical Concept	Additional Notes
	• Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • 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)	Includes the following: • Clinically isolated syndrome (CIS) • 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	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • 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)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome

Medical Concept	Additional Notes
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localised Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • 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 but not limited to: • 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

Medical Concept	Additional Notes
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include: “systemic capillary leak syndrome (SCLS)” or “Clarkson's Syndrome”
Goodpasture syndrome	• Frequently used related terms include: “pulmonary renal syndrome” and “anti-Glomerular Basement Membrane disease (anti-GBM disease)”
Immune-mediated enhancement of disease	• Includes 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 but not limited to: • Kawasaki’s disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud’s phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

Appendix 4. Centers for Disease Control and Prevention:
Case definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis

Condition	Definition
Acute myocarditis	**PROBABLE** Presence of ≥1 new or worsening of the following clinical symptoms:* • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy AND ≥1 new finding of

	• troponin level above upper limit of normal (any type of troponin) • abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis§ • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis¶ AND • No other identifiable cause of the symptoms and findings
	CONFIRMED Presence of ≥1 new or worsening of the following clinical symptoms:* • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy AND ≥1 new finding of • Histopathologic confirmation of myocarditis† • cMRI findings consistent with myocarditis¶ in the presence of troponin level above upper limit of normal (any type of troponin) AND • No other identifiable cause of the symptoms and findings
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: • acute chest pain†† • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram.

* Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

† UsingtheDallascriteria(AretzHT,BillinghamME,EdwardsWD,etal.Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol 1987; 1:3–14). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal
¶ conduction delays or intraventricular conduction defects.
Using either the original or the revised Lake Louise criteria. https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihub
** https://academic.oup.com/eurheartj/article/36/42/2921/2293375
†† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain
might occur.

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