Protocol Number: VXA-COV2-201

Official Title: A Phase 2, Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Dose-Ranging Trial to Determine the Safety, Immunogenicity and Efficacy of an Adenoviral-Vector Based Vaccine (VXA-CoV2-1.1-S) Expressing a SARS-CoV-2 S Protein and dsRNA Adjuvant Administered Orally to Healthy Adult Volunteers

NCT Number: NCT05067933

Document Date: 04 August 2022

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Dose-Ranging Trial to Determine the Safety, Immunogenicity and Efficacy of an Adenoviral-Vector Based Vaccine (VXA-CoV2-1.1-S) Expressing a SARS-CoV-2 S Protein and dsRNA Adjuvant Administered Orally to Healthy Adult Volunteers
Protocol Number:	**VXA-COV2-201**
Product Name:	SARS-CoV-2 E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant Oral Tablet Vaccine (VXA-CoV2-1.1-S)
Indication:	Prevention of Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Study Phase:	Phase 2
Sponsor:	Vaxart Inc. 170 Harbor Way; Suite 300 South San Francisco, CA 94080
IND Number:	027602
Sponsor Contact:	[redacted] Phone: [redacted] email: [redacted]
Medical Monitors:	[redacted] [redacted] Sponsor Medical Monitor Phone: [redacted]; email: [redacted] [redacted] Clinical Operations, ICON Phone: [redacted]; email: [redacted]
Version and Date:	**Version 5.0 (Amendment 4), 04 August 2022**
Prior Version:	Version 4.0 (Amendment 3), 09 November 2021

SIGNATURE PAGE/STATEMENT OF COMPLIANCE

Title: A Phase 2, Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Dose-Ranging Trial to Determine the Safety, Immunogenicity and Efficacy of an Adenoviral-Vector Based Vaccine (VXA-CoV2-1.1-S) Expressing a SARS-CoV-2 S Protein and dsRNA Adjuvant Administered Orally to Healthy Adult Volunteers

Protocol Number: VXA-COV2-201 (Amendment 4)

Vaxart, Inc.: [redacted] 8/7/2022
Date

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) E6 and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). Except where necessary to eliminate an immediate hazard(s) to the study participants, the Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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

Principal Investigator: _____ _____
Signature Date

Name: _____
(Print)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

A Phase 2, Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Dose-Ranging Trial to Determine the Safety, Immunogenicity and Efficacy of an Adenoviral-Vector Based Vaccine (VXA-CoV2-1.1-S) Expressing a SARS-CoV-2 S Protein and dsRNA Adjuvant Administered Orally to Healthy Adult Volunteers

Study Rationale and Hypothesis

VXA-Cov2-1.1-S is an E1/E3-deleted, replication-incompetent, adenovirus 5 vaccine vector designed for use as an oral vaccine for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The vaccine vector encodes the full-length Spike protein (S) of SARS-CoV-2. The adjuvant consists of a double-stranded ribonucleic acid (RNA) Toll-like receptor 3 (TLR3) agonist which enhances immune induction to expressed antigen in the gut mucosa.

SARS-CoV-2, a positive-sense single-stranded RNA virus presumed to be of zoonotic origin, is highly contagious in humans and is the cause of the ongoing worldwide pandemic of coronavirus disease 2019 (COVID-19). There is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease, including prophylactic measures, such as vaccines.

A unique and advantageous immune response elicited by oral vaccination is the induction of antibodies derived from mucosal cells. Given that the mucosal route of immunization produces superior mucosal immunity compared to injected vaccines, it is hypothesized that VXA-CoV2-1.1-S oral vaccine may enable higher degrees of mucosal protection against infection when compared to a parenteral immunization method.

VXA-CoV2-1.1-S is designed to elicit both antibody and T cell responses, mucosally and systemically, to SARS-CoV-2. Prior completed Phase 1 and 2 clinical studies with the Vaxart Vector Adjuvant Antigen Standard Technology (VAAST™) platform have demonstrated protective immunity to other viruses (influenza, norovirus, and respiratory syncytial virus) with both systemic and mucosal immune responses against the antigen of choice (Kim, 2016; Kim, 2018; Liebowitz, 2020).

A Phase 1 open-label, dose-ranging study to evaluate the safety and immunogenicity of an earlier vaccine candidate, VXA-CoV2-1, in healthy young adults is ongoing under Protocol VXA-COV2-101. VXA-CoV2-1.1-S is similar to VXA-CoV2-1 and was manufactured using the same VAAST platform, with the exception that the new construct does not express the N protein and has a slightly modified version of the S protein to provide better stability when expressed on the surface of a cell. The ongoing VXA-COV2-101 study completed enrollment with 35 subjects receiving one or two administrations of low dose vaccine ($1x10^{10}$ IU) or a single higher dose ($5x10^{10}$ IU). Solicited symptoms of reactogenicity were collected for 7 days following each vaccination and were mild to moderate in severity and transient in nature resolving without intervention/medication. Unsolicited adverse events (AEs) were collected through Day 57 (Study Active Period); five subjects reported a total of 6 unsolicited AEs that were all mild in severity. No subjects have reported any serious adverse events (SAEs) or medically attended

adverse events (MAAEs) on this study to date. Subjects are currently in the Safety Follow-up Period (through Day 390) and being monitored for SAEs and MAAEs. Refer to the Investigator's Brochure for additional information.

The current Phase 2 study, comprised of 2 parts, is designed to assess the safety, tolerability, immunogenicity, and efficacy of the VXA-CoV2-1.1-S oral vaccine with a repeat-dose vaccination schedule in healthy adult volunteers. Part 1 will utilize an open-label dose and age escalation design to evaluate the early safety, tolerability and immunogenicity of the VXA-CoV2-1.1-S vaccine at two dose levels in a stepwise manner. Subjects will be enrolled into two cohorts; Cohort 1 will enroll subjects naïve to any prior vaccination against COVID-19 or history of COVID-19 and Cohort 2 will enroll subjects who have received 2 doses of an mRNA vaccine for the prevention of COVID-19 under Emergency Use Authorization (EUA) or FDA approved at least 6 months prior to study vaccination at Day 1. Part 1 will inform on the safe and immunogenic dose with which to advance into Part 2, the randomized, double-blind, placebo-controlled phase of the study which will also evaluate the efficacy of VXA-CoV2-1.1-S compared to placebo.

Though there is prior Phase 1 experience with the similar VXA-CoV2-1 vaccine in 35 participants with doses up to $5x10^{10}$ IU under Protocol VXA-COV2-101, Vaxart intends to utilize a conservative stepwise dose escalation schedule starting at a low dose of $1x10^{10}$ IU with VXA-CoV2-1.1-S in the current protocol to allow safely advancing from the young adult population (18 – 55 years of age) into the older population (56 – 75 years of age). Two dose levels, a low dose of $1x10^{10}$ IU, and then a high dose of $1x10^{11}$ IU will be investigated with cohorts of 12 subjects each in the younger age range, and then in the older age range. These 4 cohorts will be mirrored for subjects that are COVID-19 and vaccine naïve and those with prior vaccination who have received two doses of an mRNA vaccine for the prevention of SARS-CoV-2 infection, for a total enrollment of 96 subjects in Part 1. The safety data from the prior Phase 1 study will be leveraged to move from one dose and age cohort to the next in an informed manner after evaluation of reactogenicity and unsolicited AE data through Day 8. It will be important to enroll the cohorts in Part 1 as expeditiously as possible and advance into Part 2 of the study at the selected dose of VXA-CoV2-1.1-S, especially in the naïve participant cohorts (those without prior exposure or vaccination against SARs-CoV-2 to be enrolled under this protocol) as this population is becoming increasingly difficult to recruit. Data from Part 1 will be reviewed by the IDMC and submitted to the IND for FDA review prior to initiating enrollment in Part 2.

Objectives and Endpoints

Part 1- Open Label Lead-in Phase

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of VXA-CoV2-1.1-S with a repeat-dose vaccination schedule in healthy adults at two dose levels	• Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each vaccination • Frequency, duration, and severity of unsolicited treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and medically attended AEs (MAAEs) during the study Active period (Day 57). MAAEs will be determined by (1) active monitoring for COVID-19 and vaccine-associated enhanced disease (VAED), and (2) monitoring for potential immune-mediated medical conditions including AEs of special interest (AESIs) and new onset of chronic illness (NOCIs).
Secondary	
To assess long-term safety of VXA-CoV2-1.1-S	• Frequency, duration, and severity of all SAEs, and MAAEs including monitoring for COVID-19, VAED, AESIs and NOCIs through one year post last dose
To assess the immunogenicity of VXA-CoV2-1.1-S with a repeat-dose vaccination schedule in healthy adults at two dose levels	<u>Key immunogenicity endpoints:</u> • SARS-CoV2-specific Immunoglobulin G (IgG) and Immunoglobulin A (IgA) antibody levels by Mesoscale Discovery (MSD) assay • Neutralizing serum antibody titers to SARS-CoV-2 <u>Additional immunogenicity endpoints:</u> • T cell responses by Intracellular Cytokine Cytometry (ICC) • Antigen S-specific IgA in nasal swabs • Antigen S-specific IgA in saliva • Anti-Adenovirus type 5 (Ad5) serum antibodies (optional)

Exploratory	
To assess the efficacy of prophylactic VXA-CoV2-1.1-S against confirmed COVID-19 occurring from 7 days after second dose with a repeat-dose vaccination schedule in healthy adults at two dose levels	• Frequency, duration and severity of virologically confirmed COVID-19 illness and serologically confirmed SARS-CoV-2 infection occurring from 7 days following second study drug dose administration

Part 2 – Double Blind, Placebo-Controlled Phase

Objectives	Endpoints
Primary	
To assess the efficacy of prophylactic VXA-CoV2-1.1-S against confirmed COVID-19 occurring from 7 days after second dose with a repeat-dose vaccination schedule in healthy adults compared to placebo	• Frequency duration and severity of virologically confirmed COVID-19 illness and serologically confirmed SARS-CoV-2 infection occurring from 7 days following second study drug dose administration
To evaluate the safety and tolerability of VXA-CoV2-1.1-S with a repeat-dose vaccination schedule in healthy adults compared to placebo	• Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each vaccination • Frequency, duration, and severity of unsolicited TEAEs, SAEs, and MAAEs through the active period (4 weeks post last dose), efficacy period and safety follow-up period. MAAEs will be determined by (1) active monitoring for COVID-19 and VAED through the active period (4 weeks post last dose), and (2) monitoring for potential immune-mediated medical conditions including AESIs and NOCIs for one year post last dose.
Secondary	
To assess long-term safety of VXA-CoV2-1.1-S	• Frequency, duration, and severity of all SAEs, and MAAEs including monitoring for COVID-19, VAED, AESIs and NOCIs through one year post last dose
To assess the immunogenicity of VXA-CoV2-1.1-S with a repeat-dose vaccination schedule in healthy adults compared to placebo	<u>Key immunogenicity endpoints:</u> • SARS-CoV2-specific IgG and IgA antibody levels using MSD assays • Neutralizing serum antibody titers to SARS-CoV-2 <u>Additional immunogenicity endpoints:</u> • Antigen S-specific IgA in nasal swabs • Antigen S-specific IgA in saliva •

Overall Study Design

This is a 2-part study.

Each study part will include a Screening Period, Active Period and a Safety Follow-up Period. Study assessments and visits will be conducted as shown in the Schedule of Activities (SoA) in Section 1.2 within Table 3 and Table 4 for study Part 1 and Part 2, respectively.

Part 1 Design

Part 1 utilizes an open-label, repeat-dose, dose and age escalation design to evaluate the VXA-COV2-1.1-S oral vaccine in two cohorts. Cohort 1 will evaluate approximately 36 total healthy adult participants that are naïve (no prior vaccination against SARS-CoV-2 infection and no history of prior COVID-19 or SARS-CoV-2 infection) across 3 groups of 12 subjects each, encompassing 2 age groups and 2 dose levels. Cohort 2 will evaluate approximately 36 healthy adult participants who have no history of prior COVID-19 or SARS-CoV-2 infection and have received 2 doses of an EUA or FDA approved COVID-19 mRNA vaccine across 3 groups of 12 subjects each, encompassing 2 age groups and 2 dose levels. Enrollment will be performed in a sequential manner with at least 12 subjects in the younger age group (18-55 years) completing within the dose level, prior to enrollment of the older age group (56-75 years) at that dosage.

Population	Cohort	VXA-CoV2-1.1-S Dose Levels*	Age (years)	Vaccination Timepoints	No. of Participants
Naive	1a	$1x10^{10}$ I.U. ±0.5 log	18 – 55	Day 1 & Week 4	12
Prior vaccinated	2a	$1x10^{10}$ I.U. ±0.5 log	18 – 55	Day 1 & Week 4	12
IDMC Data Review[1]					
Naive	1b	$1x10^{11}$ I.U. ±0.5 log	18 – 55	Day 1 & Week 4	12
Naive	1c	$1x10^{10}$ I.U. ±0.5 log	56 – 75	Day 1 & Week 4	12
Prior vaccinated	2b	$1x10^{11}$ I.U. ±0.5 log	18 – 55	Day 1 & Week 4	12
Prior vaccinated	2c	$1x10^{10}$ I.U. ±0.5 log	56 – 75	Day 1 & Week 4	12
IDMC Data Review[2]					

IDMC = Independent Data Monitoring Committee.

[1] IDMC to review safety data through Week 1 for 12 subjects in group a before enrollment will begin in b and c.

[2] IDMC to review safety data for all subjects within each age group and initial immunogenicity data from Part 1, to make recommendations on dose selection for randomized, placebo-controlled phase, before enrollment begins in Part 2.

Cohorts 1 and 2 (naïve and prior vaccinated subjects, respectively) will enroll in parallel, and the IDMC may review safety data for the two Cohorts separately if the enrollment rates between the two groups vary.

After signing an informed consent, participants will undergo screening assessments to determine study eligibility over a 30-day Screening Period.

On Day 1, eligible participants will be enrolled sequentially to receive their 1st oral vaccination according to their assigned treatment group as specified in Table 1.

During the Active Period, participants will record daily symptoms of reactogenicity for 1 week post each vaccination, administered on Day 1 and Week 4, using a Solicited Symptom Diary. They will return to the site at 1 and 4 weeks following each vaccination, as specified in the SoA, to have safety assessments and samples collected for evaluation of immunogenicity. Post completion of the Week 1 visit by all subjects in a specified cohort, as detailed in

Table 1, the Independent Data Monitoring Committee (IDMC) will review Day 1 to Week 1 safety data and make recommendations as to whether to proceed to the next cohort(s). Upon completion of active portion of Part 1, the IDMC will review safety and preliminary immunogenicity data from all cohorts and make recommendations to the Sponsor on the VXA-CoV2-1.1-S dose level to evaluate in Part 2. A summary of safety and immunogenicity data with the intended dose for Part 2 will be submitted to FDA for review and concurrence prior to initiation of enrollment in Part 2.

At the Week 4 visit participants will have safety assessments to evaluate suitability to receive the second vaccination as outlined in Section 3.2.2. Participants with any of the following conditions will not be eligible to receive a second vaccine dose:

- Positive pregnancy test at Day 29 (female participants),
- Occurrence of any possibly, probably or definitely treatment-related Grade 3 or 4 AE or SAE following the initial vaccination
- Occurrence of any Grade 3 or 4 AE or SAE following the initial vaccination without plausible alternative explanation
- Presence of acute illness or significant new medical condition including positive SARS-COV-2 rapid molecular test prior to dosing

Participants deemed ineligible due to presence of acute illness or new medical condition may be re-assessed during the visit window (+7 days), and if the condition resolves, may receive their second vaccination within 1 week of their scheduled Week 4 Visit. In such situations the Principal Investigator must contact the study Medical Monitor and gain consensus on the decision to continue participant with study vaccinations prior to administration of the second dose.

Upon completion of the study Active Period (Week 8 Visit) participants will enter the Safety Follow-up Period and be monitored for SAEs, MAAEs and for exposure to and/or symptomatic COVID-19 including VAED through to Month 13/End of Study (EOS). In addition, these participants will be evaluated for immunogenicity as specified in the SoA (Table 3). During the Safety Follow-up Period participants will return to the site at Months 7 and 13 for safety monitoring and collection of samples for evaluation of immunogenicity; they will also be contacted by phone monthly between site visits to query for safety and exposure to and/or symptomatic COVID-19.

Any participant who discontinues study drug early (does not receive the second dose) will enter the Safety Follow-up Period a month earlier at Week 4 and will be monitored for safety and exposure to and/or symptomatic COVID-19 as described above, and complete immunogenicity assessments through EOS per the SoA (Table 3).

Any participant reporting COVID-19 like illness or exposure to COVID-19 during the study will be asked to return to the site for an unscheduled visit to test for SARS-CoV-2 infection. Participants with confirmed SARS-CoV-2 infection, at any time during the study period, will be

asked to provide a nasal swab sample every two days after their confirmatory COVID-19 test, until they test negative, to monitor for duration of infection. The duration of q2day testing post confirmed SARS-CoV-2 infection should end after 10 days if still testing positive at that time. Any FDA Authorized rapid molecular test (e.g. LUCIRA COVID-19 Test) can be used for home or on-site testing for monitoring COVID-19 infection. They will also be monitored for clinical disease severity (see Section 7.1.1, Table 6) and outcome. The participant will be counseled to notify their Primary Care Physician of their positive SARS-CoV-2 status and seek medical care should they become symptomatic.

An IDMC will provide safety oversight throughout the duration of the study. If the protocol halting rules are met at any time during the study (refer to Section 6.1.1 for Part 1 and Section 6.1.2 for Part 2), enrollment and dosing will be suspended pending a full IDMC review (Section 8.5.2). The Sponsor's Medical Monitor(s) (or designees) will perform safety oversight (Section 8.5.1).

Part 2 Design and Overview

Part 2 will utilize a double-blind, randomized, placebo-controlled, repeat-dose design that will enroll 800 eligible participants between the ages of 18 and 75 years of age, including a minimum of 200 participants > 55 years of age. Randomization will be stratified by age (18 – 55 years and 56 – 75 years) and region (if sites in multiple countries are utilized).

After signing an informed consent, participants will complete assessments to determine their eligibility within a 30-day Screening period.

On Day 1, eligible participants will be randomized in a 1:1 ratio to either active (VXA-CoV2-1.1-S) or control (matching placebo tablets) group (Table 2):

- Active: VXA-CoV2-1.1-S (dose to be selected from Part 1)
- Control: matching placebo

During the Active Period, participants will record daily symptoms of reactogenicity for 1 week post each study drug administration (Day 1 and Week 4), using a Solicited Symptom Diary. Participants will return to the site at 1 and 4 weeks following each vaccination, as specified in the SoA to have safety assessments and samples collected for evaluation of immunogenicity (Table 4).

As in Part 1, at the Week 4 visit participants will have safety assessments to evaluate suitability to receive the second vaccination as outlined in Section 4.2.2. Participants with any of the following conditions will not be eligible to receive a second vaccine dose:

- Positive pregnancy test at Day 29 (female participants),
- Occurrence of any possibly, probably or definitely treatment-related Grade 3 or 4 AE or SAE following the initial vaccination
- Occurrence of any Grade 3 or 4 AE or SAE following the initial vaccination without plausible alternative explanation
- Presence of acute illness or significant new medical condition including positive SARS-COV-2 rapid molecular test prior to dosing

Participants deemed ineligible due to presence of acute illness or new medical may be re-assessed during the visit window (+7 days), and if the condition resolves, may have a second vaccination within 1 week of their scheduled Week 4 Visit. In such situations the Principal Investigator must contact the study Medical Monitor and gain consensus on the decision to continue participant with study vaccinations prior to administration of the second dose.

Following completion of the Active Period (Week 8 visit) participants will continue to be monitored for SAEs, MAAEs and for exposure to and/or symptomatic COVID-19 through Month 13/EOS during the study Safety Follow-up Period. In addition, these participants will be evaluated for immunogenicity as specified in the SoA (Table 4).

Any participant who discontinues study drug early (does not receive the second dose) will enter the Safety Follow-up Period a month earlier at Week 4 and will be monitored for safety and exposure to and/or symptomatic COVID-19 as described above, and complete immunogenicity assessments through EOS per the SoA (Table 4).

Any participant reporting COVID-19 like illness or exposure to COVID-19 will be asked to return to the site for an unscheduled visit to test for SARS-CoV-2 infection. Participants with confirmed SARS-CoV-2 infection, at any time during the study period, will be asked to provide a nasal swab every two days after their confirmatory COVID-19 test, until they are negative, to monitor for duration of infection. They will also be monitored for clinical disease severity (Section 7.1.1, Table 6), and outcome, including potential VAED. The participant will be counseled to notify their Primary Care Physician of their positive SARS-CoV-2 status and seek medical care should they become symptomatic.

Participants will be followed via site visits and monthly phone calls in order to monitor for COVID-19 (symptoms or exposure) starting from 7 days following their second vaccination in the Active Period. The study Efficacy Period, as described in Duration of Study Participation in Table 2, will last until the last participant randomized has completed their Month 7 visit (6 months post last study drug administration), after which the study database will be cleaned and locked, and the primary efficacy analyses performed. At this time the treatment assignments will be unblinded and Part 2 participants in the placebo group will have the opportunity to receive vaccination(s) against COVID-19 as detailed in Section 5.9.

An interim analysis for efficacy may also be performed if 18 cases of confirmed COVID-19 are reported prior to the planned efficacy analysis at completion of Month 7 visits by all participants.

The IDMC will provide safety oversight throughout the duration of the study. If the protocol halting rules are met at any time during the study (refer to Section 6.1.1 for Part 1 and Section 6.1.2 for Part 2), enrollment and dosing will be suspended pending a full IDMC review (Section 8.5.2). The Sponsor's Medical Monitor(s) (or designees) will perform safety oversight (Section 8.5.1).

Treatment Group and Number of Participants

Part 1 – Open-Label Lead-in (N = ~ 72 Participants)

This phase will include healthy male and female adult volunteers 18 to 75 years old, inclusive, in the following cohorts:

- **Cohort 1**- Healthy adults who are naïve (no prior vaccinations against COVID-19 and no history of COVID-19) and are at low risk of developing severe COVID-19 upon potential infection with SARS-CoV-2
- **Cohort 2**- Healthy adults who are prior vaccinated (have received two doses of an EUA or FDA approved mRNA COVID-19 vaccine at least 6 months prior to enrollment [Day 1] and are at low risk of developing severe COVID-19 upon potential infection with SARS-CoV-2

Approximately Seventy-two (72) subjects will be enrolled in a stepwise manner as outlined in Table 1.

Table 1 Part 1 Groups, Doses and Sample Size

Population	Cohort	VXA-CoV2-1.1-S Dose Levels*	Age (years)	Vaccination Timepoints	No. of Participants
Naive	1a	$1x10^{10}$ I.U. ±0.5 log	18 – 55	Day 1 & Week 4	12
Prior vaccinated	2a	$1x10^{10}$ I.U. ±0.5 log	18 – 55	Day 1 & Week 4	12
IDMC Data Review[1]					
Naive	1b	$1x10^{11}$ I.U. ±0.5 log	18 – 55	Day 1 & Week 4	12
Naive	1c	$1x10^{10}$ I.U. ±0.5 log	56 – 75	Day 1 & Week 4	12
Prior vaccinated	2b	$1x10^{11}$ I.U. ±0.5 log	18 – 55	Day 1 & Week 4	12
Prior vaccinated	2c	$1x10^{10}$ I.U. ±0.5 log	56 – 75	Day 1 & Week 4	12
IDMC Data Review[2]					

*Multiple tablets may be administered to deliver the full intended dose.

IDMC = Independent Data Monitoring Committee.

[1] IDMC to review safety data through Week 1 for 12 subjects in group a before enrollment will begin in b and c.

[2] IDMC to review safety data for all subjects within each age group and initial immunogenicity data from Part 1 to make recommendations to Sponsor on dose selection for randomized, placebo-controlled phase, before enrollment begins in Part 2.

Cohorts 1 and 2 (naïve and prior vaccinated subjects, respectively) will enroll in parallel. The IDMC may review safety data for the subgroups within each of these two cohorts separately if the enrollment rates between the two cohorts vary.

Duration of Study Participation

For each participant in Part 1 the duration of study activities is expected to last as follows:

Study Period (Part 1)	Duration
Screening Period:	30 days
Active Period:	8 weeks*
Safety Follow-up Period:	11 months
Total duration of participation:	~14 months

*Participants who discontinue study drug early will enter the Safety Follow-up Period at Week 4.

Part 2 – Randomized, Double-blind, Placebo-controlled (N = 800 Participants)

Healthy male and female adult volunteers 18 to 75 years old (inclusive) will be randomized in Part 2 as outlined in Table 2. A minimum of 200 of the total 800 participants in Part 2 will be >55 years of age.

Table 2 Part 2 – Treatment Arms, Dose and Sample Size

Treatment Arms	Treatment*	Treatment Timepoints	No. of Participants**
Active	Oral tableted VXA-CoV2-1.1-S vaccine (Dose to be selected after Part 1 data review)	Day 1 & Week 4	400
Control	Matching oral placebo tablet(s)	Day 1 & Week 4	400

* Multiple tablets may be administered to deliver the full intended dose.
** A minimum of 200 participants (25%) in Part 2 will be >55 years old.

Duration of Study Participation

For each participant in Part 2 the duration of study activities is expected to last as follows:

Study Period (Part 2)	Duration
Screening Period:	30 days
Active Period:	8 weeks*
Efficacy Evaluation:	*~6 months (starting 7 days after second dose)*
Safety Follow-up Period:	11 months
Total duration of participation:	~14 months

* Participants who discontinue study drug early will enter the Safety Follow-up Period at Week 4.
**The study database will be cleaned and locked following completion of the efficacy period. Treatment assignments for Part 2 will be unblinded following completion of the primary efficacy analyses.

Scheduled Study Visits

Study Period	Part 1 and Part 2 Site Visits
Screening	Day -30 to Day -1
Active	Week 0 (Day 1) – First dose administration Week 1 (Day 8) Week 4 (Day 29) – Second dose administration Week 5 (Day 36) Week 8 (Day 57) – End of Study Active Period Visit
Safety Follow-up	Months 3, 4, 5, 6, 8, 9, 10, 11 and 12 (phone calls) Month 7 Month 13 – End of Study Visit

Study Sites

Part 1: 4 to 8 qualified clinical sites in the United States (U.S.).

Part 2: 30 to 60 qualified clinical sites in the U.S., Latin America, South Africa and/or India, as required to complete study enrollment.

Independent Data Monitoring Committee (IDMC):

Refer to Section 8.5.2 for information on IDMC scheduled meetings for Part 1 and study oversight for Parts 1 and 2.

1.2. Schedule of Activities

Table 3 Schedule of Activities – Part 1

	Screening	Active Study Period					Safety Follow-up Period		Notes
Study Day/Week/Month	**Day -30 to -1**	**Wk 0 (D1)**	**Wk 1 (D8)**	**Wk 4 (D29)**	**Wk 5 (D36)**	**Wk 8/ET (D57)**	**Months 7 and 13/EOS**	**Months 3 – 6 and 8 – 12**	**Day (D), Week (Wk) Months 3 – 6 and 8 – 12 are remote visits (phone calls)**
Visit Window (days)		**N/A**	**0**	**+7**	**0**	**±2**	**±7**	**±7**	
Informed consent	X								
Inclusion/Exclusion	X	X		X					
Demographics	X								
Medical history	X								
Serology	X								HIV, HCV, HBV
Urine drug screen	X								
Physical examination	X	X*	X*	X*	X*	X*			* Targeted
Vital Signs	X	X	X	X	X	X			
Safety laboratory tests	X[#]	X[†]	X	X	X	X			[#] Coagulation tests only at screening as part of safety lab panel (PT, PTT and fibrinogen) † If screening laboratory tests are done within 2 days of baseline, no need to repeat at baseline.
Urinalysis	X	X[†]	X	X	X	X			
Pregnancy test	X	X		X					Pregnancy testing should include serum hCG at screening. Sites should confirm negative urine pregnancy test for all women on Days 1 and 29 prior to dosing
SARS-CoV-2 rapid Ab test	X[a]	X[a]							**a.** This test is only for Cohort 1 (naïve subjects). It will need to be repeated at Day 1 only if Screening test completed >7 days prior to the Day 1 Visit.
Nasal Swab for SARS-CoV-2 (RT- PCR)		X[b]							**b.** Collect swab predose at Day 1.
SARS-CoV-2 Rapid Molecular Test*		X		X					Confirm negative on-site rapid molecular test prior to each dose. Rapid molecular test to be done at any time during the study if participant reports symptoms and/or exposure to COVID-19. If positive, repeat rapid molecular test at home or on-site for monitoring COVID-19 infection q2days until negative or up to 10 days if still testing positive, refer to section 7.1.1

	Screening	Active Study Period					Safety Follow-up Period		Notes
Study Day/Week/Month	**Day -30 to -1**	**Wk 0 (D1)**	**Wk 1 (D8)**	**Wk 4 (D29)**	**Wk 5 (D36)**	**Wk 8/ET (D57)**	**Months 7 and 13/EOS**	**Months 3 – 6 and 8 – 12**	**Day (D), Week (Wk) Months 3 – 6 and 8 – 12 are remote visits (phone calls)**
Visit Window (days)		**N/A**	**0**	**+7**	**0**	**±2**	**±7**	**±7**	
Vaccination		X		X					Participants must be assessed for suitability for 2nd dose, per Section 3.2. If they are not eligible for their 2nd dose, participants will enter the Safety Follow Up period at Week 4.
Dispense Solicited Symptom Diary		X		X					
Review & Collect Solicited Symptom Diary			X		X				
Review Prior & Concurrent Medication	X	X	X	X	X	X			
Query for TEAEs, SAEs and MAAEs		X	X	X	X	X	X[c]	X[c]	**c.** Only SAEs ,and MAAEs including AESIs and NOCIs will be collected during the Safety Follow-up Period.
Query for exposure to and/or Symptoms of COVID-19[d]		X	X	X	X	X	X	X	**d.** Unscheduled visit must be completed if participant reports symptoms or exposure to COVID-19, refer to section 7.1.1
Immunogenicity Assessments									
SARS-CoV2-specific IgG/IgA (serum)		X[e]		X		X	X		**e.** An aliquot of serum collected at baseline will be stored for testing (e.g. PF4 antibody ELISA) should an AE related to blood clots be reported anytime during the study period.
Neutralizing Ab to SARS-CoV-2 (serum)		X		X		X	X		
Fixed **whole blood**		X	X	X	X				Additional exploratory immunoassays
T cell responses by ICC		X	X	X	X				
Anti Ad5 antibodies (serum) Optional		X		X		X			
Nasal swab for antigen S-specific IgA		X		X		X	X		
Saliva sample for antigen S-specific IgA		X		X		X	X		

Abbreviations: Ab, Antibody; ; COVID-19, coronavirus disease 2019; Cytof, Mass cytometry; EOS, End of Study; ET, Early Termination; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; ICC, intracellular cytokine cytometry; IgA, immunoglobulin A; IgG, immunoglobulin G; MAAE, medically attended adverse events; NP, Nasopharyngeal; PBMC, peripheral blood mononuclear cells; RT-PCR, reverse transcription polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEAE, treatment-emergent adverse events; WOCBP, women of childbearing potential; PF4, platelet factor 4.

Table 4 Schedule of Activities – Part 2

	Screening	Active Study Period					Safety Follow-up Period		Notes
Study Day/Week/Month	**Day -30 to -1**	**Wk 0 (D1)**	**Wk 1 (D8)**	**Wk 4 (D29)**	**Wk 5 (D36)**	**Wk 8/ET (D57)**	**Months 7* and 13/EOS**	**Months 3 – 6 and 8 – 12**	**Day (D), Week (Wk) Months 3 – 6 and 8 – 12 are remote visits (phone calls)**
Visit Window (days)		**N/A**	**0**	**+7**	**0**	**±2**	**±7**	**±7**	**Treatment group will be unblinded when the last participant completes Month 7 Visit (see Section 5.9)*
Informed consent	X								
Inclusion/Exclusion	X	X		X					
Demographics	X								
Medical history	X								
Physical examination	X	X†	X†	X†	X†	X†			† Targeted
Vital Signs	X	X	X	X	X	X			
Safety laboratory tests	X								
Urinalysis	X								
Pregnancy test (WOCBP)	X	X		X					Can be serum or urine.
SARS-CoV-2 rapid Ab test[a]	X	X							**a.** Test to be repeated at Day 1 only if Screening test completed >7 days prior to the Day 1 Visit.
Nasal Swab for SARS-CoV-2 (RT- PCR)		X							Collect swab predose at Day 1. Collect swab at any time during the study if participant reports symptoms and/or exposure to COVID-19. If test positive, collect samples at 2-day intervals until a negative test result is observed.
Vaccination		X		X[b]					**b.** Participants must be assessed for suitability for 2nd dose, per Section 4.2. If they are not eligible for their 2nd dose, participants will enter the Safety Follow Up period at Week 4.
Dispense Solicited Symptom Diary		X		X					
Review & Collect Solicited Symptom Diary			X		X				
Review Prior & Concurrent Medication	X	X	X	X	X	X			
Query for TEAEs, SAEs and MAAEs		X	X	X	X	X	X[c]	X[c]	**c.** Only SAEs and MAAEs will be collected during the Safety Follow-up Period.
Query for exposure to and/or Symptoms of COVID-19[d]		X	X	X	X	X	X	X	**d.** Unscheduled visit must be completed if participant reports symptoms or exposure to COVID-19.

Immunogenicity Assessments									
SARS-CoV2-specific IgG/IgA (serum)		X[e]		X		X	X		**e.** An aliquot of serum collected at baseline will be stored for testing (e.g. PF4 antibody ELISA) should an AES related to blood clots be reported anytime during the study period.
Neutralizing Ab to SARS-CoV-2 (serum)		X		X		X	X		
Fixed whole blood		X	X	X	X				Additional exploratory immunoassays
Nasal swab for antigen S-specific IgA		X		X		X	X		
Saliva sample for antigen S-specific IgA		X		X		X	X		

Abbreviations: Ab, Antibody; ; COVID-19, coronavirus disease 2019; Cytof, Mass cytometry; EOS, End of Study; ET, Early Termination; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; ICC, intracellular cytokine cytometry; IgA, immunoglobulin A; IgG, immunoglobulin G; MAAE, medically attended adverse events; NP, Nasopharyngeal; PBMC, peripheral blood mononuclear cells; RT-PCR, reverse transcription polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEAE, treatment-emergent adverse events; WOCBP, women of childbearing potential; PF4, platelet factor 4.

2. INTRODUCTION

2.1. Study Rationale

VXA-CoV2-1.1-S is an E1/E3-deleted, replication-incompetent, adenovirus 5 (Ad5) vaccine vector designed for use as an oral vaccine for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The vaccine vector encodes the full-length Spike protein (S) of SARS-COV-2. The adjuvant consists of a double-stranded RNA Toll-like receptor 3 (TLR3) agonist which enhances immune induction to expressed antigen in the gut mucosa.

SARS-CoV-2, a positive-sense single-stranded ribonucleic acid (RNA) virus presumed to be of zoonotic origin, is highly contagious in humans and is the cause of the ongoing worldwide pandemic of coronavirus disease 2019 (COVID-19). There is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease, including prophylactic measures, such as vaccines.

A unique and advantageous immune response elicited by oral vaccination is the induction of antibodies derived from mucosal cells. Given that the mucosal route of immunization produces superior mucosal immunity compared to injected vaccines, it is hypothesized that VXA-CoV2-1.1-S oral vaccine may enable higher degrees of mucosal protection against infection when compared to a parenteral immunization method.

VXA-CoV2-1.1-S is designed to elicit both antibody and T cell responses (systemic and mucosal) to SARS-CoV-2. Prior completed Phase 1 and 2 clinical studies with the Vaxart Vector Adjuvant Antigen Standard Technology (VAAST™) platform have demonstrated protective immunity to other viruses (influenza, norovirus, and respiratory syncytial virus) with both systemic and mucosal immune responses against the antigen of choice (Kim, 2016; Kim, 2018; Liebowitz, 2020).

A Phase 1 open-label, dose-ranging study to evaluate the safety and immunogenicity of an earlier vaccine candidate, VXA-CoV2-1, in healthy young adults is ongoing under Protocol VXA-COV2-101. VXA-CoV2-1.1-S is similar to VXA-CoV2-1 and was manufactured using the same VAAST platform, with the exception that the new construct does not express the N protein and has a slightly modified version of the S protein to provide better stability when expressed on the surface of a cell. The ongoing VXA-COV2-101 study completed enrollment with 35 subjects receiving one or two administrations of low dose vaccine ($1x10^{10}$ IU) or a single higher dose ($5x10^{10}$ IU). Solicited symptoms of reactogenicity were collected for 7 days following each vaccination and were mild to moderate in severity and transient in nature resolving without intervention/medication. Unsolicited adverse events (AEs) were collected through Day 57 (Study Active Period); five subjects reported a total of 6 unsolicited AEs that were all mild in severity. No subjects have reported any serious adverse events (SAEs) or medically attended adverse events (MAAEs) on this study to date. Subjects are currently in the Safety Follow-up Period (through Day 390) and being monitored for SAEs and MAAEs. Refer to the Investigator's Brochure for additional information.

The current Phase 2 study, comprised of 2 parts, is designed to assess the safety, tolerability, immunogenicity, and efficacy of the VXA-Cov2-1.1-S oral vaccine with a repeat-dose vaccination schedule in healthy adult volunteers. Part 1 will utilize an open-label dose and age escalation design to evaluate the early safety, tolerability and immunogenicity of the VXA-

CoV2.1.1-S vaccine at two dose levels in a stepwise manner. Part 1 will inform on the safe and immunogenic dose with which to advance into Part 2, the randomized, double-blind, placebo-controlled phase of the study which will also evaluate the efficacy of VXA-CoV2.1.1-S compared to placebo.

Though there is prior Phase 1 experience with the similar VXA-CoV2-1 vaccine in 35 participants with doses up to $5x10^{10}$ IU under Protocol VXA-COV2-101, Vaxart intends to utilize a conservative stepwise dose escalation schedule starting at a low dose of $1x10^{10}$ IU with VXA-CoV2-1.1-S in the current protocol to allow safely moving from the young adult population (18 – 55 years of age) into the older population (56 – 75 years of age). Two dose levels, a low dose of $1x10^{10}$ IU and then a high dose of $1x10^{11}$ IU will be investigated with cohorts of 12 subjects in the younger age range, and then 12 subjects in the older age range. These 4 cohorts will be identical for subjects that are COVID-19 and vaccine naïve (Cohort 1) and those that have been prior vaccinated with two doses of an EUA or FDA approved mRNA vaccine for the prevention of SARS-CoV-2 infection (Cohort 2), for a total enrollment of 96 subjects in Part 1. The safety data from the prior Phase 1 study will be leveraged to move from one dose and age cohort to the next in an informed and expeditious manner after evaluation of reactogenicity and unsolicited AE data through Day 8.

Data from Part 1 will be reviewed by the IDMC and submitted to the IND for FDA review prior to initiating enrollment in Part 2.

2.1.1. Justification for Dose

Based on the safety results observed in completed and ongoing studies with prior vaccines utilizing the VAAST™ platform and based on the safety and immunogenicity observed in the VXA-COV2-101 trial with similar VXA-CoV2-1 oral vaccine, the levels of VXA-CoV2-1.1-S to be investigated in Part 1 of this Phase 2 study are $1x10^{10}$ IU ± 0.5 log (low dose) and $1x10^{11}$ IU ± 0.5 log (high dose), with two doses administered 4 weeks apart.

Approximately 500 subjects have been immunized with multiple Vaxart recombinant adenovirus serotype 5 (rAd5) vaccine candidates at doses up to $1x10^{11}$ IU with repeat administration. The dose levels tested demonstrated a favorable safety profile and generated generally strong immune responses. Therefore, doses in a similar range will be used in the evaluation of the VXA-CoV2-1.1-S vaccine in Part 1 of this study. Early immunogenicity and safety data from Part 1 will be utilized to select the VXA-CoV2-1.1-S dose to be evaluated in Part 2.

2.2. Background

The rapid global spread of SARS-CoV-2 has resulted in substantial global morbidity and mortality from COVID-19 along with extensive social and economic burden. As of August 2021, SARS-CoV-2 has been responsible for more than 200 million infections and 4.3 million deaths worldwide (data from https://coronavirus.jhu.edu/).

SARS-CoV-2 is transmitted via respiratory droplets (fomites infectious particles) within a range of about 2 meters and direct contact with contaminated surfaces. The median incubation period is estimated to be 4-5 days, and the majority (97.5%) develop symptoms within 11.5 days (confidence interval (CI), 8.2 to 15.6 days) of infection (Guan, 2020; Lauer, 2020). Infection with SARS-CoV-2 leads to a wide range of clinical manifestations ranging from asymptomatic, mild, moderate, severe to critical. Clinical symptoms usually include fever, cough, and dyspnea

(Guan, 2020; Jiang, 2020; Rodriguez-Morales, 2020; Rothan, 2020); a small population of patients also may suffer from gastrointestinal symptoms (Guan, 2020; Guo, 2020). The majority of patients will have uncomplicated or mild disease whereas others will develop severe disease requiring oxygen therapy, and some will progress to require mechanical ventilation and intensive care unit support. Approximately 14% (95%, CI 6.2-21.5%) of hospitalized patients have fatal outcomes (case fatality rate, CFR) (Rodriguez-Morales, 2020). The elderly and people with preexisting conditions, especially heart disease, respiratory conditions, and diabetes, appear to be more susceptible to severe infection and death.

The SARS-CoV-2 virus contains four structural proteins (spike (S), nucleocapsid (N), envelope (E), and membrane (M) proteins). The S glycoprotein, being a large multi-functional trans-membrane protein, plays the vital role of viral attachment, fusion, and entry into the host cell by binding to the human angiotensin-converting enzyme 2 (ACE2) receptor (Kuba, 2010; Guo, 2020; Kaur, 2020; Wan, 2020; Wrapp, 2020). High expression levels of ACE2 are present in alveolar cells of the lungs, absorptive enterocytes of the ileum and colon, and possibly even in oral tissues such as the tongue (Xu, 2020).

Many efforts are currently directed towards the development of vaccines against COVID-19 to avert the pandemic; most of the developing vaccine candidates are using the S-protein of SARS-CoV-2 with injected technologies for administration of proteins, RNA or DNA (Kaur, 2020). The mucosal route is critical for transmission of coronaviruses, yet most vaccine candidates do not engage it, instead relying solely on high serum antibody concentrations to reach the lungs. Vaxart has a different approach that uses a tablet to administer a well-characterized gene-based vaccine backbone, and a more sophisticated antigen.

Vaxart's Ad5 vector is replication incompetent, as a consequence of lacking the E1 and E3 gene regions, which have been removed recombinantly. Replication incompetent Ad5 (and oral adenoviral vaccines) have been used in over 200 gene therapy and vaccine studies in humans. Human and animal experience with Vaxart's orally administered vaccine platform has demonstrated that substantial transgene specific nasal and intestinal IgA responses can be generated in addition to systemic IgG responses to the expressed antigen (influenza) (Kim, 2016; Kim, 2018; Liebowitz, 2020). These platform attributes may allow for better protection against coronavirus infection than an injected protein-based vaccine, or any approach focused on inducing serum antibody responses.

A detailed description of the chemistry, pharmacology, efficacy, and safety of VXA-CoV2-1.1-S is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of VXA-CoV2-1.1-S may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug VXA-CoV2-1.1-S		
Vaccine-associated enhanced disease (VAED)	This is a theoretical risk. Animal studies on other coronaviruses have revealed low risk possibility that appearance of low-level IgG	Monitor COVID-19 symptoms throughout the study. Severity will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	antibodies to non-neutralizing S protein epitopes can enhance coronavirus infection (antibody-dependent enhancement, ADE). In macaques, an inactivated injected vaccine has produced some evidence of ADE, and in hamsters, an S protein-based vaccine also produced ADE (Kam, 2007; Wang, 2016).	assessed using case definition (Section 7.1.1).
Potential for vaccine related hypersensitivity, including anaphylaxis	Similar to other drugs, vaccines have the potential to cause allergic reactions. Vaccine components including immunizing antigens, adjuvants, culture derived proteins (e.g. gelatin) and other agents may have the potential to cause complications.	Monitor participants for any allergic reactions and onset of new illness during the trial duration.
Potential for systemic and gastrointestinal events (fever, headache, myalgia, abdominal pain, anorexia, nausea, vomiting, vomiting, diarrhea, and malaise/fatigue) following vaccination.	These systemic events are common adverse reactions seen with other vaccines, as noted in the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical studies. Given the route of delivery and mechanism of action for an ingestible vaccine some additional gastrointestinal (GI) events may also be observed.	Actively monitor systemic and GI-associated reactions (solicited symptoms) for 7 days following each study drug administration.
Potential for severe events of thrombosis in combination with thrombocytopenia (Thrombosis with thrombocytopenia syndrome, TTS), in some cases accompanied by bleeding, as reported in rare cases following vaccination with two injected adenovirus-vectored COVID-19 vaccines.	Severe cases of TTS have been reported following vaccination with two adenovirus-vectored COVID-19 vaccines: the AstraZeneca COVID-19 vaccine (ChAdOx1; replication-deficient chimpanzee adenoviral vector ChAdOx1) and the Johnson and Johnson COVID-19 vaccine (Ad26.COV2.S; replication-incompetent adenovirus serotype 26 vector). Reports include cases of thrombocytopenia in combination with arterial and venous thrombosis at unusual sites, such as cerebral venous sinus thrombosis (CVST) and splanchnic vein thrombosis, as well as more common sites such as veins of the lower extremity. Onset of symptoms associated with these AEs has typically occurred within 4 weeks after vaccination, and most commonly within 1-2 weeks after vaccination, although some cases have been reported with later onset of symptoms. Cases have been reported mostly in women under 60 years of age, although cases have also been reported in men and in women older than 60 years. Some of these cases have been fatal. A causal relationship between these events and the two vaccines is considered	Exclude enrollment of participants at higher risk of clotting events per review of medical history, physical exam and safety laboratory tests at screening. Actively monitor for signs and symptoms of thromboembolism and/or thrombocytopenia. Study participants should be instructed to seek immediate medical attention if they develop symptoms including, but not limited to, shortness of breath, chest pain, leg pain and/or swelling, persistent abdominal pain, severe or persistent headaches, blurred vision or other vision changes, mental status changes or seizures, petechia, purpura beyond the site of vaccination,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	plausible. The exact pathophysiology of TTS is still under investigation. At this time, a mechanism related to the adenovirus vectors cannot be excluded.	and/or easy bruising/ bleeding.

2.3.2. Benefit Assessment

Benefits to individual participants may include receipt of a potentially efficacious COVID-19 vaccine during a global pandemic, access to COVID-19 diagnostic testing, and contribution to research to help others in a time of global pandemic.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to be utilized to minimize risk to participants taking part in this study, the potential risks identified in association with the VXA-CoV2-1.1-S vaccine for the prevention of COVID-19 are justified by the anticipated benefits that may be afforded to healthy naïve and prior vaccinated participants.

3. PART 1 - OPEN-LABEL LEAD-IN

3.1. Part 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of VXA-CoV2-1.1-S with a repeat-dose vaccination schedule in healthy adults at two dose levels	• Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each vaccination • Frequency, duration, and severity of unsolicited treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and medically attended AEs (MAAEs) during the study Active period (Day 57). MAAEs will be determined by (1) active monitoring for COVID-19 and vaccine-associated enhanced disease (VAED), and (2) monitoring for potential immune-mediated medical conditions including AEs of special interest (AESIs) and new onset of chronic illness (NOCIs).
Secondary	
To assess long-term safety of VXA-CoV2-1.1-S	• Frequency, duration, and severity of all SAEs, and MAAEs including monitoring for COVID-19, VAED, AESIs and NOCIs through one year post last dose
To assess the immunogenicity of VXA-CoV2-1.1-S with a repeat-dose vaccination schedule in healthy adults at two dose levels	<u>Key immunogenicity endpoints:</u> • SARS-CoV2-specific Immunoglobulin G (IgG) and Immunoglobulin A (IgA) antibody levels by Mesoscale Discovery (MSD) assay • Neutralizing serum antibody titers to SARS-CoV-2 • <u>Additional immunogenicity endpoints:</u> • T cell responses by Intracellular Cytokine Cytometry (ICC) • Antigen S-specific IgA in nasal swabs • Antigen S-specific IgA in saliva • Anti-Adenovirus type 5 (Ad5) serum antibodies (optional)

Exploratory	
To assess the efficacy of prophylactic VXA-CoV2-1.1-S against confirmed COVID-19 occurring from 7 days after second dose with a repeat-dose vaccination schedule in healthy adults at two dose levels	• Frequency, duration and severity of virologically confirmed COVID-19 illness and serologically confirmed SARS-CoV-2 infection occurring from 7 days following second study drug dose administration

3.2. Part 1 Study Design

Part 1 is an open-label, lead-in, dose and age escalation phase evaluating VXA-COV2-1.1-S oral vaccine in healthy adult participants with repeat dose administration; this part of the study will enroll a total of approximately 72 subjects across 2 cohorts. Cohort 1 will evaluate 36 total healthy adult participants that are naïve (no prior vaccination against SARS-CoV-2 infection and no history of prior COVID-19 or SARS-CoV-2 infection) across 3 groups of 12 subjects each, encompassing 2 age groups and 2 dose levels. Cohort 2 will evaluate 36 healthy adult participants who have no history of prior COVID-19 or SARS-CoV-2 infection and have received 2 doses of an EUA or FDA approved COVID-19 mRNA vaccine across 3 groups of 12 subjects each, encompassing 2 age groups and 2 dose levels. Enrollment will be performed in a sequential manner with at least 12 subjects in the younger age group (18-55 years) completing within their dose level, prior to enrollment of the older age group (56-75 years) at that dosage.

- **Cohort 1**- Healthy adults who are naïve (no prior vaccinations against COVID-19 and no history of COVID-19) and are at low risk of developing severe COVID-19 upon potential infection with SARS-CoV-2
- **Cohort 2**- Healthy adults who are prior vaccinated (have received two doses of an EUA or FDA approved mRNA COVID-19 vaccine at least 6 months prior to enrollment [Day 1], no history of COVID-19 and are at low risk of developing severe COVID-19 upon potential infection with SARS-CoV-2

The study includes a Screening Period, Active Period and a Safety Follow-up Period. Study assessments will be conducted as shown in the Schedule of Activities (SoA) in Section 1.2 (Table 3).

After signing an informed consent, participants will undergo screening assessments to determine study eligibility over a 30-day Screening Period.

3.2.1. Part 1: Enrollment and Initial Vaccination

On Day 1, eligible participants will be enrolled sequentially to receive their 1st oral vaccination according to their assigned treatment group as specified in Table 1.

Population	Cohort	VXA-CoV2-1.1-S Dose Levels*	Age (years)	No of Doses	No. of Participants
Naive	1a	Low Dose: $1x10^{10}$ I.U. ±0.5 log	18 – 55	2	12
Prior vaccinated	2a	Low Dose: $1x10^{10}$ I.U. ±0.5 log	18 – 55	2	12
IDMC Data Review[1]					
Naive	1b	High Dose: $1x10^{11}$ I.U. ±0.5 log	18 – 55	2	12
Naive	1c	Low Dose: $1x10^{10}$ I.U. ±0.5 log	56 – 75	2	12
Prior vaccinated	2b	High Dose: $1x10^{11}$ I.U. ±0.5 log	18 – 55	2	12
Prior vaccinated	2c	Low Dose: $1x10^{10}$ I.U. ±0.5 log	56 – 75	2	12
IDMC Data Review[2]					

* Multiple tablets may be administered to deliver the full intended dose.
† Doses will be administered on Day 1 and Week 4.
[1] IDMC to review safety data through Week 1 for 12 subjects in a before enrollment will begin in b or c.

[2] IDMC to review safety data for all subjects within each age group and initial immunogenicity data from Part 1 to make recommendations to Sponsor on dose selection for randomized, placebo-controlled phase, before enrollment begins in Part 2

Cohorts 1 and 2 (naïve and prior vaccinated subjects, respectively) will enroll in parallel. The IDMC may review safety data for the subgroups within each of these two cohorts separately if the enrollment rates between the two cohorts vary.

During the Active Period, participants will record daily symptoms of reactogenicity for 1 week post each vaccination, administered on Day 1 and Week 4, using a Solicited Symptom Diary. They will return to the site at 1 and 4 weeks following each vaccination, as specified in the SoA, to have safety assessments and samples collected for evaluation of immunogenicity. Post completion of the Week 1 visit by all subjects in a specified cohort, as detailed in

Table 1, the IDMC will review Day 1 to Week 1 safety data and make recommendations as to whether to proceed to the next cohort(s). Upon completion of enrollment in Part 1, the IDMC will review safety and preliminary immunogenicity data from all cohorts and make recommendations to the Sponsor on the VXA-CoV2-1.1-S dose level to evaluate in Part 2. A summary of Part 1 safety and immunogenicity data with the intended dose for Part 2 will be submitted to FDA for review and concurrence prior to initiation of enrollment in Part 2.

3.2.2. Part 1: Eligibility for Second Vaccination

At the Week 4 visit participants will have safety assessments to evaluate suitability to receive the second vaccination including physical exam, vital signs, pregnancy test (female participants), SARS-CoV-2 rapid molecular test, and assessment of adverse events and new concomitant medication usage. Participants meeting any of the following exclusion criteria will not be eligible to receive their second vaccine administration:

Exclusion Criteria for Second Vaccine Dose:

- Positive pregnancy test at Day 29 (female participants),

- Occurrence of any possibly, probably or definitely treatment-related Grade 3 or 4 AE or SAE following the initial vaccination
- Occurrence of any Grade 3 or 4 AE or SAE following the initial vaccination without plausible alternative explanation
- Presence of acute illness or significant new medical condition including positive SARS-COV-2 rapid molecular test prior to dosing

Participants deemed ineligible due to presence of acute illness or new medical condition may be re-assessed during the visit window (+7 days), and if the condition resolves, may receive their second vaccination within 1 week of their scheduled Week 4 Visit. In such situations the Principal Investigator must contact the study Medical Monitor and gain consensus on the decision to continue participant with study vaccinations prior to administration of the second dose.

Upon completion of the study Active Period (Week 8 Visit) participants will enter the Safety Follow-up Period and be monitored for SAEs, MAAEs and for exposure to and/or symptomatic COVID-19, including the potential for VAED, through the Month 13/End of Study (EOS). In addition, these participants will be evaluated for immunogenicity as specified in the SoA (Table 3). During the Safety Follow-up Period participants will return to the site at Months 7 and 13 for safety monitoring and collection of samples for evaluation of immunogenicity; they will also be contacted by phone monthly between site visits to query for safety and exposure to and/or symptomatic COVID-19.

Any participant who discontinues study drug early (does not receive the second dose) will enter the Safety Follow-up Period a month earlier at Week 4 and will be monitored for safety and exposure to and/or symptomatic COVID-19 as described above, and complete immunogenicity assessments through EOS per the SoA (Table 3).

Any participant reporting COVID-19 like illness or exposure to COVID-19 during the study will be asked to return to the site for an unscheduled visit to test for SARS-CoV-2 infection. Participants with confirmed SARS-CoV-2 infection, at any time during the study period will be asked to provide a nasal swab sample every two days after their confirmatory COVID-19 test, until they test negative, to monitor for duration of infection. The duration of q2day testing post confirmed SARS-CoV-2 infection should end after 10 days if still testing positive at that time. Any FDA Authorized rapid molecular test (e.g. LUCIRA COVID-19 Test) can be used for home or on-site testing for monitoring COVID-19 infection. They will also be monitored for clinical disease severity (see Section 7.1.1, Table 6) and outcome. The participant will be counseled to notify their Primary Care Physician of their positive SARS-CoV-2 status and seek medical care should they become symptomatic.

An Independent Data Monitoring Committee (IDMC) will provide safety oversight throughout the duration of the study. If the protocol halting rules are met at any time during the study (refer to Section 6.1.1 for Part 1 and Section 6.1.2 for Part 2), enrollment and dosing will be suspended pending a full IDMC review (Section 8.5.2). The Sponsor's Medical Monitor(s) (or designees) will perform safety oversight (Section 8.5.1).

3.2.3. Part 1 Scientific Rationale for Study Design

Part 1 is an open-label, lead-in, dose and age escalation lead-in phase to allow assessing the following parameters in subjects that are naïve to prior vaccination and COVID-19 and those who have received two prior vaccinations against SARS-CoV-2 with an EUA or FDA approved mRNA vaccine:

- Collection of additional safety data in young adults. Though doses as high as two times $1x10^{11}$ IU ± 0.5 log have been tested with other oral vaccines using the VAAST™ platform, in the Phase 1 study with VXA-CoV2-1 (S and N protein construct), the highest dose tested was $5x10^{10}$ IU ± 0.5 log due to limited drug product availability. Safety of VXA-CoV2-1.1-S will be evaluated at two dose levels in Part 1 to allow optimal dose selection for the larger, placebo-controlled phase in Part 2; doses to be tested will include $1x10^{10}$ IU ± 0.5 log (low dose) and $1x10^{11}$ IU ± 0.5 log (high dose).
- Collection of safety data in older healthy adults with repeat dose administration at the lower dose level . Safety data collected in Part 1 will inform inclusion of this population in Part 2.
- Collection of preliminary data on the immunogenicity of VXA-CoV2-1.1-S vaccine at 2 potentially clinically active doses, $1x10^{10}$ IU ± 0.5 log (low dose) and $1x10^{11}$ IU ± 0.5 log (high dose). Based on early (Day 8) immunogenicity data from Part 1, the dose level for Part 2 will be selected.

3.2.4. Study Duration

Each subject is expected to participate in the study as follows:

Study Period (Part 1)	**Duration**
Screening Period:	30 days
Active Period:	8 weeks*
Safety Follow-up Period:	11 months
Total duration of participation:	~14 months

*Participants who discontinue study drug early (do not receive the second dose) for any reason will enter the Safety Follow-up Period at Week 4.

3.3. Part 1 Eligibility Criteria

3.3.1. Part 1 Inclusion Criteria

To be eligible for this study, participants must meet all the following criteria:

Age

1. 18 – 75 years of age (inclusive) at the time of signing the Informed Consent Form (ICF).

Type of Participants

2. **Cohort 1 ONLY** – Naive of any prior vaccination for the prevention of COVID-19 (tested using a rapid antibody test) at screening and within 7 days prior to the enrollment (Day 1).

3. **Cohort 2 ONLY –** Have received prior immunizations (both doses) with an EUA or FDA approved mRNA vaccine for the prevention of COVID-19, at least 6 months prior to enrollment (Day 1).
4. In stable and good health, without significant medical illness, based on medical history, physical examination, vital signs, and clinical laboratory tests[1] as determined by the Investigator.
5. Safety laboratory values[1] within the following range criteria at screening:
    a. Laboratory values within normal range or grade 1 outside the range of normal with no clinical significance (NCS) for the following analytes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, blood urea nitrogen (BUN), creatinine, glucose, potassium, and sodium
    b. Laboratory values within normal range for platelet counts[2] and the following coagulation tests: PT/INR, aPTT and fibrinogen
6. Body mass index (BMI) between 17 and 32 kg/m^2 at screening. Investigators must ensure subjects with BMI between 30-32 do not have any additional risk factors for severe COVID-19, per the CDCs guidelines as listed under exclusion criteria #3.
7. Capable of providing signed informed consent.
8. Available for all planned visits and phone calls, and willing to complete all protocol-defined procedures and assessments (including ability and willingness to swallow multiple small enteric-coated tablets per vaccine dose).

Gender and Reproductive Considerations

9. Male or female participants.

Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Refer to Appendix 4 (Section 9.4).

10. Female participants must not be breastfeeding and must have a negative pregnancy test at screening and before each vaccination and fulfill one of the following criteria:
    a. At least 1 year post-menopausal (defined as amenorrhea for ≥12 consecutive months prior to Screening without an alternative medical cause).

       Women under 60 years will need to verify post-menopausal status via a follicle-stimulating hormone (FSH) test if another option to prevent potential pregnancy will not be utilized for 30 days prior to baseline vaccination and until 60 days after the last vaccination.
    b. Surgically sterile
    c. Use of oral, implantable, transdermal or injectable contraceptives for 30 days prior to initial vaccination and until 60 days after the last vaccination.

[1] Clinical laboratory tests (hematology, serum chemistry, and urinalysis). Abnormal lab values should be graded using the site's testing lab reference range for guidance, whether local or central.
[2] If platelets are abnormal, a normal NaCitrate platelet test is needed

d. A reliable form of contraception must be approved by the Investigator (e.g., double barrier method, Depo-Provera, intrauterine device, Norplant, oral contraceptives, contraceptive patches).
e. Not be sexually active (abstinent) or be in a relationship with partner who is sterile (must be discussed with site staff and documented).

3.3.2. Part 1 Exclusion Criteria

Participants must be excluded from this study if they meet any of the following criteria:

Medical Conditions

1. Clinically significant acute illness within 72 hours prior to vaccination defined as the presence of a moderate or severe illness (as determined by the Investigator through medical history and physical exam) (assessment may be repeated during screening period).
2. Current or known previous infection with SARS-CoV-2 or receipt of any therapeutic for the prevention or treatment of COVID-19, Middle East Respiratory Syndrome (MERS), or severe acute respiratory syndrome (SARS). [**EUA or FDA approved mRNA vaccines for the prevention of SARS-CoV-2 infection taken at least 6 months prior to enrollment are permitted in Cohort 2**]
3. Individuals with the following underlying medical conditions who are at higher risk (or might be at higher risk) of severe illness from COVID-19 per the guidance from the Centers for Disease Control and Prevention (CDC):
    a. Cancer, including history of cancer or treatment within past 3 years (excluding basal cell carcinoma or squamous cell carcinoma)
    b. Chronic kidney disease
    c. Chronic obstructive pulmonary disease (COPD)
    d. Immunocompromised state from solid organ transplant, or other medical condition
    e. Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
    f. Sickle cell disease
    g. Uncontrolled type 2 diabetes mellitus
    h. Asthma (moderate to severe)
    i. Cerebrovascular disease
    j. Cystic fibrosis
    k. Uncontrolled hypertension or high blood pressure
    l. Immunocompromised state from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
    m. Neurologic conditions, such as dementia

n. Liver disease

o. Pregnancy or breast feeding

p. Pulmonary fibrosis

q. Chronic smoking (≥ 1 cigarette per day)

r. Thalassemia

s. Type 1 diabetes mellitus

4. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic.
5. Any condition that resulted in the absence or removal of the spleen.
6. Any other condition that in the clinical judgment of the Investigator would jeopardize the safety or rights of a participant participating in the study, would render the participant unable to comply with the protocol or would interfere with the evaluation of the study endpoints.

Diagnostic Assessments

7. Temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned study vaccination (assessment may be repeated during screening period).
8. Positive HIV, Hepatitis B surface antigen (HBsAg) or HCV tests at the screening visit.
9. History of gastrointestinal bleeding (e.g. melena or hematochezia)

Prior/Concurrent Therapy

Note: The Active Period is defined as the time period from Day 1 through Week 8, or 4 weeks post last vaccination.

10. Receipt of a licensed influenza vaccine within 14 days prior to baseline vaccination or another licensed vaccine within 28 days prior to baseline vaccination, or planned administration during the study active period.
11. Use of antiviral medications, including anti-retrovirals within 1 week before vaccination or planned use during the active study period.
12. Use of antibiotics, proton pump inhibitors, H2 blockers or antacids within 1 week before vaccination or planned use during the active study period.
13. Use of medications known to affect the immune function (e.g., systemic corticosteroids and others) within 14 days before vaccination or planned use during the active study period.
14. Daily use of nonsteroidal anti-inflammatory drugs, sulfonylureas, and angiotensin II blockers within 1 week before vaccination or planned use during the active study period.
15. Positive urine drug screen for drugs of abuse at screening (except for previous marijuana use); concurrent or planned use of marijuana during the active study period.
16. Administration of any investigational vaccine, drug or device within 8 weeks preceding vaccination, or planned use within the duration of the study.

Other Exclusions

17. Donation or use of blood or blood products within 4 weeks prior to vaccination or planned donation during the study period.
18. Any significant hospitalization within the last year which in the opinion of the Investigator or Sponsor could interfere with study participation.
19. History of drug, alcohol or chemical abuse within 1 year of screening.
20. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin.
21. Any of the following history or conditions that may lead to higher risk of clotting events and/or thrombocytopenia:
    a. Family or personal history of bleeding or thrombosis
    b. History of heparin-related thrombotic events, and/or receiving heparin treatments
    c. History of autoimmune or inflammatory disease
    d. Presence of any of the following conditions known to increase risk of thrombosis within 6 months prior to screening:
        - Recent surgery other than removal/biopsy of cutaneous lesions
        - Immobility (confined to bed or wheelchair for 3 or more successive days)
        - Head trauma with loss of consciousness or documented brain injury
        - Receipt of anticoagulants for prophylaxis of thrombosis
        - Recent clinically significant infection

4. PART 2 – DOUBLE-BLIND PLACEBO-CONTROLLED

4.1. Part 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of prophylactic VXA-CoV2-1.1-S against confirmed COVID-19 occurring from 7 days after second dose with a repeat-dose vaccination schedule in healthy adults compared to placebo	• Frequency duration and severity of virologically confirmed COVID-19 illness and serologically confirmed SARS-CoV-2 infection occurring from 7 days following second study drug dose administration
To evaluate the safety and tolerability of VXA-CoV2-1.1-S with a repeat-dose vaccination schedule in healthy adults compared to placebo	• Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each vaccination • Frequency, duration, and severity of unsolicited TEAEs, SAEs, and MAAEs through the active period (4 weeks post last dose), efficacy period and safety follow-up period. MAAEs will be determined by (1) active monitoring for COVID-19 and VAED through the active period (4 weeks post last dose), and (2) monitoring for potential immune-mediated medical conditions including AESIs and NOCIs for one year post last dose.
Secondary	
To assess long-term safety of VXA-CoV2-1.1-S	• Frequency, duration, and severity of all SAEs, and MAAEs including monitoring for COVID-19 and potential VAED, AESIs and NOCIs through one year post last dose.
To assess the immunogenicity of VXA-CoV2-1.1-S with a repeat-dose vaccination schedule in healthy adults compared to placebo	<u>Key immunogenicity endpoints:</u> • SARS-CoV2-specific IgG and IgA antibody levels using MSD assays • Neutralizing serum antibody titers to SARS-CoV-2 <u>Additional immunogenicity endpoints:</u> • Antigen S-specific IgA in nasal swabs • Antigen S-specific IgA in saliva

4.2. Part 2 Study Design

Part 2 will utilize a double-blind, randomized, placebo-controlled, repeat-dose design that will enroll 800 eligible participants between the ages of 18 and 75 years of age, including a minimum of 200 participants > 55 years of age. Randomization will be stratified by age (18 – 55 years and 56 – 75 years) and region (if sites in multiple countries are utilized).

After signing an informed consent, participants will complete assessments to determine their eligibility within a 30-day Screening period.

4.2.1. Part 2: Enrollment and Initial Vaccination

On Day 1, eligible participants will be randomized in a 1:1 ratio to either active (VXA-CoV2-1.1-S) or control (matching placebo tablets) group. (Table 2):

- Active: VXA-CoV2-1.1-S (dose to be selected from Part 1)
- Control: matching placebo

During the Active Period, participants will record daily symptoms of reactogenicity for 1 week post each study drug administration (Day 1 and Week 4), using a Solicited Symptom Diary. Participants will return to the site at 1 and 4 weeks following each vaccination, as specified in the SoA to have safety assessments and samples collected for evaluation of immunogenicity (Table 4).

4.2.2. Part 2: Eligibility for Second Dose of Study Drug

Similar to Part 1, at the Week 4 visit participants will have safety assessments to evaluate suitability to receive the second vaccination including physical exam, vital signs, pregnancy test (female participants) and assessment of adverse events and new concomitant medication usage. Participants meeting any of the following exclusion criteria will not be eligible to receive their second vaccine administration:

Exclusion Criteria for Second Vaccine Dose:

- Positive pregnancy test at Day 29 (female participants),
- Occurrence of any possibly, probably or definitely treatment-related Grade 3 or 4 AE or SAE following the initial vaccination
- Occurrence of any Grade 3 or 4 AE or SAE following the initial vaccination without plausible alternative explanation
- Presence of acute illness or significant new medical condition

Participants deemed ineligible due to presence of acute illness or new medical condition may be re-assessed during the visit window (+7 days), and if the condition resolves, may have a second vaccination within 1 week of their scheduled Week 4 Visit. In such situations the Principal Investigator must contact the study Medical Monitor and gain consensus on the decision to continue participant with study vaccinations prior to administration of the second dose.

Following completion of the Active Period (Week 8 visit) participants will continue to be monitored for SAEs, MAAEs and for exposure to and/or symptomatic COVID-19 including potential VAED through Month 13/End of Study (EOS) during the study Safety Follow-up

Period. In addition, these participants will be evaluated for immunogenicity as specified in the SoA (Table 4).

Any participant who discontinues study drug early (does not receive the second dose) will enter the Safety Follow-up Period a month earlier at Week 4 and will be monitored for safety and exposure to and/or symptomatic COVID-19 as described above, and complete immunogenicity assessments through EOS per the SoA (Table 4).

Any participant reporting COVID-19 like illness or exposure to COVID-19 will be asked to return to the site for an unscheduled visit to test for SARS-CoV-2 infection. Participants with confirmed SARS-CoV-2 infection, at any time during the study period, will be asked to provide a nasal swab every two days after their confirmatory COVID-19 test, until they are negative, to monitor for duration of infection. They will also be monitored for clinical disease severity (Section 7.1.1, Table 6), and outcome, including the potential for VAED. The participant will be counseled to notify their Primary Care Physician of their positive SARS-CoV-2 status and seek medical care should they become symptomatic.

Participants will be followed via site visits and monthly phone calls in order to monitor for COVID-19 (symptoms or exposure) starting from 7 days following their second vaccination in the Active Period. The study Efficacy Period will last until the last participant randomized has completed their Month 7 visit (6 months post last study drug administration), after which the study database will be cleaned and locked, and the primary efficacy analyses performed. At this time the treatment assignments will be unblinded and Part 2 participants in the placebo group will have the opportunity to receive vaccination(s) against COVID-19 as detailed in Section 5.9.

An interim analysis for efficacy may also be performed if 18 cases of confirmed COVID-19 are reported prior to the planned efficacy analysis at completion of Month 7 visits by all participants.

The IDMC will provide safety oversight throughout the duration of the study. If the protocol halting rules are met at any time during the study (refer to Section 6.1.1 for Part 1 and Section 6.1.2 for Part 2), enrollment and dosing will be suspended pending a full IDMC review (Section 8.5.2). The Sponsor's Medical Monitor(s) (or designees) will perform safety oversight (Section 8.5.1).

4.2.3. Part 2 Scientific Rational for Study Design

Part 2 is a double-blind placebo-controlled, repeat-dose phase to evaluate the safety, immunogenicity and efficacy of VXA-CoV2-1.1-S compared to placebo in the target population.

4.2.4. Part 2 Study Duration

Each subject is expected to participate in the study as follows:

Study Period (Part 2)	**Duration**
Screening Period:	30 days
Active Period:	8 weeks*
*Efficacy Evaluation:***	*~6 months (starting 7 days after second dose)*
Safety Follow-up Period:	11 months
Total duration of participation:	~14 months

* Participants who discontinue study drug early will enter the Safety Follow-up Period at Week 4.
**The study database will be cleaned and locked following completion of the efficacy period. Treatment assignments for Part 2 will be unblinded following completion of the primary efficacy analyses.

4.3. Part 2 Eligibility Criteria

4.3.1. Part 2 Inclusion Criteria

To be eligible for this study, participants must meet all of the following criteria:

Age

1. 18 – 75 years of age (inclusive) at the time of signing the ICF.

Type of Participants

2. Negative for current or prior SARS-CoV-2 infection (tested using a rapid antibody test) at screening and within 7 days prior to the Baseline visit.
3. In stable and good health, without significant medical illness, based on medical history, physical examination, vital signs, and clinical laboratory tests as determined by the Investigator.
4. Safety laboratory values within the range of normal for platelet counts[2] and the following coagulation tests: PT/INR, aPTT and fibrinogen
5. BMI between 17 and 32 kg/m^2 at screening.
6. Capable of providing signed informed consent.
7. Available for all planned visits and phone calls, and willing to complete all protocol-defined procedures and assessments (including ability and willingness to swallow multiple small enteric-coated tablets per vaccine dose).

Gender and Reproductive Considerations

8. Male or female participants.

   Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Refer to Appendix 4 (Section 9.4).

9. Female participants must not be breastfeeding and must have a negative pregnancy test at screening and before each vaccination and fulfill one of the following criteria:
   a. At least 1 year post-menopausal (defined as amenorrhea for ≥12 consecutive months prior to Screening without an alternative medical cause).

      Women under 60 years will need to verify post-menopausal status via a follicle-stimulating hormone (FSH) test if another option to prevent potential pregnancy will not be utilized for 30 days prior to baseline vaccination and until 60 days after the last vaccination.
   b. Surgically sterile
   c. Use of oral, implantable, transdermal or injectable contraceptives for 30 days prior to initial vaccination and until 60 days after the last vaccination.

[2] If platelets are abnormal, a normal NaCitrate platelet test is needed.

d. A reliable form of contraception must be approved by the Investigator (e.g., double barrier method, Depo-Provera, intrauterine device, Norplant, oral contraceptives, contraceptive patches).
e. Not be sexually active (abstinent) or be in a relationship with partner who is sterile (must be discussed with site staff and documented).

4.3.2. Part 2 Exclusion Criteria

Participants must be excluded from this study if they meet any of the following criteria:

Medical Conditions

1. Clinically significant acute illness within 72 hours prior to vaccination defined as the presence of a moderate or severe illness (as determined by the Investigator through medical history and physical exam) (assessment may be repeated during screening period).
2. Known previous infection with SARS-CoV-2 or receipt of any therapeutic for the prevention or treatment of COVID-19, Middle East Respiratory Syndrome (MERS), or severe acute respiratory syndrome (SARS).
3. Individuals with the following underlying medical conditions:
    a. Cancer, including history of cancer or treatment within past 3 years (excluding basal cell carcinoma or squamous cell carcinoma)
    b. Chronic kidney disease
    c. Chronic obstructive pulmonary disease (COPD)
    d. Immunocompromised state from solid organ transplant, or other medical condition
    e. Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
    f. Sickle cell disease
    g. Uncontrolled type 2 diabetes mellitus
    h. Asthma (moderate to severe)
    i. Cerebrovascular disease
    j. Cystic fibrosis
    k. Uncontrolled hypertension or high blood pressure
    l. Immunocompromised state from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
    m. Neurologic conditions, such as dementia
    n. Liver disease

o. Pregnancy or breast feeding

p. Pulmonary fibrosis

q. Chronic smoking (≥ 1 cigarette per day)

r. Thalassemia

s. Type 1 diabetes mellitus

4. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic.
5. Any condition that resulted in the absence or removal of the spleen.
6. Any other condition that in the clinical judgment of the Investigator would jeopardize the safety or rights of a participant participating in the study, would render the participant unable to comply with the protocol or would interfere with the evaluation of the study endpoints.

Diagnostic Assessments

7. Temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned study vaccination (assessment may be repeated during screening period).

Prior/Concurrent Therapy

Note: The Active Period is defined as the time period from Day 1 through Week 8, or 4 weeks post last vaccination.

8. Receipt of a licensed influenza vaccine within 14 days prior to baseline vaccination or another licensed vaccine within 28 days prior to baseline vaccination, or planned administration during the study active period.
9. Use of antiviral medication , including anti-retrovirals, within 1 week before vaccination or planned use during the active study period.
10. Use of antibiotics, proton pump inhibitors, H2 blockers or antacids within 1 week before vaccination or planned use during the active study period.
11. Use of medications known to affect the immune function (e.g., systemic corticosteroids and others) within 14 days before vaccination or planned use during the active study period.
12. Daily use of nonsteroidal anti-inflammatory drugs, sulfonylureas, and angiotensin II blockers within 1 week before vaccination or planned use during the active study period.
13. Positive urine drug screen for drugs of abuse at screening (except for previous marijuana use); concurrent or planned use of marijuana during the active study period.
14. Administration of any investigational vaccine, drug or device within 8 weeks preceding vaccination, or planned use within the duration of the study.

Other Exclusions

15. Donation or use of blood or blood products within 4 weeks prior to vaccination or planned donation during the study period.
16. Any significant hospitalization within the last year which in the opinion of the Investigator or Sponsor could interfere with study participation.

17. History of drug, alcohol or chemical abuse within 1 year of screening.
18. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin.
19. Any of the following history or conditions that may lead to higher risk of clotting events and/or thrombocytopenia:
    e. Family or personal history of bleeding or thrombosis
    f. History of heparin-related thrombotic events, and/or receiving heparin treatments
    g. History of autoimmune or inflammatory disease
    h. Presence of any of the following conditions known to increase risk of thrombosis within 6 months prior to screening:
        - Recent surgery other than removal/biopsy of cutaneous lesions
        - Immobility (confined to bed or wheelchair for 3 or more successive days)
        - Head trauma with loss of consciousness or documented brain injury
        - Receipt of anticoagulants for prophylaxis of thrombosis
        - Recent clinically significant infection

5. STUDY DRUG, CONCOMITANT THERAPY AND LIFE-STYLE CONSIDERATIONS

Study drug is defined as investigational drug (VXA-CoV2-1.1-S), or placebo, intended to be administered to a study participant according to the study protocol.

5.1. Study Drug Administration

VXA-CoV2-1.1-S is an E1/E3-deleted, replication-incompetent, adenovirus 5 vaccine vector designed for use as an oral vaccine. The vaccine vector encodes the full-length Spike protein (S) of SARS-COV-2 specific antigen. The adjuvant consists of a double-stranded RNA Toll-like receptor 3 (TLR3) agonist which enhances immune induction to expressed antigen in the gut mucosa.

Table 4 Study Drug

Intervention Name	**VXA-CoV2-1.1-S (Part 1 and Part 2)**	**Placebo (Part 2 only)**
Type	biologic	Matching placebo
Dose Formulation	enteric-coated tablets	enteric-coated tablets
Unit Dose Strength(s)	The target concentration of drug product (DP) per tablet will vary per manufacturing lot (e.g. $5x10^9$ to $1.7x10^{10}$ International Units [IU] each). Multiple tablets may be dispensed to deliver the target dose.	
Dosage Level(s)	**Low dose**: $1x10^{10}$ IU ± 0.5 log **High dose:** $1x10^{11}$ IU ± 0.5 log The number of tablets per dose will be determined based on potency assay during release testing of each DP tablet lot. Multiple tablets may be administered to constitute the full dose. Dosing instructions will be described in detail within the Pharmacy Manual.	Matching placebo tablets in appearance and number of tablets administered.
Route of Administration	Oral	
Administration instructions	Participants should fast and refrain from ingesting solid food for at least 4 hours prior to oral dosing. A trained member of the site study staff will dispense the tablet(s) constituting the assigned dose to the participant. The participants will swallow the tablets with 360 to 480 mL of water followed by a light snack (e.g., crackers) at time of dosage administration to aid in tablet transit out of the stomach. Normal food consumption may resume 90 minutes after dosing. For more information refer to the Study Pharmacy Manual.	
Sourcing	Study drug will be provided to the site centrally by the Sponsor or designated representative.	
Packaging and Labeling	The tablets are packaged in foil-sealed, high-density polyethylene (HDPE) screw-cap containers with 10 tablets per bottle. All packaging and labeling operations for study drug will be performed according to Good Manufacturing Practices (GMP) for Medicinal	

Intervention Name	VXA-CoV2-1.1-S (Part 1 and Part 2)	Placebo (Part 2 only)
	Products and the relevant regulatory requirements. Label text for the study drug bottle will at a minimum include name of the manufacturer, the protocol number, the name of the product, the lot number of the product, the concentration of the vaccine, and the date of manufacturing or expiration. Secondary packaging of the study drug upon dispensing from the pharmacy to the clinical staff for participant dosing will be determined with consideration of the sites' pharmacy standard operating procedures and outlined in the study pharmacy manual. The final dispensing container (cup or secondary bottle) will be appropriately labeled with the participant's unique identifier, the time/date of dose preparation within the pharmacy and additional information as deemed necessary per the site's Standard Operating Procedures (SOPs).	
Storage Condition	VXA-CoV2-1.1-S vaccine tablets will be stored at 2 to 8°C at the clinical site until ready for use. Tablets should not be frozen. Do not use and contact Sponsor if DP tablets have been frozen.	

5.2. Compliance of Study drug

Participants will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic Case Report Form (eCRF). The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

5.2.1. Dose Adjustments/Modifications/Delays

Dose adjustments and or modifications are not planned or allowed under this clinical protocol. All participants should receive the full dose they are assigned to, either the low dose ($1x10^{10}$ IU ± 0.5 log) or the high dose ($1x10^{11}$ IU ± 0.5 log) at the protocol-defined study visits (Day 1 and Week 4) after meeting eligibility. Any modification from this schedule or planned dose should be recorded as a protocol violation and reported to the Sponsor (or designee).

5.3. Handling and Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for study drug received and any discrepancies are reported and resolved before use of study drug.
2. Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

4. At the end of the study, the monitor will conduct a final drug reconciliation for all participants and the study site overall. All records of study drug administration, accountability records and study drug disposition records will be examined and reconciled by the study monitor. Further details will be provided in the Study Pharmacy Manual.

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

5.4. Measures to Minimize Bias: Randomization and Blinding

5.4.1. Assignment of a Participant Number

Each participant who signs informed consent will be assigned a participant number. This number will be used as the primary identification for the complete duration of the study. After the participant has signed the informed consent form (ICF), the Investigator will enter the participant into the Screening section of the electronic case report form (eCRF).

5.4.2. Randomization (Part 2 only)

Participants in Part 2 will be randomized in a 1:1 ratio to receive VXA-CoV2-1.1-S (at dose selected from Part 1 of the study) or matching placebo.

Randomization will be centralized across all study sites by region using the Randomization and Trial Supply Management (RTSM) system.

Randomization will be stratified by age (18 – 55 years and 56 – 75 years) and region (if sites in multiple countries are utilized).

5.4.3. Blinding and Unblinding (Part 2 only)

Participants, Investigators, site personnel and the Sponsor (except as described below) will be blinded to individual participant treatment assignment in Part 2.

Study drug doses will be prepared at the study sites by an unblinded research pharmacist(s) who will be provided treatment assignment through a RTSM System.

Sponsor representative(s) will also have access to unblinded individual participant treatment assignments for the purposes of study-required activities, including management of study drug inventory, production of summaries of data for IDMC review, and performance of bioanalytical analysis. These personnel will not be directly involved in the conduct of the study.

An IDMC will periodically convene to review unblinded overall safety and emerging efficacy results (Section 8.5).

The RTSM system will be programmed with blind-breaking instructions. In case of a medical emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. The Investigator should notify the Sponsor's Medical Monitor (or designee) prior to unblinding using the RTSM system. The Investigator(s) must document and report to the Medical Monitor any breaking of the treatment code. The date and reason that the blind was broken must be recorded in the source documentation.

Appropriate personnel at the Sponsor (or designee) will unblind suspected unexpected serious adverse reactions (SUSARs) for the purpose of reporting to authorities as required per each local

regulation. The Sponsor will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

5.5. Treatment of Overdose

Any overdose of study drug should be recorded in the eCRF (including quantity of the excess dose and the duration of the overdose). AEs associated with an overdose or incorrect administration of study drug should be recorded in the AE eCRF. An overdose will not be considered an SAE unless the outcome of the overdose meets seriousness criteria.

There is no specific management of an overdose of VXA-CoV2-1.1-S. Participants should be closely monitored for toxicities and managed appropriately.

5.6. Concomitant Therapy

Concomitant medication is defined as any prescription or over-the-counter preparation.

Use of concomitant medication from 4 weeks before Day 1 (Part 1 or Part 2) through 4 weeks after the last dose of study (completion of Active Period) must be recorded in the eCRF from the participant's medical file along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Medications for pre-existing medical conditions or required for a medical condition during the study are allowed if not considered exclusionary.

The Sponsor's Medical Monitor (or designee) should be contacted if there are any questions regarding concomitant or prior therapy.

5.6.1. Prohibited Concomitant Medication

Medications specifically prohibited in the exclusion criteria are not allowed during the Active Period (Section 3.3.2 prior/concurrent therapy), unless deemed medically necessary by the Investigator.

5.7. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure candidates to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Re-screening/re-assessment outside the Screening period will be possible on a case-by-case basis following Sponsor approval. Participants allowed to be re-screened will be assigned a new screening number (with referral in eCRF to the previous screening number); such participants will be determined a permanent screen failure after the second screening determines the participant is ineligible.

5.8. End of Study Definition

In both Part 1 and Part 2, a participant is considered to have completed the study if they complete the EOT visit at Week 8 (end of Active period). Participants are considered to complete Safety Follow-up if they complete the EOS visit at Month 13.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.9. Intervention after the End of the Study

Following completion of the study Efficacy period in Part 2, the study database will be cleaned and locked and the treatment assignments unblinded. At this time subjects who were randomized to the placebo group under the current protocol will have the opportunity to receive vaccination(s) against COVID-19 via one of the following options:

- Receipt of an approved COVID-19 vaccine (standard-of care) in the region within which they are located (paid for by the Sponsor), or
- Receipt of a Vaxart oral tableted vaccine for the prevention of COVID-19 under an open-label extension protocol

The specific approach to be utilized will be further defined and added to the protocol based on the availability of approved COVID-19 vaccines closer to the completion of Part 2.

6. DISCONTINUATION OF STUDY DRUG AND SUBJECT WITHDRAWAL FROM STUDY

6.1. Study Halting Rules

The study will be halted (no new enrollments and no further study vaccinations) pending an IDMC safety review if any of the below rules are met prior to the start of randomization in Part 2, or the end of the Active Period (4 weeks after the last study drug) in Part 1, whichever is later.

6.1.1. Part 1 Halting Rules

1. Any participant experiences a vaccine-related SAE.
2. Two or more participants experience the same or similar Grade ≥3 solicited AE (first and second vaccinations to be assessed separately).
3. Two or more participants experience the same or similar Grade ≥3 unsolicited single AE preferred term or clinical laboratory AE which the investigator assesses as possibly, probably or definitely related to study vaccine.
4. Occurrence of severe COVID-19 in any participant as defined below. If this halting rule is met, all available clinical, nonclinical safety and immunogenicity data will be reviewed by the IDMC to evaluate for potential vaccine enhanced COVID-19.

Per FDA's June 2020 Guidance Development and Licensure of Vaccines to Prevent COVID-19, severe COVID-19 disease is defined as virologically confirmed SARS-CoV-2 infection with any of the following:

a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 beats per minute, heart rate > 125 per minute, peripheral hemoglobin oxygen saturation [SpO_2] <93% on room air at sea level or partial pressure of oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] < 300 mm Hg)
b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
c. Evidence of shock (Systolic blood pressure < 90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors)
d. Significant acute renal, hepatic, or neurologic dysfunction
e. Admission to an intensive care unit (ICU)
f. Death

6.1.2. Part 2 Halting Rules

1. Any participant experiences a vaccine-related SAE.
2. Five or more participants experience the same or similar Grade ≥3 solicited AE (first and second vaccinations to be assessed separately).
3. Five or more participants experience the same or similar grade ≥3 unsolicited single AE preferred term or clinical laboratory AE which the investigator assesses as possibly, probably or definitely related to study drug administration.
4. Occurrence of severe COVID-19 in any participant, per the definition above, and IDMC determines there is evidence of vaccine enhanced COVID-19. If this halting rule is met, all available clinical and preclinical safety and immunogenicity data will be reviewed by

the IDMC to evaluate for potential vaccine enhanced COVID-19.

6.2. Discontinuation of Study Drug

In some instances, it may be necessary for a participant to permanently discontinue study drug (that is, not receive the second vaccination). Please also refer to halting rules described in Section 6.1.

Permanent discontinuation of study drug does not mean withdrawal from the study, and the participant will be encouraged to remain in the study and continue to complete all study visits. At the time of treatment completion or study drug discontinuation, the Early Termination (ET) visit should be completed as shown in the SoA (Section 1.2). Participants should continue to be followed for safety, immunogenicity and efficacy even if they discontinue study drug prematurely unless they withdraw consent.

Participants may discontinue or be discontinued from study drug at any time. A participant may discontinue study drug for reasons including but not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by participant* (*only for discontinuing study drug, but will remain in study)

The reason for participant discontinuation from study drug will be recorded in the eCRF.

6.3. Participant Withdrawal from the Study

Participants have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the institution. A participant may withdraw from the study for reasons including but not limited to:

- Death
- Withdrawal by participant
- Lost to follow-up
- Study terminated by Sponsor

The reason for participant withdrawal from the study will be recorded in the eCRF.

At the time of withdrawal from the study, the ET visit should be completed, as shown in the SoA (Section 1.2).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

6.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, (Section 1.2) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Participants who experience any serious or severe TEAEs, MAAEs or experience any event of concern including symptoms of, or a potential exposure to, SARS-CoV-2 should be instructed to contact the study site and be scheduled for a visit for further evaluation. If an unscheduled visit occurs, the reason for the visit and data collected during the visit should be recorded and entered into the unscheduled eCRF.

7.1. Efficacy and Immunogenicity Assessments

Planned time points for efficacy assessments are provided in the SoA in Section 1.2.

7.1.1. SARS-CoV-2 Infection and COVID-19 Diagnosis

Participants will be monitored for SARS-CoV-2 infection and/or symptomatic COVID-19 in the following manner:

- Testing for prior exposure by rapid antibody (Ab) test at Screening and Baseline (pre-vaccination) if Screening test >7 days prior to Baseline Visit (**Part 1 Cohort 1 only**).
- Testing by an FDA authorized rapid molecular test at any time a participant reports illness compatible with COVID-19 or reports known/ possible exposure to COVID-19. A sample will also be collected at Baseline to test for potential of pre-dose exposure should confirmation of negative infection be needed in participants who contract COVID-19 during the study.
- A negative onsite rapid molecular test is required prior to dosing at Days 1 and 29. This testing is needed given the high rates of COVID-19 being observed at clinical sites with the spread of Omicron variant.

Any participant reporting COVID-19 like illness or exposure to COVID-19 during the study will be asked to return to the site for an unscheduled visit to test for SARS-CoV-2 infection. Any FDA authorized rapid molecular test (e.g. LUCIRA COVID-19 Test) may be used for home or on-site testing for monitoring COVID-19 infection.. Participants with confirmed SARS-CoV-2 infection at any time during the study period will be asked to provide a nasal sample for rapid molecular test every two days after their confirmatory test until they test negative. The duration of q2day testing should end after 10 days if still testing positive at that time. They will also be monitored for clinical disease duration, severity, and outcome. The participant will be counseled

to notify their Primary Care Physician of their positive SARS-CoV-2 status and seek medical care should they become symptomatic.

The occurrence of virologically confirmed (by polymerase chain reaction [PCR] or rapid molecular test to SARS-CoV-2) symptomatic mild, moderate, or severe COVID-19 is defined in Table 5.

Subjects with confirmed COVID-19 will be evaluated for severity of disease as well as for the potential for vaccine-associated enhanced disease (VAED).

Table 5 Definitions of COVID-19 Severity

Mild	At least one or more of the following: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough • ≥ 2 COVID-19 respiratory/non-respiratory symptoms in Table 6 **AND** • Does not meet criteria for moderate or severe disease
Moderate	At least one or more of the following: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) + any 2 COVID-19 symptoms in Table 6 for ≥ 3 days (need not be contiguous days) • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) Any evidence of significant LRTI: - Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) - Tachypnea: 20 to 29 breaths per minute at rest - SpO2: 94% to 95% on room air - Abnormal chest x-ray or chest CT consistent with pneumonia or LRTI - Adventitious sounds on lung auscultation (e.g., crackles/rales, wheeze, rhonchi, pleural rub, stridor) **AND** • Does not meet criteria for severe disease
Severe	At least one or more of the following: • Tachypnea: ≥ 30 breaths per minute at rest • Resting heart rate ≥ 125 beats per minute • SpO_2: ≤ 93% on room air or PAO_2/FiO_2 < 300 • High flow oxygen therapy or NIV/NIPPV (e.g., CPAP or BiPAP) • Mechanical ventilation or ECMO • One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: o ARDS o Acute renal failure o Acute hepatic failure o Acute right or left heart failure o Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR o DBP < 60 mm Hg o Acute stroke (ischemic or hemorrhagic)

	○ Acute thrombotic event: AMI, DVT, PE ○ Requirement for: vasopressors, systemic corticosteroids, or hemodialysis • Admission to an ICU • Death

Abbreviations: AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; BiPAP = bi-level positive airway pressure; CPAP = continuous positive air pressure; CT = computed tomography; DBP = diastolic blood pressure; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; LRTI = lower respiratory tract infection; NIV = non-invasive ventilation; NIPPV = non-invasive positive pressure ventilation; PAO_2 = partial pressure of oxygen in the alveolus; PE = pulmonary embolism; SBP = systolic blood pressure; SpO_2 = oxygen saturation.

Table 6 Qualifying Symptoms of Suspected COVID-19

- Fever
- New onset cough
- New onset or worsening of shortness of breath or difficulty breathing compared to baseline
- New onset fatigue
- New onset generalised muscle or body aches
- New onset headache lasting ≥ 48 hours
- New loss of taste or smell
- Acute onset of sore throat, congestion, and runny nose
- New onset nausea, vomiting, or diarrhea lasting ≥ 48 hours

7.1.2. Immunogenicity

Samples will be collected from all participants for immunogenicity assessment according to the time points specified in the SoA (Section 1.2; Table 3 and Table 4). The following immunoassays will be performed:

Key immunogenicity assessments:

Part 1:

- SARS-CoV2-specific IgG/IgA by MSD (Serum)
- Neutralizing antibody titers to SARS-CoV-2 (Serum)
-

Part 2:

- SARS-CoV2-specific IgG/IgA by MSD (Serum)
- Neutralizing antibody titers to SARS-CoV-2 (Serum)

Additional Immunogenicity Assessments:

Part 1:

- T cell responses by intracellular cytokine cytometry (ICC)
- Antigen S-specific IgA (Nasal Swabs)

- Antigen S-specific IgA (Saliva)
- Anti Ad5 antibodies (optional), (Serum)

Part 2:

- Antigen S-specific IgA (Nasal Swabs)
- Antigen S-specific IgA (Saliva)

Additional exploratory immunoassays may also be run to further characterize the immune response of the VXA-CoV2-1.1-S vaccine. Sample collection, processing and shipping details are provided within the General and Immunogenicity Laboratory Manuals.

7.2. Safety Assessments

The safety of VXA-CoV2-1.1-S will be evaluated through the reporting of solicited symptoms of reactogenicity for 1 week following each study drug administration, unsolicited TEAEs for 4 weeks following each study drug administration, and SAEs and MAAEs including AESIs, NOCIs for up to 56 weeks following the first vaccine dose. Because the VXA-CoV2-1.1-S vaccine contains a double-stranded RNA (dsRNA), adjuvant MAAEs will be collected through one year post last dose to address the theoretical potential for induction of autoimmune or auto-inflammatory diseases, as is standard for this class of vaccines. The conditions listed in Appendix 5 (Section 9.5), as well as any other unexpected medical conditions requiring medical attention will be monitored during the Safety Follow-up period. Subjects will also be monitored for exposure to SARS-CoV2 and symptomatic SARS-CoV2 infection (COVID-19) as noted in section 7.1.1. Subjects with symptomatic COVID-19 will be further evaluated for severity of disease and the potential for VAED.

Planned time points for all safety assessments are provided in the SoA.

7.2.1. Physical Examination

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular system, respiratory system, abdomen (gastrointestinal, liver and spleen) and neurological system. Height and weight will also be measured and recorded at Screening.

A targeted, symptom-directed physical examination will include, at a minimum, assessments of the skin, respiratory system, cardiovascular system, and abdomen (liver and spleen).

7.2.2. Vital Signs

Blood pressure, heart rate, and respiratory rate will be measured after the participant has been resting for 5 minutes. Vital signs will be measured prior to any blood draw that occurs at the same timepoint.

7.2.3. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 9.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significant during participation in the study or within 14 days after the last dose of study drug should be repeated

until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor's Medical Monitor (or designee). If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

- Laboratory values which are abnormal AND lead to either the requirement for an intervention, the requirement for additional medications, or are felt to otherwise be medically important should be recorded as adverse events in the eCRF. Only abnormal labs that are clinically significant, per the judgement of the investigator, should be reported as treatment-emergent adverse events, which should be graded based on the clinical scenario. Further, the grading of these adverse events should be based on guidance provided in protocol Section 9.3.4.1 – Grading the Severity of TEAEs.
- Hematology or serum chemistry parameters will be graded according to the FDA toxicity grading scale (Section 9.3.4.1.2) and will be adjusted to align with local laboratory reference ranges (Part 1 only) for clinically significant abnormal laboratory tests. Subjects have the ability to rescreen once should screening values fall outside of the allowed eligibility criteria, per the discretion of the Investigator. Post-screening abnormal lab results with toxicity grade 3 or above that are deemed not clinically significant by the investigator and not captured as adverse events will be included separately in the clinical study report.
- Pregnancy testing should include serum hCG at screening. Negative urine pregnancy test should be confirmed on Days 1 and 29 prior to dosing..

7.3. Treatment-Emergent Adverse Events and Serious Adverse Events

The definitions of a TEAE (solicited and unsolicited), MAAE and SAE can be found in Appendix 3 (Section 9.3).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of a TEAE (solicited and unsolicited), MAAE, or SAE. Investigators remain responsible for following up TEAEs, MAAEs, SAEs and other reportable safety events for outcome.

7.3.1. Time Period and Frequency for Collecting TEAE, MAAE SAE and Other Reportable Safety Event Information

All TEAEs (solicited and unsolicited), MAAEs, SAEs and other reportable safety events that occur after the consent form is signed but before study administration must be reported by the Investigator if the event cause the participant to be excluded from the study or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

Table 7 below summarizes the different reporting timelines for TEAEs (unsolicited and solicited), MAAE, SAEs, SUSAR, and pregnancy.

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours from awareness, as indicated in Appendix 3 (Section 9.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Table 7 Adverse Event Reporting Timelines to the Sponsor

Type of Event	TEAE (unsolicited)	TEAE (solicited)	MAAE	SAE / SUSAR	Pregnancy
Reporting period	From first dose until 4 weeks after last dose of study drug	1 week after each study drug administration	From first dose until EOS	From first dose until EOS.	From first dose until EOS
Reporting Timelines to the Sponsor	Entered into the clinical database on an ongoing basis	Entered into the clinical database on an ongoing basis	Within 24 hours	Within 24 hours	Within 24 hours
Reporting Method	AE eCRF	Solicited Symptom Diary	AE eCRF	AE eCRF	Pregnancy form

Abbreviations: AE = adverse event; eCRF = electronic Case Report Form; EOS = end of study; MAAE = medically attended adverse event; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; TEAE = treatment-emergent adverse event

7.3.2. Method of Detecting TEAEs, MAAEs and SAEs

Appendix 3 provides the method of recording (Section 9.3.4), evaluating severity (Section 9.3.4.1), and assessing causality (Section 9.3.4.2) of AEs, MAAEs and SAEs and the procedures for completing and transmitting SAE reports (Section 9.3.5).

Care will be taken not to introduce bias when detecting AEs, MAAEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

7.3.3. Follow-up of AEs, MAAEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, MAAE, or SAE as fully as possible. This may include laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally submitted documents.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

AEs, including pregnancy, will be followed by the Investigator as specified in Appendix 4.

7.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.
- For all studies, Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.5. Death Events

Events resulting in death will be an SAE regardless of association to study drug. Death is an outcome and should not be reported as an event term. The event that leads to the death should be reported as the SAE term.

7.3.6. Pregnancy

- In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study drug but may remain in the study.

- Details of all pregnancies in female participants and female partners of male participants will be collected as outlined in Appendix 4 (Section 9.4).
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 9.4).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size Determination

8.1.1. Part 1

Part 1 is an open-label, lead in, repeat-dose, dose and age escalation design to evaluate the VXA-COV2-1.1-S oral vaccine in two cohorts with repeat dose administration. Cohort 1 will enroll approximately a total of 36 healthy adult participants that are naive (no prior vaccination against SARS-CoV-2 infection and no history of prior COVID-19 or SARS-CoV-2 infection) across 3 groups of 12 subjects each, encompassing 2 age groups and two dose levels. Cohort 2 will enroll approximately a total of 36 healthy adult participants who have received two doses of an EUA or FDA approved mRNA vaccine for the prevention of SARS-CoV-2 infection across 3 groups of 12 subjects each, encompassing 2 age groups and two dose levels.

There are no sample size calculations utilized for Part 1; the cohort size is estimated to provide informative safety and immunogenicity data to allow dose selection for safely proceeding to Part 2.

8.1.2. Part 2

The number of participants to be randomized in Part 2 (VXA-CoV2-1.1-S and placebo) is predicted to yield meaningful immunogenicity and efficacy results to inform how best to proceed into later stage studies. In previous human studies with Ad5 vectored oral tableted vaccines using the same vaccine platform (Ad5 vectored vaccine coding for target virus-specific antigens and a dsDNA adjuvant), the vaccine was well tolerated at total doses up to $2x10^{11}$ IU.

All testing will be performed at alpha = 0.05. All tests will be two-sided. Assuming attack rate in unvaccinated group (ARU) = 5% and vaccine efficacy (VE) = 90%, 341 participants would be required per treatment arm, yielding 95% power.

The total sample size for Part 2 of this study (2 arms) would be 682. To allow for a ~15% dropout rate, 800 participants will be randomized.

Unvaccinated Attack Rate (ARU): 5%

2-sided Alpha	**0.05**	**0.05**	**0.05**	**0.05**	**0.05**	**0.05**	**0.05**	**0.05**
ARU	5%	5%	5%	5%	5%	5%	5%	5%
VE	90%	90%	90%	90%	95%	95%	95%	95%
Power	80%	85%	90%	95%	80%	85%	90%	95%
SS/Arm	207	236	276	341	177	202	236	292
Sample Size (part 2 of study, two arms)	414		472	682	354	404	472	584

Interim looks at the efficacy using O'Brien Fleming Boundaries. One interim analysis may be conducted during the study by the IDMC if 18 confirmed cases of COVID-19 are observed prior to the completion of Month 7 visits, 6 months following the second vaccination, by all subjects. Given a power estimate of 95%, the study may be stopped by the Sponsor for overwhelming efficacy at the interim look if alpha $\leq$ 0.003. The study will continue if this criterion is not met (and may be continued even if it is met per Sponsor's review and FDA agreement). If the decision is made to continue the study until completion at 6 months post last vaccination, alpha $\leq$ 0.05.

8.2. Populations for Analyses

Analysis Population	Description
Screened	All subjects who enter screening (assigned a screening number)
Randomized	All participants who are assigned a randomization number
Dose 1 evaluable immunogenicity	All eligible randomized participants who receive the study intervention to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the study intervention to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations.
Dose 1 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all study intervention dose(s) as randomized within the predefined window and have no other important protocol deviations.
All-available efficacy	All randomized participants who receive at least 1 dose of the study intervention.
Safety	All randomized participants who receive at least 1 dose of the study drug.

8.3. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock for any of the planned analyses. It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

8.3.1. Part 1 - Open Label Lead-in Phase

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics (counts and percentages) will be used to present the following: • Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each vaccination • Frequency, duration, and severity of unsolicited treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and medically attended AEs (MAAEs). MAAEs include (1) active monitoring for COVID-19 and vaccine-associated enhanced disease (VAED), and (2) monitoring for potential immune-mediated medical

	conditions including AEs of special interest (AESIs) and new onset of chronic illness (NOCIs) Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 8 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.
Secondary	Frequency, duration, and severity of all SAEs, and MAAEs including monitoring for COVID-19, VAED, AESIs and NOCIs through one year post last dose <u>Key immunogenicity endpoints:</u> • SARS-CoV2-specific Immunoglobulin G (IgG) and Immunoglobulin A (IgA) antibody levels by Mesoscale Discovery (MSD) assay • Neutralizing serum antibody titers to SARS-CoV-2 <u>Additional immunogenicity endpoints:</u> • T cell responses by intracellular cytokine cytometry (ICC) • Antigen S-specific IgA in nasal swabs • Antigen S-specific IgA in saliva • Anti-Ad5 serum antibodies (optional) Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S-binding IgG level, , and S-binding IgA levels serum, nasal and saliva), GMTs/GMCs and 2-sided 95% CIs and other reported antigens will be provided for by treatment group at the following time points: • Day 1, Week 4, Week 8, Optional (Month 7, and Month 13) • Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. The geometric mean fold rise (GMFR) of SARS-CoV-2 neutralizing titers, S-binding IgG level, and S-binding IgA level. For SARS-CoV-2 neutralizing titers, S-binding IgG levels, and S-binding IgA levels, the GMFRs and 2-sided 95% CIs will be provided by treatment group at the following time points: • Week 4, Week 8, Optional (Month 7, and Month 13) GMFRs will be limited to participants with non-missing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

	Percentage of participants with ≥4-fold rise (or other assessments as per the SAP) in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level will be summarized by treatment group at the following timepoints. • Week 4, Week 8, Optional (Month 7, and Month 13) For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Additional immunogenicity data will be assessed as per the SAP. Missing serology data will not be imputed.
Exploratory	Descriptive statistics (counts and percentages) will be used to present the following: • Frequency, duration and severity of virologically confirmed COVID-19 illness and serologically confirmed SARS-CoV-2 infection occurring from 7 days following second study drug dose administration

8.3.2. Part 2- Double Blind, Placebo Controlled

Endpoint	**Statistical Analysis Methods**
Primary: 1. Primary Efficacy 2. Secondary Efficacy 3. Safety	**All analyses will be performed at 6 months post last vaccination. The database will be locked and unblinded at this time the efficacy and safety analysis will be conducted.** The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed. 1. Primary Efficacy Frequency of virologically confirmed COVID-19 illness and serologically confirmed SARS-CoV-2 infection occurring from 7 days following second study drug dose administration. Ratio of confirmed COVID-19 illness from 1 week after the Dose 2 per 1000 person-years of follow-up in participants without evidence of infection for the active vaccine group to the placebo group VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 1 week after the Dose 2. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. Ratio of confirmed COVID-19 illness from 1 week after the Dose 2 per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 1 week after

	receipt of Dose 2) for the active vaccine group to the placebo group VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 1 week after the second dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of missing at random (MAR). A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP. 2. Secondary Efficacy First: Ratio of confirmed COVID-19 illness from 1 week after the second dose per 1000 person-years of follow-up in participants without evidence of infection for the active vaccine group to the placebo group. Second: Ratio of confirmed COVID-19 illness from 1 week after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection for the active vaccine group to the placebo group. These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints. The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs. Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 1 week after the second dose per 1000 person-years of follow-up in participants without evidence of infection for the active vaccine group to the placebo group Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 1 week after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection for the active vaccine group to the placebo group VE = 100 × (1 – IRR) will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 1 week after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti (Agresti, 2002). Missing efficacy data will not be imputed. 3. Safety and tolerability The safety population will be used for all safety analyses.

	Descriptive statistics will be used to present the following, for each treatment group: • Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each vaccination • Frequency, duration, and severity of unsolicited TEAEs, SAEs, and MAAEs through the active period (4 weeks post last dose) efficacy period and safety follow-up period. MAAEs include (1) active monitoring for COVID-19 and VAED through the active period (4 weeks post last dose); and (2) monitoring for potential immune-mediated medical conditions including AESIs and NOCIs for one year post last dose.
Secondary: Long-term Safety	Frequency, duration, and severity of all SAEs, and MAAEs including monitoring for COVID-19, AESIs and NOCIs through one year post last dose See section 8.2 (Populations for Analyses) for a descriptive of the populations used for these analyses.
Immunogenicity	Key immunogenicity endpoints: • SARS-CoV2-specific IgG and IgA antibody levels using MSD assays • Neutralizing serum antibody titers to SARS-CoV-2 Additional immunogenicity endpoints: • Antigen S-specific IgA in nasal swabs • Antigen S-specific IgA in saliva Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S-binding IgG level, and S- binding IgA level for SARS-CoV-2 neutralizing titers, S-binding IgG levels, and S-binding IgA levels, GMTs/GMCs and 2-sided 95% CIs will be provided for by treatment group at the following time points: • Day 1, Week 4, Week 8, Month 7, and Month 13 after Dose 1 Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits. GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level. For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided by treatment group at the following time points: • Day 1, Week 4, Week 8, Month 7, and Month 13 after Dose 1 GMFRs will be limited to participants with non-missing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided

	CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. Percentage of participants with ≥4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level will be summarized by treatment group. For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise will be provided for by treatment group at the following time points: • Day 1, Week 4, Week 8, Month 7, and Month 13 after Dose 1 The Clopper-Pearson method will be used to calculate the CIs. GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level. For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided by treatment group at the following time points: • Day 1, Week 4, Week 8, Month 7, and Month 13 after Dose 1 GMRs will be limited to participants with non-missing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (e.g., SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits. For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

8.4. Interim Analysis

During Part 1, following completion of the Active Period by all Cohorts, the database will be cleaned and locked.

During Part 2, an interim analysis will occur at 18* confirmed cases of SARS-CoV2 infection. In addition to efficacy, this interim analysis would also include evaluation of safety and immunogenicity through Week 8. If 18 confirmed cases are not identified, the study will be considered complete at 6 months post last vaccination and the database will be locked and unblinded. At this time the efficacy analysis will be conducted, O'Brien-Fleming methods will be used for halting rules (O'Brien, 1979):

- If P = 0.003 at the interim analysis, the study may be stopped for overwhelming efficacy.
- If the study completes as planned (i.e., 6 months post last vaccination), it will be determined to be successful if P ≤ 0.05.

*VE null = 30% (since that is lower bound from the FDA) and VE_Alt = 80% and ARU = 0.05 we get p0 = 0.41 and p1 = 0.17 which gives a total target number of events of around 31 (with ~5 from vaccine group and 26 in placebo so if we add in the other dose then looking at around 36 total events) using POT0 if we simplify down to one primary dose vs placebo calculation. So interim analysis at 1/2 * 36 = 18 events (or 6 months post last vaccination, whichever is first) (Follmann, 2020).

The SAP will describe the planned interim analysis in greater detail.

8.5. Safety Oversight

8.5.1. Internal Sponsor Review

Safety data will be monitored on an ongoing basis by the Investigator (or medically qualified designee) and the Sponsor's Medical Monitor (or designee) in order to promptly identify and flag any event that potentially contributes to a halting rule (Section 6.1).

A Sponsor's Medical Monitor (or designee) will perform the oversight of safety for this study. Additional local medical monitors may also be employed to aid with safety oversight locally. The lead Medical Monitor will be a physician experienced in the conduct of research clinical studies whose primary responsibility will be to monitor participant safety. The Medical Monitor will be responsible for reviewing the cumulative safety data, including a review of safety laboratory test results and adverse event reporting. The Medical Monitor will be familiar with study-specific data as well as relevant background information about the disease, investigational drug, and target population under study. The Medical Monitor(s) will be empowered to request an IDMC safety review which can suspend the study, recommend amendments to the protocol, and/or to request further information.

8.5.2. Independent Data Monitoring Committee (IDMC)

An IDMC will be assigned by the Sponsor prior to the beginning of the study and will provide ongoing oversight of the study.

The IDMC will provide study oversight throughout the duration of the study period (Day 1 through EOS). The IDMC will perform a review of safety data of all participants in Part 1. Enrollment and dosing in Part 2 will only commence following the IDMC's recommendation to proceed. A summary of safety and immunogenicity data with the intended dose for Part 2 will also be submitted to FDA for review and concurrence prior to initiation of enrollment in Part 2.

In Part 2, unblinded data will be provided to the IDMC to ensure halting rules are applied based on observations of events in the vaccine treatment groups, regardless of dose level.

Additionally, *ad hoc* meetings will be convened if any predefined halting rules (see Section 6.1) are met, any serious vaccine related events or trends are observed, or the IDMC has concerns of potential vaccine enhanced disease (following the occurrence of a COVID-19, as defined in Section 7.1.1).

Further details regarding data safety monitoring guidelines will be included in the IDMC Charter, which is the governing document that supersedes this section of the protocol.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

9.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

9.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

9.1.4. Exclusion of Women, Minorities, and Children (Special Populations)

This clinical study will include women and men who are 18 years of age and older and volunteers of all races and ethnicities who meet the inclusion/exclusion criteria, regardless of religion, sex, or ethnic background.

9.1.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.1.6. Dissemination of Clinical Study Data

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be an integrated clinical and statistical report prepared according to the ICH E3 guidelines.

Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

9.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain attributable, legible, contemporaneous, original, accurate, and complete documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Details describing monitoring strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality review of the data.

The Sponsor maintains ultimate responsibility for the quality and integrity of study data, even if study-related duties and functions are transferred to other individuals or organizations (e.g., contractors or contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the Case Report Form (CRF) by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH-GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

9.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents should be generated utilizing good documentation practices and are filed at the Investigator’s site.

Source documents are original documents, data, and records from which the participant’s CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request

previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

9.1.9. Publication Policy

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement. Requests for publication of site specific data should be presented to the Sponsor for review and approval at least 90 days prior to submission for publication.

9.2. Appendix 2: Safety Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by either the central testing laboratory or the local laboratory, unless otherwise specified.
- All safety laboratories, hematology and serum chemistry are to be drawn by standard phlebotomy techniques, into the central lab provided tubes or the site prescribed appropriate tubes for the specific tests and amounts prescribed by local laboratory. Refer to the laboratory manual for further details on specimen collection and handling procedures.
- Protocol-specific requirements for inclusion or exclusion of participant are detailed in Section 3.3 for Part 1 and Section 4.3 for Part 2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 8 Protocol-Required Safety Laboratory Assessments

Test*	Testing Panel/Analytes
Hematology	Hemoglobin, hematocrit, platelet count[1], and complete white blood cell count
Serum Chemistry	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, BUN, creatinine, random glucose, potassium and sodium
Coagulation Tests	Tests for clotting parameters: PT/INR, aPTT and fibrinogen (performed as part of the safety laboratory testing at Screening)
Urinalysis	Protein, glucose ketones and hemoglobin
Other laboratory assessments	Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody types 1 and 2 (Screening only)
Urine drug screen	Amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine, phencyclidine, tetrahydrocannabinol
Other laboratory assessments	Female participants: Serum (screening) or urine pregnancy test, (human chorionic gonadotropin)

*Refer to the Schedule of Activities for Part 1 (Table 3) and Part 2 (Table 4) to determine which safety laboratory assessments are required for each study phase and specific site visits.

[2] If platelets are abnormal, a normal NaCitrate platelet test is needed

9.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

9.3.1. Definition of TEAE (Unsolicited and Solicited)

TEAE Definition
• A TEAE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention, occurring after first dose of study drug. • NOTE: A TEAE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited TEAE
• Unsolicited TEAEs are any TEAEs reported spontaneously by the participant, observed by the study personnel during study visits or those identified during review of medical records or source documents. Unsolicited TEAEs (all TEAEs not collected in the Solicited Symptom Diary during the first week following each vaccination) will be monitored and collected from the time of each vaccination through 4 weeks post each vaccination (1st vaccination through Week 4 and 2nd vaccination through Week 8). • Solicited TEAEs are predefined systemic signs and symptoms of reactogenicity for which the participant is specifically questioned, and which are noted by the participant in their Solicited Symptom Diary, including: ▪ fever (any temperature 100°F or higher) ▪ headache ▪ myalgia (muscle pain) ▪ abdominal pain ▪ anorexia (defined and not eating) ▪ nausea ▪ vomiting ▪ diarrhea ▪ malaise/fatigue Participants will utilize a Solicited Symptom Diary issued on the day of each vaccination to record solicited TEAE daily for the 1 week following each vaccination on Day 1 and Week 4.

9.3.2. Definition of MAAE

Medically Attended Adverse Events Definition
MAAEs are defined as TEAEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Routine study visits will not be considered medically-attended visits. New onset of chronic illness/diseases (NOCI) and AEs of Special Interest (AESIs) will be collected as part of the MAAEs. MAAEs are to be reported for all participants from the moment of vaccination until 12 months after the vaccination. Refer to Appendix 5 (Section 9.5) for list of AESIs that should be monitored in this study.

Events Meeting the TEAE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as TEAE or SAE if they fulfill the definition of TEAE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an TEAE or SAE.

Events <u>NOT</u> Meeting the TEAE Definition
• Events that occurred from consent to pretreatment • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.3.3. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
3. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

An SAE is defined as any serious adverse event that, at any dose:
4. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Is a suspected transmission of any infectious agent via a medicinal product
7. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. ○ Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

9.3.4. Recording of TEAE, MAAE and/or SAE

AE and SAE Recording
• When a TEAE/MAAE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant TEAE/MAAE/SAE information. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Sponsor required form. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

9.3.4.1. Grading the Severity of TEAEs

Assessment of Severity
All TEAEs will be assessed by the investigator using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity: Mild: events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Life threatening: any adverse drug experience that places the participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

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

9.3.4.1.1. Grading of Solicited Treatment-Emergent Adverse Events

Subjects should be instructed to rate solicited symptoms of reactogenicity that are collected within their Solicited Symptom Diary based on the severity scale presented in Table 9. Grading should be reviewed with the participant at each site occurring through 1 week post each vaccination (Day 1 - Week 1 and Week 4 - Week 5).

Table 9 Grading of Solicited Symptoms of Reactogenicity

	Grading				
Symptom	**Normal 0**	**Mild Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Life Threatening Grade 4**
Fever (oral temp)	< 100.4°F (< 38.0°C)	100.4 – 101.1°F (38.0 – 38.4°C)	101.2 – 102.0°F (38.5 – 38.9°C)	102.1 – 104°F (39.0 – 40°C)	> 104.0°F (>40°C)
Headache	None	No interference with activity	Repeated use of nonnarcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Myalgia	None	Easily tolerated, causing minimal discomfort and does not interfere with everyday activities[a]	Sufficiently discomforting to interfere with everyday activities	Prevents normal everyday activities or requires medical advice	ER visit or hospitalization
Abdominal Pain	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Anorexia	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Nausea/ Vomiting	None	No interference with activity or 1 to 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	None	2 to 3 loose stools or < 400 gms/24 hours	4–5 stools or 400 to 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Malaise/ Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

[a] Everyday activities include attendance at work, school and usual habits of the participants.

9.3.4.1.2. Grading of Laboratory Abnormalities

Only abnormal labs that are clinically significant, per the judgement of the investigator, should be reported as treatment-emergent adverse events, which should be graded based on the clinical scenario. Further, the grading of these adverse events should be based on guidance provided in protocol Section 9.3.4.1 for events not included in the protocol-defined grading system.

Tables 10 (serum chemistry), 11 (hematology) and 12 (urinalysis) present FDA toxicity grading information for vaccine studies, which include guidance to consider institutional normal ranges in determining lab toxicity grade. These ranges may be utilized by the Sponsor when evaluating any overall trends in lab abnormalities observed across study (sites and central labs) but should not be utilized when reporting clinically significant unsolicited AEs. Only post-screening safety laboratory tests will have toxicity grades assessed in Part 1 analysis. Post-screening abnormal lab results with toxicity grade 3 or above that are not deemed clinically significant by the investigator and not captured as adverse events will be displayed separately in the clinical study report.

Table 10 Grading of Laboratory Abnormalities (Serum Chemistry)

Serum[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium – Hyponatremia mEq/L	132 to 134	130 to 131	125 to 129	< 125
Sodium – Hypernatremia mEq/L	144 to 145	146 to 147	148 to 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 to 5.2	5.3 to 5.4	5.5 to 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 to 3.6	3.3 to 3.4	3.1 to 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 to 69	55 to 64	45 to 54	< 45
Glucose – Hyperglycemia				Insulin requirements or hyperosmolar coma
Fasting – mg/dL	100 to 110	111 to 125	>125	
Random – mg/dL	110 to 125	126 to 200	>200	
BUN mg/dL	23 to 26	27 to 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 to 1.7	1.8 to 2.0	2.1 to 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 to 8.4	7.5 to 7.9	7.0 to 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 to 11.0	11.1 to 11.5	11.6 to 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 to 1.5	1.1 to 1.2	0.9 to 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 to 2.5	2.0 to 2.2	1.6 to 1.9	< 1.6
CPK – mg/dL	1.25 to 1.5 x ULN	1.6 to 3.0 x ULN	3.1 to 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 to 3.1	2.5 to 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 to 6.0	5.0 to 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 to 2.0 x ULN	2.1 to 3.0 x ULN	3.1 to 10 x ULN	> 10 x ULN
Liver Function Tests – ALT, AST increase by factor	1.1 to 2.5 x ULN	2.6 to 5.0 x ULN	5.1 to 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 to 1.25 x ULN	1.26 to1.5 x ULN	1.51 to 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 to 1.5 x ULN	1.6 to 2.0 x ULN	2.0 to 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 to 1.5 x ULN	1.6 to 2.0 x ULN	2.1 to 5.0 x ULN	> 5.0 x ULN

ULN = upper limit of normal

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. Refer to section 9.3.4.1.2.

Table 11 Grading of Laboratory Abnormalities (Hematology)

Hematology[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female), gm/dL	11.0 to 12.0	9.5 to 10.9	8.0 to 9.4	< 8.0
Hemoglobin (Female) change from baseline value, gm/dL	Any decrease to 1.5	1.6 to 2.0	2.1 to 5.0	> 5.0
Hemoglobin (Male), gm/dL	12.5 to 13.5	10.5 to 12.4	8.5 to 10.4	< 8.5
Hemoglobin (Male) change from baseline value, gm/dL	Any decrease to 1.5	1.6 to 2.0	2.1 to 5.0	> 5.0
WBC increase, cell/mm^3	10,800 to 15,000	15,001 to 20,000	20,001 to 25,000	> 25,000
WBC decrease, cell/mm^3	2,500 to 3,500	1,500 to 2,499	1,000 to 1,499	< 1,000
Lymphocytes decrease, cell/mm^3	750 to 1,000	500 to 749	250 to 499	< 250
Neutrophils decrease, cell/mm^3	1,500 to 2,000	1,000 to 1,499	500 to 999	< 500
Eosinophils, cell/mm^3	650 to 1500	1501 to 5000	> 5000	Hypereosinophilic
Platelets Decreased, cell/mm^3	125,000 to 140,000	100,000 to 124,000	25,000 to 99,000	< 25,000
PT, increase by factor	1.0 to 1.10 x ULN	1.11 to 1.20 x ULN	1.21 to 1.25 x ULN	> 1.25 ULN
PTT, increase by factor	1.0 to 1.2 x ULN	1.21 to 1.4 x ULN	1.41 to 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase, mg/dL	400 to 500	501 to 600	> 600	--
Fibrinogen decrease, mg/dL	150 to 200	125 to 149	100 to 124	< 100 or associated with gross bleeding or DIC

DIC = disseminated intravascular coagulation; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal; WBC = white blood cell

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. Refer to section 9.3.4.1.2

Table 12 Grading of Laboratory Abnormalities (Urinalysis)

Urine*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic), red blood cells per high power field	1 to 10	11 to 50	> 50 and/or gross blood	Hospitalization or packed red blood cells transfusion

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. Refer to section 9.3.4.1.2

9.3.4.2. Assessment of Causality

Assessment of Causality
• For all solicited symptoms and unsolicited TEAEs, including SAEs and MAAEs, the Investigator will make a judgment regarding the relationship of the AE to the study vaccine. All TEAEs must be recorded in the source documents as well as eCRF. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each TEAE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the TEAE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
The relationship of the AE to study vaccine administration will be specified as follows: **Not related**: In the Investigator's opinion, there is no causal relationship between study vaccine administration and the TEAE; **Possibly Related**: The TEAE follows a reasonable temporal sequence from the time of study vaccine administration but there may be another equally likely explanation for the event (e.g., the participant's clinical state or other medications); **Probably Related**: The TEAE follows a reasonable temporal sequence from the time of study vaccine administration and cannot be reasonably explained by the known characteristics of the participant's clinical state; **Definitely Related**: The TEAE follows a known temporal sequence from the time of study vaccine administration, cannot be explained by other disease or medications and the event is an objective and specific medical disorder or a recognized pharmacological phenomenon.

9.3.5. Reporting of SAEs and MAAEs

SAE Reporting to Sponsor (or designee) via an Electronic Data Collection Tool. MAAEs should be reported to the Sponsor in a similar manner to SAEs.
• The primary mechanism for reporting an SAE to the Sponsor (or designee) will be the electronic data collection tool.

SAE Reporting to Sponsor (or designee) via an Electronic Data Collection Tool. MAAEs should be reported to the Sponsor in a similar manner to SAEs.
• If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual.

9.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

9.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterilized (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

9.4.2. Contraception Guidance

Male Subjects:

Male participants are eligible to participate if they agree to the following from informed consent through 60 days after the last dose of study drug:

- Refrain from donating sperm, except for the purpose of fertility analysis as part of this protocol

  PLUS**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier (a male condom)

Female Subjects:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency (see table below), from consent through 60 days after the last dose of study drug, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study drug.
  - A WOCBP must have negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at extension enrollment visit before first administration of study drug in this study

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. A reliable form of contraception must be approved by the Investigator (e.g., double barrier method, Depo-Provera, intrauterine device, Norplant, oral contraceptives, contraceptive patches).

Highly Effective Methods[a] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[b]
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[a] That Are User-Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

[a] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[b] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

9.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant:

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The Sponsor will attempt to follow the female partner to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. The Sponsor will follow the female partner until birth or termination of pregnancy when possible. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

Any female participant who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study. Additionally:

- The investigator will collect pregnancy information, which will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. The participant will be followed until birth or termination of pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study drug by the investigator will be reported to the Sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

9.5. Appendix 5: Medically Attended Adverse Events (MAAEs)

MAAEs are defined as TEAEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. New onset of chronic illness/diseases (NOCI) and AEs of Special Interest (AESIs) will be collected as part of the MAAEs. The following adverse events (AEs) for potential immune-mediated medical conditions as well as events associated with thrombosis and thrombocytopenia are AEs of special interest (AESIs) and include new onset of chronic illness (NOCIs). These events should be monitored for actively and reported to the Sponsor in an expedited manner as outlined in Section 9.3.5.

Gastrointestinal disorders:	**Liver disorders:**
• Celiac disease	• Autoimmune cholangitis
• Crohn's disease	• Autoimmune Hepatitis
• Ulcerative colitis	• Primary biliary cirrhosis
• Ulcerative proctitis	• Primary sclerosing cholangitis
Metabolic diseases:	
• Addison's disease	• Diabetes mellitus type 1
• Autoimmune thyroiditis (including Hashimoto thyroiditis)	• Grave's or Basedow's disease
Coagulopathy:	
• Acquired amegakaryocytic thrombocytopenia	• Amegakaryocytic thrombocytopenia
• Axillary vein thrombosis	• Cavernous sinus thrombosis
• Cerebral venous thrombosis	• Deep vein thrombosis
• Disseminated intravascular coagulation	• Embolism venous
• Hepatic vein thrombosis	• Immune thrombocytopenia
• Intracranial venous sinus thrombosis	• Mesenteric vein thrombosis
• Portal vein thrombosis	• Pulmonary embolism
• Pulmonary thrombosis	• Pulmonary venous thrombosis
• Severe fever with thrombocytopenia syndrome	• Subclavian vein thrombosis
• Thrombocytopenia	• Thrombocytopenia purpura
• Thrombotic thrombocytopenia purpura	• Thrombosis
• Transverse sinus thrombosis	• Vena cava embolism
• Vena cava thrombosis	• Venous thrombosis
Musculoskeletal disorders:	
• Antisynthetase syndrome	• Polymyalgia rheumatic
• Dermatomyosotis	• Polymyositis
• Juvenile chronic arthritis (including Still's disease)	• Psoriatic arthropathy
• Mixed connective tissue disorder	• Relapsing polychondritis
• Scleroderma, including diffuse systemic form and CREST Syndrome	• Rheumatoid arthritis
• Systemic lupus erythematous	• Systemic sclerosis

• Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis.	
Neuroinflammatory disorders:	
• Acute disseminated encephalomyelitis, including site specific variants (e.g., non-infections encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis)	
• Immune related peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy	
• Cranial nerve disorders, including paralysis/paresis (e.g., Bell's palsy)	• Guillain-Barre syndrome, including Miller Fisher syndrome and other variants
• Multiple sclerosis	• Narcolepsy
• Optic neuritis	• Transverse Myelitis
• Myasthenia gravis, including Eaton-Lambert syndrome	
Skin disorders:	
• Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis	• Rosacea
• Alopecia aerate	• Cutaneous lupus erythematosus
• Erythema nodosum	• Psoriasis
• Morphoea	• Sweet's syndrome
• Lichen planus	• Vitiligo
Vasculitis:	
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis	
• Medium sized/and or small vessels vasculitis including: polyarthritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angititis), Buerger's disease thromboangitis obliterans), nerotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leulocytoclassic vasculitis	
Others:	
• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranaoprolifative glomerulonephritis, and mesangioproliferative glomerulonephritis)	
• Antiphospholipid syndrome	• Pernicious anemia
• Autoimmune hemolytic anemia	• Raynaud' phenomenon
• Autoimmune myocarditis/cardiomyopathy	• Sarcoidosis
• Autoimmune thrombocytopenia	• Sjogren's syndrome
• Goodpasture syndrome	• Stevens-Johnson Syndrome
• Idiopathic pulmonary fibrosis	• Uveitis

9.6. Appendix 6: Abbreviations

Term	Description
Ab	Antibody
ACE2	Angiotensin-converting enzyme 2
Ad5	Adenovirus type 5
ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ARDS	Acute respiratory distress syndrome
ARU	Attack rate in unvaccinated
ASC	Antibody secreting cells
AST	Aspartate aminotransferase
BiPAP	Bi-level positive airway pressure
BMI	Body mass index
BUN	Blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Case fatality rate
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CPAP	Continuous positive air pressure
CPK	Creatine phosphokinase
CRF	Case report form
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
Cytof	Mass Cytometry
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DP	Drug product
dsRNA	Double-stranded RNA
DVT	Deep vein thrombosis
E	Envelope
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EOS	End of Study
ET	Early Termination

FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
FSH	Follicle-stimulating hormone
GCP	Good clinical practices
GI	Gastrointestinal
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMP	Good manufacturing practice
GMT	Geometric mean titer
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICC	Intracellular cytokine cytometry
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International units
LRTI	Lower respiratory tract infection
M	Membrane
MAAE	Medically attended adverse event
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MSD	Mesoscale Discovery
N	Nucleocapsid
NCS	No clinical significance
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NP	Nasopharyngeal
NOCI	New Onset of Chronic Illness
PaO_2	Partial pressure of oxygen
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction

PE	Pulmonary embolism
PF4 Antibody ELISA	Platelet Factor 4 antibody ELISA
aPPT	Partial Thromboplastin Time
PT/INR	Prothrombin time and international normalized ratio
rAd5	Recombinant adenovirus serotype 5
RBD	Receptor binding domain
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
RTSM	Randomization and Trial Supply Management
S	Spike
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SpO_2	Peripheral hemoglobin oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TLR3	Toll-like receptor 3
TTS	Thrombolytic and thrombocytopenic syndrome
U.S.	United States
VAAST™	Vector adjuvant antigen standard technology
VAED	Vaccine-associated enhanced disease
VE	Vaccine efficacy
WOCBP	Women of childbearing potential

9.7. Appendix 7: Summary of Changes to Protocol

PROTOCOL VXA-COV2-101 HISTORY:	
Document	**Date**
Protocol Amendment 4, Version 5.0	04 August 2022
Protocol Amendment 3, Version 4.0	09 November 2021
Protocol Amendment 2, Version 3.0	17 August 2021
Protocol Amendment 1; Version 2.0	06 July 2021
Original Protocol; Version 1.0	27 May 2021

VXA -COV2-201 Protocol Amendment 4 (Vers. 5.0) 04 August 2022

The changes incorporated into Amendment 4 are all of the clarifications that were noted and instructed to sites to perform during the conduct of the part 1 of the trial. The protocol has been amended to include the following;

Clarification that for subjects with suspected COVID-19 illness or exposure during the study period (Section 7.1.1):

a. Any FDA Authorized rapid molecular test (e.g. LUCIRA COVID-19 Test) can be used for home or on-site testing for monitoring COVID-19 infection

b. The duration of q2day testing post confirmed SARS-CoV-2 infection should end after 10 days if still testing positive at that time

2. Add an onsite rapid molecular COVID-19 Test at Day 1 and 29 Visits, prior to study vaccine administration. This testing is needed given the high rates of COVID-19 being observed at clinical sites with the spread of the Omicron variant.

3. Clarify that all women who participate in the study should have a pregnancy test at Screening (serum) and Days 1 and 29 pre-dose (urine). Currently the protocol is inconsistent with the requirement across different sections.

4. Clarify that for subjects in the higher range of BMI (30 – 32), investigators must ensure that these subjects do not have any additional risk factors for severe COVID-19, per the CDC's guidelines, as listed under exclusion criterion #3 in Section 3.3.2. The higher risk to subjects with BMI of 30 – 32 will also be added to the ICF. This clarification was requested by the FDA per their review of the current version of the protocol (Amendment 3).

5. Clarify that abnormal lab values should be graded using the site's testing lab reference range for guidance, whether local or central. Only abnormal labs that are clinically significant, per the judgement of the investigator, should be reported as treatment-emergent adverse events, which should be graded based on the clinical scenario. Further, the grading of these adverse events should be based on guidance provided in protocol Section 9.3.4.1 – Grading the Severity of TEAEs

Additional minor changes have also been incorporated for added clarity and consistency. A description of the changes as well as well as a brief rationale for each is presented within the table below.

Section No. & Title	Description of Change	Brief Rationale
1.1 Synopsis Part 1 and part 2 3.1 Part 1 Objectives and Endpoints	Secondary endpoints, key immunogenictiy endpoints (Antibody secreting cells (ASC) IgG in peripheral blood mononuclear cells (PBMCs) removed	To align and reflect with the assessments that were actually collected and the SAP.
	Additional immunogenicity endpoints (Immunophenotyping by Flow or Mass Cytometry (Cytof) removed	To clarify the additional immunogenicity samples collected
Overall Study Design 8.5.2 IDMC	Independent Data Monitoring Committee table 1 revised	Language revised to align with the IDMC meeting for part 1
3.2.3 Part 1: Scientific Rational for Study Design 8.1 Sample Size Determination	High dose cohorts removed for the elderly population Planned sample size decreased from 96 to 72. Each cohort size was decrease to 36 instead of 48	Enrollment goals adjusted to account for challenges in recruiting appropriate vaccine- and covid infection- naïve subjects for the last cohorts. Data collected without this group is felt to be adequate for informing future Part 2 dosing.
3.2.2 Part 1: Eligibility for Second Vaccination	Presence of acute illness or significant new medical condition" added |" including positive SARS-COV-2 rapid molecular test prior to dosing"	Added to align with clarification memo issued to sites
	The duration of q2day testing post confirmed SARS-CoV-2 infection should end after 10 days if still testing positive at that time. Any FDA Authorized rapid molecular test (e.g. LUCIRA COVID-19 Test) can be used for home or on-site testing for monitoring COVID-19 infection	Added to align with clarification memo issued to sites
1.2 Schedule of Activities	Pregnancy Testing- Pregnancy testing should include serum hCG at screening. Sites should confirm negative urine pregnancy test for all women on Days 1 and 29 prior to dosing	Clarifying that all women (not just WOCBP) should be tested.
3.2.2 Part 1: Eligibility for Second Vaccination	SARS=CoV-2 Rapid Molecular Test added	Added to confirm that rapid molecular test to be used only for home or on-site testing for monitoring COVID-19 infection refer to section 7.1.1

7.1 Efficacy and Immunogenicity Assessments		
	Immunophenotyping by Flow or Cytof removed	To Clarify and specify fixed whole blood which includes the immunophenotyping
	Optional added to the Anti Ad5 antibodies (serum)	To align with clarification memo issued to sites
3.2.2 Part 1: Eligibility for Second Vaccination	Participants with confirmed SARS-CoV-2 infection, at any time during the study period will be asked to provide a nasal swab sample every two days after their confirmatory COVID-19 test, until they test negative, to monitor for duration of infection. The duration of q2day testing post confirmed SARS-CoV-2 infection should end after 10 days if still testing positive at that time. Any FDA Authorized rapid molecular test (e.g. LUCIRA COVID-19 Test) can be used for home or on-site testing for monitoring COVID-19 infection	Updated to align with clarification memo
3.3 Eligibility Criteria	Eligibility criterion #6 Body mass index (BMI) between 17 and 32 kg/m^2 at screening. Investigators must ensure subjects with BMI between 30-32 do not have any additional risk factors for severe COVID-19, per the CDCs guidelines as listed under exclusion criteria #3.	Clarification of the eligibility criteria to sites
7.2.3 Clinical Safety Laboratory	Only abnormal labs that are clinically significant, per the judgement of the investigator, should be reported as treatment-emergent adverse events, which should be graded based on the clinical scenario. Further, the grading of these adverse events should be based on guidance provided in protocol Section 9.3.4.1 for events not included in the protocol-defined grading system.– Grading the Severity of TEAEs,	
	Post-screening abnormal lab results with toxicity grade 3 or above that are	

	deemed not clinically significant by the investigator and not captured as adverse events will be included separately in the clinical study report.	
	Pregnancy testing should include serum hHCG may be utilized at screening. Negative urine pregnancy test should be confirmed on Days 1 and 29 prior to dosing., per the discretion of the Investigator.	Added to incorporate clarification memo language.
8.3.1 Statistical Analysis	• The following were removed from the Secondary Immunogenicity Endpoints; Antibody secreting cells (ASC) IgG and IgA, in peripheral blood mononuclear cells (PBMCs) • Additional Endpoint Immunophenotyping by Flow or Mass Cytometry (Cytof) • Language update to reflect S binding IgG and IgA levels along with other antigens will be provided by the treatment groups. • Timepoints for the Additional Endpoints are updated to reflect that Months 7 and 13 as optional GMRs and ASC response were removed	To align with secondary endpoints collected during the trial
9.3.4.1.2 Grading Laboratory Abnormalities	Only abnormal labs that are clinically significant, per the judgement of the investigator, should be reported as treatment-emergent adverse events, which should be graded based on the clinical scenario. Further, the grading of these adverse events should be based on guidance provided in protocol Section 9.3.4.1 for events not included in the protocol-defined grading system. Tables 10 (serum chemistry), 11 (hematology) and 12 (urinalysis) present FDA toxicity grading information for vaccine studies, which include guidance to consider institutional normal ranges in determining lab toxicity grade. For safety analysis, lab abnormalities will	Further clarification of abnormal lab toxicity grading and clinically significant lab-related adverse event severity grading

	be graded by these tables while using the site's testing lab reference range for guidance, whether local or central. Only post-screening safety laboratory tests will have toxicity grades assessed in Part 1 analysis. Post-screening abnormal lab results with toxicity grade 3 or above that are not deemed clinically significant by the investigator and not captured as adverse events will be included separately in the clinical study report.	
9.5	MAAEs are defined as TEAEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. New onset of chronic illness/diseases (NOCI) and AEs of Special Interest (AESIs) will be collected as part of the MAAEs	Clarification to the MAAEs definition

VXA-COV2-201 Protocol Amendment 3 (Vers. 4.0), 09 November 2021

The changes incorporated into Amendment 3 are following the initiation of enrollment under the prior VXA-COV2-201 Amendment 2 (Vers. 3). The modifications made were based on learnings from screening / enrollment activities and feedback from clinical sites. As the percentage of the adult population receiving vaccines against COVID-19, both primary and boost doses, continues to rise, the availability of suitable vaccine naïve subjects continues to decrease. The Sponsor has reviewed the eligibility criteria with site investigators and the study Medical Monitors and implemented modifications with the intent to aid in enrollment of eligible subjects without impacting subject safety. These modifications are summarized in the table below.

Additional minor changes have also been incorporated for added clarity and consistency. A description of the changes as well as well as a brief rationale for each is presented within the table below.

Section No. & Title	Description of Change	Brief Rationale
Schedule of Activities (Table 3 and 4)	Clarified that the SARS-CoV-2 rapid Ab test is only for required for naïve subjects that are being screened for participation in Cohort 1 (no prior vaccination against SARS-CoV-2 infection and no history of prior COVID-19 or SARS-CoV-2 infection).	The rapid Ab test to determine prior exposure to SARS-CoV-2 is only needed to confirm eligibility within Cohort 1 (vaccine and COVID-19 naïve subjects). The schedule of activities did not clarify that this test was not needed in the prior vaccinated subjects to be

		enrolled within Cohort 2. This point has been clarified within the current amendment.
Section 3.3.1 (Inclusion Criteria), Appendix 2: Safety Clinical Laboratory Tests (Table 8)	Safety labs testing panels have been modified to be more clinically relevant and applicable for the study population. Serum Chemistry will include ALT, AST, total bilirubin, BUN, creatinine, random glucose, potassium and sodium. Urinalysis will include protein, glucose ketones and hemoglobin Coagulation Tests at screening will include PT/INR, APTT and fibrinogen	The general safety lab panel within the prior amendment included analytes that were not deemed clinically significant to evaluate for the healthy subject population being enrolled in the study. The extra tests were leading to long turnaround times and the need for repeat tests for clinically insignificant results. Therefore, the testing panel was reviewed by the medical monitors and revised for added trial efficiency.
Sections 3.3.1 and 4.3.1 (Inclusion Criteria)	Modified the eligibility criterion for BMI from between 17 - 30 kg/m^2 to between 17 - 32 kg/m^2 at screening	BMIs above 30 kg/m^2 was the prime reason for screen failures observed in the study to date. The Study Medical Monitors reviewed the data and concluded that subjects with a BMI slightly higher than 30 kg/m^2 were presenting in otherwise good health without additional risk factors of developing severe COVID if they were to contract COVID-19 during the study period. Therefore, the recommendation to slightly broaden the BMI range was proposed. Investigators will be advised to closely evaluate subjects with BMI values between 30 – 32 kg/m^2 for comorbidities prior to enrollment to ensure they are appropriate for study participation.
Section 3.3.2: Part 1 Exclusion Criteria	The exclusion for occult blood, via collection and testing of a stool sample, has been removed from the screening assessments. A new exclusion criterion of history of gastrointestinal (GI) bleeding (melena or hematochezia) has been added.	Vaxart has dosed ~600 adult subjects up to age 80 years with its oral Ad5 vaccines. A safety signal (solicited and/or unsolicited AEs) related to GI bleeding has not been observed. Hence to facilitate the screening process, the test for occult blood at screening has been removed. However, a new exclusion criterion which specifically excludes individuals with any history of GI bleed has been added.
Section 3.3.2: Part 1 Exclusion Criteria	Exclusion criterion #11 has removed "any prescriptive medications for the prevention of COVID-19 " language, and the updated exclusion will read "Use of antiviral medications or anti-retrovirals within 1 week before vaccination or planned use during the active study period." The exclusion of prior medications (prevention and treatment) for COVID-19 is explained within exclusion criterion #2.	This change has been implemented for increased clarity and consistency.

Section 8.3 Statistical analysis	Within this section the reporting of AEs using a 3-tier classification approach has been removed.	All TEAEs will be presenting in listings and tables by treatment group, severity, relationship and impact on study drug administration. The tiering approached may be used in later stage trials where there is more data if what events are expected with the VXA-CoV2-1.1-S vaccine.

VXA-COV2-201 Protocol Amendment 2 (Vers. 3.0), 17 August 2021

Overall Rationale for the Amendment:

Recent advances in Vaxart's manufacturing process indicate that the per tablet potency (I.U. content) for upcoming GMP drug product lots of the VXA-CoV2-1.1-S vaccine will be in the range of 1 to $2x10^{10}$ I.U/tablet. Since the protocol defines a low dose of $1x10^{10} \pm 0.5$ log I.U., the difference from a medium dose of $3x10^{10}$ I.U would not be significantly different or as informative as previously anticipated with a lower I.U per tablet DP lot yield. Therefore, the protocol has been modified to remove the mid dose and include just two dose levels: the low dose (a single tablet dose) and the higher dose, which will be composed of multiple tablets to deliver a $1x10^{11}$ I.U. dose. As there is prior clinical experience with doses up to $5x10^{10}$ I.U. with a prior COVID-19 oral vaccine candidate (VXA-CoV2-1 under Protocol VXA-COV2-101), and with repeat doses of up to $1x10^{11}$ I.U. in multiple trials with other Vaxart oral Ad5 tableted vaccines, removal of the mid dose will allow the trial to progress to Part 2 more efficiently without adding undue safety risk. Ongoing oversight and data reviews between cohorts by the IDMC will further ensure a safe progression from the low dose to the high dose vaccine for each age group.

Another key change incorporated into Amendment 2 is the inclusion of participants that have received prior vaccinations with an mRNA vaccine for the prevention of COVID-19. These subjects (N=48) will be enrolled within Cohort 2 and mirror the 4 subgroups (low and high dose in younger and older adults) that will be enrolled in Cohort 1, the COVID-19 and vaccine naïve participants. Adding in the prior exposed subjects will allow the collection of safety and immunogenicity data in this population in an expeditious manner.

Additional changes have also been incorporated for added clarity and consistency. The changes are presented within the table below in the order of initial appearance within the document:

Section No. & Title	Description of Change	Brief Rationale
1.1 Synopsis 2.1 Study Rationale 3.2 Part 1 Study Design 7.1 Efficacy and Immunogenicity Assessments 8. Statistical Determination	The protocol design for Part 1 has been modified to remove the two medium dose ($3x10^{10}$ I.U.) cohorts in naïve subjects. Additionally, 4 cohorts have been added to include enrollment of subjects that have received prior vaccinations with an EUA or FDA approved mRNA vaccine. Therefore, the total Part 1 enrollment has increased from 72 to 96 total participants.	As the single tablet I.U. is expected to be a slightly higher than $1x10^{10}$ I.U., the nominal low dose will comprise of a single tablet of $1x10^{10} \pm 0.5$ log I.U. Therefore, the protocol has been modified to remove the medium dose of $3x10^{10} \pm 0.5$ log I.U. as this would not be meaningfully different than the low dose and not yield useful information. Cohort 2 (N=48) had been added to evaluate the vaccine's ability to boost immune responses in prior vaccinated persons. Dose and age escalation will be conducted in a stepwise manner with IDMC review of reactogenicity/safety data between cohorts.
1.1 Synopsis 2.1 Study Rationale	Language has been added to clarify that data from Part 1 will be submitted to FDA for review prior to initiation of Part 2.	This Part 1 data review was added based on feedback received from FDA on the initial IND submission. The Part 1 safety and early immunogenicity data provided to the IDMC, and the rationale for the proposed dose for Part 2, will

		be submitted to FDA for review and consensus before initiation of enrollment under Part 2.
1.1 Synopsis 4.3 Part 2 Objectives and Endpoints 8.3 Statistical Analyses	The secondary endpoint for evaluation for long term safety was added as a separate endpoint in Part 2: *Frequency, duration, and severity of all SAEs, and MAAEs including monitoring for COVID-19, VAED, AESIs and NOCIs through one year post last dose.*	Though the prior version of the protocol also monitored safety through the safety follow-up period, this endpoint was inadvertently omitted for Part 2 in prior versions of the protocol. This inconsistency has been corrected in the current version.
1.2 Schedule of Events	Note added to clarify that coagulation tests will be part of the screening safety laboratory tests	Incorporated to add clarity to the schedule of events. Did not impact study conduct from prior version of the protocol.
2.2 Background	The figures for COVID-19 infections and deaths have been updated.	Information modified to current rates to provide more undated information within protocol.
3.3 Part 1 Eligibility	Eligibility criteria for type of participant modified into 2 separate criteria for Cohort 1 (naïve) and Cohort 2 (prior vaccinated). **Cohort 1 ONLY** – Naive of any prior vaccination for the prevention of COVID-19 (tested using a rapid antibody test) at screening and within 7 days prior to the enrollment (Day 1). **Cohort 2 ONLY –** Have received prior immunizations (both doses) with an EUA or FDA approved mRNA vaccine for the prevention of COVID-19, at least 6 months prior to enrollment (Day 1). Exclusion criterion #2 has been modified to allow subjects with prior vaccinations in Cohort 2.	Modification incorporated to accommodate enrollment of Cohort 2 subjects with prior vaccinations with an mRNA vaccine.
3.2 Part 1 Study Design 7.2 Safety Assessments	Protocol language has been modified to clarify that any subjects who experience COVID-19 will also be monitored for potential vaccine-associated enhanced disease (VAED)	
8.3.1 Part 1 Lead-in Phase	The method for categorization of AEs under the primary safety endpoint was clarified to remove errors in last protocol version. A description of the approach for evaluating ASC Responses was added under Secondary Endpoints.	The prior protocol included language on analysis of AEs between active and placebo groups, which was not pertinent to Part 1, the open-label portion of the trial. Erroneous wording was removed from the Part 1 statistical sections within the protocol. ASC response analysis information was inadvertently left out of prior versions of the

		protocol; it has been added for completeness and clarity.
8.4 Interim Analysis	A sentence has been added to clarify that for Part 1, following completion of the Active Period by all Cohorts, the database will be cleaned and locked.	Information added for sake of completeness and clarity.
Appendix 2: Safety Clinical Laboratory Tests	Coagulation Tests have been listed out as separately from the Serum Chemistry Tests	Modification incorporated to increase clarity in lab testing schedule for Part 1. No change in testing schedule made from prior protocol version.

VXA-COV2-201 Protocol Amendment 1 (Vers. 2.0), 06 July 2021

Overall Rationale for the Amendment:

Per the request of the FDA, Vaxart has amended this clinical protocol to incorporate information on the risk of Thrombosis with Thrombocytopenia Syndrome (TTS) that has been reported with administration of two injected adenovirus-vectored COVID-19 vaccines being used under EUA. The eligibility criteria within this protocol have been modified to screen for and exclude individuals at high risk of TTS from study participation.

Additionally, the study Halting Rules have been modified to clarify that they are applicable to the observance of similar AEs and not just identical AEs, and also to clarify that they are applicable during the entire study period, not just the 7 days post each vaccination.

Additional changes have also been incorporated for added clarity and consistency. The changes are presented within the table below in the order of initial appearance within the document:

Section No. & Title	Description of Change	Brief Rationale
1.2 Synopsis 8.5.2 Independent Data Monitoring Committee (IDMC)	The criteria for advancing from study Part 1 to Part 2 have been modified to include an FDA review of preliminary Part 1 summary safety and immunogenicity information, and the Agency's agreement on the proposed approach prior to initiation of Part 2 enrollment.	As the specific criteria for advancing from Part 1 to Part 2 are not well defined within the protocol, FDA has offered this approach as a path that allows gaining timely consensus on the best path forward from Part 1 to Part 2 of the study.
1.1 Synopsis 3.2.2. Part 1: Eligibility for Second Vaccine 4.2.2 Part 2: Eligibility for Second Dose of Study Drug	The assessments and criteria that participants must meet at Week 4 to be eligible to receive their second vaccination/study drug administration has been described in additional detail for both Part 1 and Part 2. *Exclusion Criteria for Second Vaccine Dose:* • *Positive pregnancy test at Day 29 (female participants),* • *Occurrence of any possibly, probably or definitely treatment-related Grade 3 or 4 AE or SAE following the initial vaccination*	The additional detail regarding eligibility for the second dose was incorporated at the request of FDA.

	• *Occurrence of any Grade 3 or 4 AE or SAE following the initial vaccination without plausible alternative explanation* • *Presence of acute illness or significant new medical condition*	
Tables 3 and 4: Schedule of Events, Part 1 and Part 2, respectively	Tables 3 and 4 have been updated to include allocation of an aliquot of serum collected at baseline to be stored for testing (e.g. PF4 antibody ELISA) should an AESI related to blood clots be reported anytime during the study period.	Per the direction of the FDA, a blood sample will be collected at baseline and stored for analysis should a participant experience a clotting adverse event.
2.3.1 Risk Assessment	The risk section has been updated to include language describing the AEs reported with two injected adenovirus-vectored vaccines (thromboembolism and/or thrombocytopenia), as well as with general information on how to monitor for and report the events should they occur in study participants.	Because Vaxart's VXA-CoV2-1 investigational vaccine utilizes an adenovirus vectored design, and per the director of the FDA, information on the risks of thromboembolism and /or thrombocytopenia have been added to Section 2.3.1 of the protocol.
3.3 Part 1 Eligibility 4.3 Part 2 Eligibility Table 9: Protocol-Required Safety Laboratory Assessments	The eligibility criteria for both Part 1 and Part 2 have been modified to provide more granular information on abnormal tests, medical history and current conditions which are exclusionary due to potential risk of TTS.	Safety Laboratory tests that may be utilized to identify the potential for higher risk of TTS, as well as assessments of medical history and current medical conditions have been added to the study protocol under Amendment 1 to mitigate potential risks with Ad vaccines and TTS.
3.3 Part 1 Eligibility 4.3 Part 2 Eligibility	The eligibility criteria for both Part 1 and Part 2 have been modified to provide additional clarify those females who are breast-feeding are ineligible for study participation.	Though the breast-feeding exclusion was already present within the original protocol, it was described somewhat inconsistently at places. Per the request of FDA, this exclusionary criterion has been described more consistently throughout the revised protocol.
6.1. Study Halting Rules	The Halting Rules for both Part 1 and Part 2 have been updated to clarify that the rules are applicable to the observance of similar AEs (not just the same AEs) that are deemed as possibly, probably or definitely not related.	The additional detail regarding the Halting Rules was incorporated at the request of FDA.
9.1.3 Informed Consent Process	Wording in Section 9.1.3 indicating that a separate ICF would be utilized to collect consent for exploratory endpoint analyses has been removed.	As the evaluation of a wide range of exploratory assays is key to understanding the mechanism of action for Vaxart's oral vaccine candidates, enrollment will be focused on those participants that are willing to provide samples for exploratory assays.

9.5. Appendix 5: Medically Attended Adverse Events	The List of Medically Attended Adverse Events (MAAEs) including AEs of special interest has been updated to include events to be monitored under the category of Coagulopathy	Per the guidance of the FDA, the list of MAAEs of special interest have been updated to allow sites to monitor study participants for the occurrence of TTS events.

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