CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Phase 1b, Open-Label, Boost-Optimization Study of an Adenoviral-vector Based Oral Norovirus Vaccine (VXA-G1.1-NN) Expressing GI.1 VP1 Administered Orally to Healthy Adult Volunteers
Protocol Number:	**VXA-NVV-105**
Product Name:	Norovirus GI.1 Norwalk VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with double-stranded RNA Adjuvant (VXA-G1.1-NN)
Indication:	Prevention of noroviral gastroenteritis caused by norovirus GI.1
Study Phase	Phase 1b
Sponsor Name and Address	Vaxart Biosciences, Inc. 170 Harbor Way, Suite 300 South San Francisco, CA 94080
U.S. IND Number	IND: 16796
Sponsor Contact	Shaily J. Garg, PMP SVP, Clinical Development and Project Management Phone: 650-521-4496 Email: sgarg@vaxart.com
Medical Monitor	Dave Liebowitz, MD, PhD Phone: +1 (408) 340-8605 Email: dliebowitz@vaxart.com
Version and Approval Date	**Amendment 1; August 25, 2021**
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SIGNATURE PAGE/STATEMENT OF COMPLIANCE

Title: A Phase 1b, open-label, boost-optimization study of an adenoviral-vector based oral norovirus vaccine (VXA-G1.1-NN) expressing GI.1 VP1 administered orally to healthy adult volunteers

Protocol Number: VXA-NVV-105 (Amendment 1)

Vaxart, Inc.: _____ Date _____

The study will be conducted in accordance with the International Council for 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)

Site & Address: _____

_____

_____

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

A Phase 1b, open-label, boost-optimization study of an adenoviral- vector based oral norovirus vaccine (VXA-G1.1-NN) expressing GI.1 VP1 administered orally to healthy adult volunteers.

Study Rationale and Hypothesis

VXA-G1.1-NN is an E1/E3-deleted, replication-incompetent, adenovirus 5 (Ad5) vaccine vectors designed for use as an oral vaccine for the prevention of noroviral gastroenteritis caused by norovirus genogroups GI.1. The monovalent vaccine vector encodes the full-length of viral protein 1 (VP1) gene of Norwalk virus (Norovirus GI.1). 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.

Noroviruses are a genetically diverse group of small, non-enveloped, single-stranded positive sense RNA viruses belonging to the Caliciviridae family (Bresee, 2002). Norovirus infections are a leading cause of sporadic and epidemic gastroenteritis across all age groups worldwide (Hoa Tran, 2013; de Graaf, 2016). 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 (Esposito, 2020).

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-G1.1-NN oral vaccine may enable higher degrees of mucosal protection against infection when compared to a parenteral immunization method.

VXA-G1.1-NN is designed to elicit both antibody and T cell responses, mucosally and systemically, to Norovirus GI.1 Norwalk VP1. Prior completed Phase 1 studies with the Vaxart Vector Adjuvant Antigen Standard Technology (VAAST^{TM}) platform have demonstrated protective immunity to viruses, such as norovirus, influenza, and respiratory syncytial virus, with both systemic and mucosal immune responses against the antigen of choice (Kim, 2016; Kim, 2018; Liebowitz, 2020).

Clinical data is available from 3 Phase 1 studies (VXA- NVV-101, VXA-NVV-102, and VXA-NVV-103) which evaluated multiple single- and multi-dose ranging of the monovalent vaccine VXA-G1.1-NN in over 200 healthy young adult subjects (18 to 49 years old). These studies indicate that the vaccine was tolerated well and generated robust immune responses including systemic and mucosal antibodies as well as memory immunoglobulin A (IgA)/ immunoglobulin G (IgG). In addition to increase in serum blocking titer fifty assay (BT50) titers, vaccine recipients also developed mucosally primed VP1-specific circulating antibody secreting cells (ASCs), IgA^{+} memory B cells expressing gut-homing receptor ($\alpha4\beta7$), and fecal IgA, indicating substantial and local responses potentially relevant to prevent norovirus infection (Kim, 2018).

Over the past year, global efforts for the development of effective COVID-19 vaccines have been strongly reliant, among other technologies, on the use of adeno-associated viral vectors (AAV) (Callaway, 2020). AAV-based COVID-19 vaccines from AstraZeneca, Johnson & Johnson, and the Gamaleya Research Institute of Epidemiology and Microbiology have been granted emergency use authorization in many countries worldwide. Contextually, emerging evidence generated in clinical settings with the AstraZeneca COVID-19 vaccine (AZD1222) indicates that a 12-week interval between vaccine doses might significantly improve efficacy and immunogenicity of AAV-based vaccination strategies compared to a shorter 4- or 6-week dosing interval (Voysey et al., 2021; Hung and Poland, 2021). Specifically, subjects who received two vaccine doses with a dose interval of at least 12 weeks showed neutralizing and anti-SARS-CoV-2 spike IgG antibody responses more than two-fold higher than those who received the two-dose regimen at an interval of less than 6 weeks. Accordingly, AZD1222 vaccine efficacy increased from 55% (<6-week interval) to 81% with an interval of at least 12 weeks. In light of these findings, the current Phase 1b study VXA-NVV-105 is designed to assess the safety and immunogenicity of the VXA-G1.1-NN vaccine with a 2-dose vaccination schedule using different repeat-dosing intervals (4, 8, or 12 weeks apart) in healthy young adults (18 to 55 years old).

The current phase 1b, open-label, boost-optimization study objectives and endpoints for an adenoviral- vector based oral norovirus vaccine (VXA-G1.1-NN) expressing GI.1 VP1 administered orally to healthy adult volunteers is presented below.

Objectives and Endpoints (Primary and Secondary)

Objectives	Endpoints
Primary	
• To evaluate the immunogenicity of VXA-G1.1-NN with repeat-dose administration at Day 1 and varying boost schedules (Week 4, 8 or 12 post initial dose) in healthy adults aged 18-55, inclusive	• VP1 specific IgA ASC by enzyme-linked immunospot (ELISpot) • Norovirus G1.1 histo-blood group antigen (HBGA) blocking antibodies (BT50) • VP1 specific serum IgG by Mesoscale Discovery (MSD) assay •
Secondary	
• To assess the safety and tolerability of VXA- G1.1-NN with repeat-dose administration at varying boost schedules (Week 4, 8 or 12) in healthy adults aged 18-55, inclusive	• Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each dose of study drug • Frequency, duration, and severity of unsolicited serious AEs (SAEs), AEs of special interest (AESIs) and New Onset of Chronic Illness (NOCIs) through each Study Period (4 weeks post each vaccination)

Overall Design

This is an open-label study in healthy adult participants age 18-55 years old. The study will enroll 30 subjects to one of three treatment cohorts.

Cohort 1: (4-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 4

Cohort 2: (8-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 8

Cohort 3: (12-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 12

The study will include a screening period, Study Period 1 (Day 1 to 4 weeks post initial vaccination), Study Period 2 (4 Weeks from second vaccination will be initiated at Week 4 for Cohort 1, Week 8 for Cohort 2 and Week 12 for Cohort 3), and a follow-up period of 6 months post second vaccination in each cohort. Study assessments will be conducted as shown in the Schedule of Activities (SoA) in Section 1.2 (Table 2). In addition, participants will be contacted by phone between site visits to monitor for safety as specified in the SoA.

After signing an informed consent, participants will undergo screening assessments to determine study eligibility within a 45-day screening period.

Eligible participants will be enrolled and receive their first dose of study vaccine on Day 1.

During the Active study period, participants will record any potential symptoms of reactogenicity daily for 1 week post each vaccination, administered on Day 1 and Week 4, 8 or 12, depending on cohort assignment, using a Solicited Symptom Diary. Participants will return to the site as specified in the SoA to have safety assessments and samples collected for evaluation of immunogenicity.

At the participant's second vaccination visit (Week 4, 8 or 12 depending on Cohort assignment) they will have pre-dose safety assessments to determine eligibility to continue with the second vaccination. Additionally, female participants of childbearing potential must have a negative pregnancy test before receiving their second vaccination. Participants deemed ineligible for the second vaccination due to acute illness or new medical condition may be re-assessed, and if the condition resolves, may have a delayed second vaccination within 1 week of their scheduled vaccination Visit (+7 days window from Week 4, 8 or 12 depending on Cohort assignment). Participants with a delayed second vaccination will follow the delayed schedule through the rest of their Active Period as specified in the SoA.

If a subject remains ineligible for the second vaccination, they will complete an Early Termination visit and then enter the scheduled follow-up period per Cohort assignment as outlined in the SoA (1.2).

All participants will enter the follow-up period 4 weeks after their last vaccination and will be monitored for SAEs including AESIs and NOCIs through End of Study. Participants will also have samples collected for evaluation of immunogenicity as specified in the SoA.

Intervention Group and Number of Participants

Table 1 Treatment Arm, Doses and Sample Size

Group	Study Drug	Dose (IU ±0.5 log)	No. of Doses	Dosing Schedule	No. of Subjects
Cohort 1	VXA-G1.1-NN	$1x10^{10}$	2	Day 1 & Week 4[a]	10
Cohort 2	VXA-G1.1-NN	$1x10^{10}$	2	Day 1 & Week 8[a]	10
Cohort 3	VXA-G1.1-NN	$1x10^{10}$	2	Day 1 & Week 12[a]	10
				Total	**30**

[a] Subjects not eligible for the second dose (within the 7-day dosing window) will immediately enter the follow-up period.

Study Duration for Each Participant

For each subject, study participation is expected to last as follows:

Study Period	Cohort 1 (Day 1 and Week 4)	Cohort 2 (Day 1 and Week 8)	Cohort 3 (Day 1 and Week 12)
Screening Period:	45 days	45 days	45 days
Study Period 1:	4 weeks (Day 1 – Week 4)	4 weeks (Day 1 – Week 4)	4 weeks (Day 1 – Week 4)
Study Period 2:	4 weeks (Week 4 – 8)	4 weeks (Week 8 – 12)	4 weeks (Week 12 – 16)
Follow-Up Period:	6 months following boost	6 months following boost	6months following boost
Total Duration	**7 Months**	**8 Months**	**9 Months**

Safety Monitoring Committee (SMC): No

1.2 Schedule of Activities

Active Period										
	Screen	**Study Period 1 – Cohorts 1, 2, 3**								
				Study Period 2 – Cohort 1						
						Study Period 2 – Cohort 2				
								Study Period 2 – Cohort 3		
Study Day	**-45d to –1 d**	**Day 1 (Wk 0)**	**Day 8 (Wk 1)**	**Day 29 (Wk 4)**	**Day 36 (Wk 5)**	**Day 57 (Wk 8) /ET[1]**	**Day 64 (Wk 9)**	**Day 85 (Wk 12)/ET[2]**	**Day 92 (Wk 13)**	**Day 113 (Wk16)/ET[3]**
Visit Window (days)		n/a	0	**±2**	0	**±2**	0	**±2**	0	**±2**
Informed consent	X									
Inclusion/Exclusion	X	X		X						
Demographics	X									
Medical history	X									
Stool for occult blood	X									
Blood Sample (HBsAg, HCV, HIV)	X									
Urine drug screen	X									
Alcohol Testing	X									
Pregnancy Test[a]	X	X		X^{1}		X^{2}		X^{3}		
Physical examination	X	X^{b}	X^{b}	X^{b}	X^{b}	X^{b}	X^{b}	X^{b}	X^{b}	X^{b}
Vital Signs	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests	X	X^{c}	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
COVID vaccination status	X									
Vaccination		X		$X^{1, d,e}$		$X^{,2, d,e}$		$X^{3, d,e}$		
Dispense Solicited Symptom Diary		$X^{1,2,3}$		X^{1}		X^{2}		X^{3}		
Review & Collect Solicited Symptom Diary			X		X^{1}		X^{2}		X^{3}	
Review prior & concomitant medication	X	X	X	X	X	X	X	X	X	X
Query for AEs, SAEs, AESIs and NOCIs		X	X	X	$X^{1,f}$	$X^{1,f}$	$X^{2,f}$	$X^{2,f}$	$X^{3,f}$	$X^{3,f}$
Sample Collection Immunogenicity Assessments										
Serum		$X^{1,2,3,g}$		$X^{1,2,3}$		$X^{1,2}$		$X^{2,3}$		X^{3}
Whole blood (Flow Based)		$X^{1,2,3}$	$X^{1,2,3}$	X^{1}	X^{1}	X^{2}	X^{2}	X^{3}	X^{3}	
Whole blood (PBMC)		$X^{1,2,3}$	$X^{1,2,3}$	X^{1}	X^{1}	X^{2}	X^{2}	X^{3}	X^{3}	
Nasal Swab (Sam Device)		$X^{1,2,3}$		$X^{1,2,3}$		$X^{1,2}$		$X^{2,3}$		X^{3}
Saliva Sample		$X^{1,2,3}$		$X^{1,2,3}$		$X^{1,2}$		$X^{2,3}$		X^{3}

AE, adverse vent; AESI, Adverse event of special interest; EOS, End of Study; ET, Early Termination (7.2); HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; NP, Nasopharyngeal; NOCI, New Onset of Chronic Illness; PBMC, peripheral blood mononuclear cells; SAE, serious adverse event.
[1] = Cohort 1; [2] = Cohort 2; [3] = Cohort 3.
[a] For women of childbearing potential. Test at Day 1 and at second dose (boost). Test can be serum or urine test.
[b] Targeted.
[c] If screening lab tests are performed within 2 days prior to dosing, no need to repeat at Day 1.
[d] Assess eligibility to receive second dose. Participants with acute illness or new medical condition may be re-assessed, and if the condition resolves, have a delayed 2nd dose within 1 week of scheduled visit.
[e] If participants are not eligible to receive their 2nd dose, they immediately enter the follow-up period.
[f] AEs will only be collected for 4 weeks following each study drug administration.
[g] An aliquot of serum collected at baseline will be stored for testing (e.g. Platelet Factor 4 [PF4] antibody ELISA) should an AESI related to blood clots be reported anytime during the study period.

Follow-Up Period						
	COHORT 1		**COHORT 2**		**COHORT 3**	
Study Day	**Months 3, 4, 5, 6**	**Month 7 (Wk 28)/ EOS**	**Months 4, 5, 6, 7**	**Month 8 (Wk 32)/EOS**	**Months 5, 6, 7, 8**	**Month 9 (Wk 36)/ EOS**
Telephone Visit	X		X		X	
Visit Window (days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Query for SAEs, AESIs and NOCIs	X	X	X	X	X	X
Sample Collection Immunogenicity Assessments						
Serum		X		X		X
Whole blood (Flow Based)						
Whole blood (PBMC)[a]		X		X		X
Nasal Swab (Sam Device)		X		X		X
Saliva		X		X		X

AE, adverse event; AESI, Adverse event of special interest; EOS, End of Study; ET, Early Termination; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; NP, Nasopharyngeal; NOCI, New Onset of Chronic Illness; PBMC, peripheral blood mononuclear cells; SAE, serious adverse event.
[a] Optional.

2. INTRODUCTION

2.1. Study Rationale

VXA-G1.1-NN is an E1/E3-deleted, replication-incompetent, adenovirus 5 (Ad5) vaccine vectors designed for use as an oral vaccine for the prevention of noroviral gastroenteritis caused by norovirus genogroups GI.1. The monovalent vaccine vector encodes the full-length of viral protein 1 (VP1) gene of Norwalk virus (Norovirus GI.1). 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.

Noroviruses are a genetically diverse group of small, non-enveloped, single-stranded positive sense RNA viruses belonging to the Caliciviridae family (Bresee, 2002). Norovirus infections are a leading cause of sporadic and epidemic gastroenteritis across all age groups worldwide (Hoa Tran, 2013; de Graaf, 2016). 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 (Esposito, 2020).

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-G1.1-NN oral vaccine may enable higher degrees of mucosal protection against infection when compared to a parenteral immunization method.

VXA-G1.1-NN is designed to elicit both antibody and T cell responses, mucosally and systemically, to Norovirus GI.1 Norwalk VP1. Prior completed Phase 1 studies with the Vaxart Vector Adjuvant Antigen Standard Technology (VAAST^{TM}) platform have demonstrated protective immunity to viruses, such as norovirus, influenza, and respiratory syncytial virus, with both systemic and mucosal immune responses against the antigen of choice (Kim, 2016; Kim, 2018; Liebowitz, 2020).

Clinical data is available from 3 Phase 1 studies (VXA- NVV-101, VXA-NVV-102, and VXA-NVV-103) which evaluated multiple single- and multi-dose ranging of the monovalent vaccine VXA-G1.1-NN in over 200 healthy young adult subjects (18 to 49 years old). These studies indicate that the vaccine was tolerated well and generated robust immune responses including systemic and mucosal antibodies as well as memory immunoglobulin A (IgA)/ immunoglobulin A (IgG). In addition to increase in serum blocking titer fifty assay (BT50) titers, vaccine recipients also developed mucosally primed VP1-specific circulating antibody secreting cells (ASCs), IgA^{+} memory B cells expressing gut-homing receptor (α4β7), and fecal IgA, indicating substantial and local responses potentially relevant to prevent norovirus infection (Kim, 2018).

The current Phase 1b study is designed to assess the immunogenicity of VXA-G1.1-NN with repeat-dose administration at Day 1 and 2nd vaccination at Weeks 4, 8 or 12 (depending on Cohort assignment) in healthy adults aged 18-55, inclusive, with varying boost schedules.

2.2. Background

Noroviruses are a leading cause of foodborne disease and outbreaks of gastroenteritis worldwide and are responsible for substantial morbidity, mortality, and healthcare costs (Bányai, 2018). The

virus affects people of all ages; however, the incidence of disease is higher in younger children and in adults ≥65 years old (Lopman, 2016; Esposito, 2020). Noroviruses are highly infectious with major mode of transmission by fecal-oral spread, usually via contaminated food or water (Teunis, 2008; de Graaf, 2016; Gaythorpe, 2018). The incubation period of norovirus is 10-51 hours.

Noroviruses are genetically diverse viruses. Genogroups I, II and IV are human-transmitted. Genogroup I and II account for the majority of norovirus outbreaks (Vega, 2014). Each genogroup is further divided into genotypes based on the similarity of the amino acid sequence of the major viral capsid protein, VP1. Genotypes GI.1 and GII.4 represent the genogroups responsible for most outbreaks and the majority of the disease burden globally (Lopman, 2016).

Norovirus causes extensive morbidity with clinical symptoms of nausea, vomiting, non-bloody diarrhea, and abdominal cramps. Fever, headache, and body aches have been reported as well. These symptoms usually last 2-4 days. Additionally, asymptomatic infections are estimated to occur in approximately one-third of infected people. Currently no specific therapy exists for norovirus gastroenteritis. The standard treatment is oral rehydration with fluids and electrolytes (Glass, 2009). There are currently no licensed vaccines for norovirus.

Norovirus is an enteric pathogen and infects the epithelial cells of the small intestine. Vaxart's platform is based on oral delivery of the vaccine to the intestinal mucosa, which is analogous to the natural route of norovirus infection and entry. Human and animal experience with Vaxart's orally administered platform has demonstrated that substantial transgene specific intestinal IgA responses can be generated in addition to systemic IgG responses to the expressed antigen (influenza HA and norovirus VP1). These platform attributes may allow for better protection against norovirus infection than an injected protein-based vaccine.

As indicated, VXA-G1.1-NN was well tolerated in 3 Phase 1 studies and generate robust immune responses. In study VXA-NVV-101, the primary immunological endpoint (increase in BT50 titers) was met in the high-dose group (P = 0.0003), with 78% showing a ≥2-fold rise in titers after a single immunization (Kim, 2018). Statistically significant increases in geometric mean titers were also seen in Study VXA-NVV-103 with VXA-G1.1-NN compared with placebo (p=0.0008), with 43% of subjects showing a ≥4-fold increase in titers post vaccination.

A detailed description of the chemistry, pharmacology, efficacy, and safety of VXA-G1.1-NN is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of VXA-G1.1-NN may be found in the IB.

Table 3 Risk Assessment

Clinically Significant Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug VXA-G1.1-NN		
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 active and follow-up period.
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 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 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 plausible. The exact patho-physiology of TTS is still under investigation. At this time, a mechanism related to the adenovirus vectors cannot be excluded.	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, and/or easy bruising/ bleeding.

2.3.1. Benefit Assessment

Benefits to individual participants may include receipt of a potentially efficacious norovirus vaccine. Clinical data from Phase 1 studies demonstrated that VXA-G1.1-NN generated robust immune responses.

2.3.2. 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-G1.1-NN vaccine for the prevention of norovirus infection are justified as by the anticipated benefits that may be afforded to healthy stable adult participants.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the immunogenicity of VXA-G1.1-NN with repeat-dose administration at Day 1 and varying boost schedules (Week 4, 8 or 12 post initial dose) in healthy adults aged 18-55, inclusive	• VP1 specific IgA ASC by enzyme-linked immunospot (ELISpot) • Norovirus G1.1 histo-blood group antigen (HBGA) blocking antibodies (BT50) • VP1 specific serum IgG by Mesoscale Discovery (MSD) assay
Secondary	
• To assess the safety and tolerability of VXA- G1.1-NN with repeat-dose administration at varying boost schedules (Week 4, 8 or 12) in healthy adults aged 18-55, inclusive	• Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each dose of study drug • Frequency, duration, and severity of unsolicited serious AEs (SAEs), AEs of special interest (AESIs) and New Onset of Chronic Illness (NOCIs) through each Study Period (4 weeks post each vaccination)
Exploratory	
• To assess additional safety parameters	• Occurrence of clinically significant abnormalities in laboratory parameters (chemistry, hematology and urinalysis) at 1 week after each study drug dose and in vital signs immediately following each dose
• To assess long-term safety of VXA-G1.1-NN through 6 months after last vaccination	• Frequency, duration, and severity of all SAEs, AESIs and NOCIs through 6 months after last vaccination
• To assess additional immunogenicity parameters of VXA-G1.1-NN (Note: Additional exploratory immunogenicity assays may also be performed to further evaluate the activity of the VXA-G1.1-NN vaccine candidate)	• VP1 specific IgG ASC • VP1 specific serum IgA • Ad5 neutralizing antibodies • VP1 specific IgG and IgA memory B cells • B cell immunophenotyping • Saliva VP1 IgA • Nasal Swab VP1 IgA

4. OVERALL STUDY DESIGN

This is an open-label, boost-optimization study of an adenoviral- vector based oral norovirus vaccine (VXA-G1.1-NN) expressing GI.1 VP1 administered orally to health adult participants 18-55, inclusive. This study will enroll approximately 30 participants in three cohorts stratified by varying boost vaccination schedules.

The study will include a Screening period, Active study period through 4 weeks post last vaccination dose (Week 8 for Cohort 1, Week 12 for Cohort 2 and Week 16 for Cohort 3), and a Follow-up period of 6 months post vaccination (Month 7 for Cohort 1, Month 8 for Cohort 2 and Month 9 for Cohort 3). Study assessments will be conducted as shown in the SoA in Section 1.2 (Table 2). In addition, participants will be contacted monthly by phone between site visits to monitor for safety as specified in the SoA.

After signing an informed consent, participants will undergo screening assessments to determine study eligibility over a 45-day screening period.

On Day 1, participants will be enrolled sequentially in order of eligibility. Participants may be assigned to cohorts based on their availability for the second dose (boost). Cohorts 3 and 2 may be enrolled prior to Cohort 1 to optimize the overall study timeline.

Group	Study Drug	Dose (IU ±0.5 log)	Doses	Dosing Schedule	Subjects
Cohort 1	VXA-G1.1-NN	$1x10^{10}$	2	Day 1 & Week 4	10
Cohort 2	VXA-G1.1-NN	$1x10^{10}$	2	Day 1 & Week 8	10
Cohort 3	VXA-G1.1-NN	$1x10^{10}$	2	Day 1 & Week 12	10
				Total	**30**

Eligible participants will be enrolled to receive their first dose of study vaccine on Day 1.

During the Active period, participants will record symptoms of reactogenicity daily for 1 week post each vaccination, administered based on Cohort assignment, using a Solicited Symptom Diary. Participants will return to the site as specified in the SoA to have safety assessments and samples collected for evaluation of immunogenicity.

Additionally, female participants of childbearing potential must have a negative pregnancy test before their second dose of study drug. Participants deemed unsuitable for the second dose due to acute illness or new medical condition may be re-assessed, and if the condition resolves, may have a delayed second dose administered within 1 week of their originally scheduled second-dose visit (+7 days window). Participants with a delayed second study drug administration will follow the delayed schedule through their active period.

All participants will enter the follow-up period 4 weeks after their second dose and will be monitored for SAEs, including AESI and NOCI, through End of Study. Participants will also be evaluated for immunogenicity as specified in the SoA.

Any participants who are not eligible to receive the second study drug administration will enter the follow-up period at that visit rather than receiving the second dose and will be monitored for safety and evaluated for immunogenicity through their End of Study as specified in the SoA.

4.1. Scientific Rational for Study Design

Emerging evidence generated in clinical settings with the AstraZeneca COVID-19 vaccine (AZD1222) indicates that a 12-week interval between vaccine doses might significantly improve efficacy and immunogenicity of AAV-based vaccination strategies compared to a shorter 4- or 6-week dosing interval (Voysey et al., 2021; Hung and Poland, 2021). In light of these findings, the current Phase 1b study is designed to assess the safety and immunogenicity of the VXA-G1.1-NN vaccine with a 2-dose vaccination schedule using different repeat-dosing intervals (4, 8, or 12 weeks apart) in healthy young adults (18 to 55 years old).

4.2. Justification for Varying Dose Schedules

Based on the safety results observed in completed and ongoing studies with prior vaccines utilizing the VAAST platform, the multiple dosing schedules of VXA-G1.1-NN selected for this Phase 1b study are second dose at 4 weeks for Cohort 1, 8 weeks in Cohort 2 and 12 weeks at Cohort 3, with participants receiving at $1x10^{10}$ IU± 0.5 at both visits.

Over 200 subjects have been immunized with multiple Vaxart recombinant adenovirus serotype 5 (rAd5) vaccine candidates at $1x10^{10}$ IU and a similar number of subjects have been immunized at $1x10^{11}$ IU. These dose levels demonstrated a favorable safety profile and generated strong immune responses. Repeat dosing with the VXA-G1.1-NN oral vaccine has previously been tested at doses up to $1x10^{11}$ IU at Days 1 and 29 in two prior trials (VXA-G11-101 and VXA-G11-102). These studies showed the vaccine to be safe and immunogenic. The current study will evaluate different dosing schedules of VXA-G1.1-NN in healthy adults at doses of $1x10^{10}$ IU.

4.3. Study Duration

For each participant participation is expected to last as follows:

Study Period	Cohort 1 (Day 1 and Week 4)	Cohort 2 (Day 1 and Week 8)	Cohort 3 (Day 1 and Week 12)
Screening Period:	45 days	45 days	45 days
Study Period 1:	4 weeks (Day 1 – Week 4)	4 weeks (Day 1 – Week 4)	4 weeks (Day 1 – Week 4)
Study Period 2:	4 weeks (Week 4 – 8)	4 weeks (Week 8 – 12)	4 weeks (Week 12 – 16)
Follow-Up Period:	6 months following boost	6 months following boost	6 months following boost
Total Duration	7 Months	8 Months	9 Months

4.4. End of Study Definitions

A participant is considered to have completed the study if they complete through the study Active and Follow-Up Period for their Cohort.

4.5. Safety and Final Database Lock

Following completion of the Active Period by all Cohorts, the database will be cleaned and locked. The Clinical Study Report (CSR) will be written based on the last Active Visit dataset (Cohort 1- Week 8; Cohort 2- Week 12, Cohort 3 – Week 16).

Following completion of End of Study visit for all subjects, the safety database will be cleaned and locked and data collected during the Follow-Up Period will be amended to the Study CSR.

5. ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

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

Age

1. 18 to 55 years old inclusive at the time of signing the Informed Consent Form (ICF).

Type of Participants

2. General good health, without significant uncontrolled medical illness, based on medical history, physical examination, vital signs, and clinical laboratories (CBC, chemistry, and urinalysis) as determined by the investigator in consultation with the Research Monitor and Sponsor
3. Body mass index (BMI) between 17 and 35 kg/m^2 at screening
4. 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 study dose).

Gender and Reproductive Considerations

5. 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 10.4)

a. Female participants must provide a negative pregnancy test at each required visit and fulfill one of the following criteria:

- 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.
- Surgically sterile
- Use of oral, implantable, transdermal or injectable contraceptives for 30 days prior to initial vaccination and until 60 days after the last vaccination. The form of contraception must be approved by the Investigator
- 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).
- Not be sexually active (abstinent) or be in a relationship with partner who is sterile (must be discussed with site staff and documented).

Informed Consent

6. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

The participants must be excluded from participating in the study if they meet any of the following:

Medical Conditions

1. Presence of significant uncontrolled medical or psychiatric illness (acute or chronic) including institution of new medical/surgical treatment or significant dose alteration for uncontrolled symptoms or drug toxicity within 3 months of screening and reconfirmed at baseline
2. Cancer, or received treatment for cancer, within past 3 years (excluding basal cell carcinoma or squamous cell carcinoma)
3. Presence of immunosuppression or medical condition possibly associated with impaired immune responsiveness, including diabetes mellitus 1 and 2
4. History of irritable bowel disease or other inflammatory digestive or gastrointestinal condition that could affect the distribution/safety evaluation of an orally administered vaccine targeting the mucosa of the small intestine.

   Such conditions may include but are not limited to:

   a. Esophageal Motility Disorder
   b. Malignancy
   c. Malabsorption
   d. Pancreaticobiliary disorders
   e. Irritable bowel syndrome
   f. Inflammatory Bowel Disease
   g. Surgical Resection
   h. GERD
   i. Hiatal Hernia
   j. Peptic Ulcer
      (History of cholecystectomy is not exclusionary)
5. History of any form of angioedema
6. History of serious reactions to any vaccination such as anaphylaxis, respiratory problems, hives or abdominal pain
7. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic
8. Any condition that resulted in the absence or removal of the spleen
9. Acute disease 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.)
10. Presence of a fever $\geq 38^{o}$C measured orally at baseline (Assessment may be repeated during screening period)
11. Any significant hospitalization within the last year which in the opinion of the Investigator or Sponsor could interfere with study participation.
12. Any other condition that in the clinical judgment of the investigator would jeopardize the

safety or rights of a participant taking 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

13. Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) tests at the screening visit
14. Positive urine drug screen for drugs of abuse at screening
15. Positive breath or urine alcohol test at screening and baseline

Prior/Concurrent Therapy

16. Receipt of a licensed vaccine within 14 days prior to baseline vaccination or planned administration during the study active period (4 weeks post each study vaccination).
17. Use of antibiotics, proton pump inhibitors, H2 blockers or antacids within 7 days prior to study drug administration or planned use during the active study period
18. Use of medications known to affect the immune function (e.g., systemic corticosteroids and others) within 2 weeks before study drug administration or planned use during the active study period
19. Daily use of nonsteroidal anti-inflammatory drugs within 7 days prior to study drug administration or planned use during the active study period
20. Administration of any investigational vaccine, drug or device within 8 weeks preceding study drug administration (Day 1), or planned use within the duration of the study

Other Exclusions

21. Donation or use of blood or blood products within 30 days prior to study drug administration or planned donation during the active study period
22. History of drug, alcohol or chemical abuse within 1 year of screening
23. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin

5.3. 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; such participants will be determined a permanent screen failure after the second screening determines the participant is ineligible.

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

Study drug is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Drug Administration

VXA-G1.1-NN is an E1/E3-deleted, replication-incompetent, Ad5 vaccine vectors designed for use as an oral vaccine. The monovalent vaccine vector encodes the full-length of VP1 gene of Norovirus GI.1. The adjuvant consists of a double-stranded RNA TLR3 agonist which enhances immune induction to expressed antigen in the gut mucosa.

Table 4 VXA-G1.1-NN Study Drug

Intervention Name	**VXA-G1.1-NN**
Type	Biologic
Dose Formulation	Enteric-coated tablets
Unit Dose Strength(s)	$6.7x10^9$ IU per tablet (Drug Product Lot: DP-05.19004)
Dosage Level(s)	$1x10^{10}$ IU ± 0.5 log (2 tablets of VXA-G1.1-NN (Lot DP-05.19004) will be dispensed to deliver each dose)
Route of Administration	Oral
Administration instructions	Participants should fast and refrain from ingesting solid food for at least 8 hours prior to oral dosing. A trained member of the site study staff will dispense the tablet(s) constituting their assigned dose to the participant. The participants will swallow the tablets with 360 to 480 mL of water or clear fruit juice (acidic, such as cranberry juice) 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 by the Sponsor or designated representative.
Packaging and Labeling	The tablets are packaged into 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 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

Intervention Name	VXA-G1.1-NN
	product, the concentration of the vaccine, the date of manufacturing or expiration. 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.
Storage Condition	VXA-G1.1-NN 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.

6.2. 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 eCRF. The 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.

6.2.1 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 of $1x10^{10}$ IU ± 0.5 log at the protocol-defined study visits by Cohorts as specified in the SoA 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).

6.3. 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 bottles of 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 active period, 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.

6.4. 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-G1.1-NN. Participants should be closely monitored for toxicities and managed appropriately.

6.5. Concomitant Therapy

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

Use of concomitant medication from 4 weeks before Day 1 through 4 weeks after the last dose administration (completion of Active Study period) must be recorded onto 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.

6.5.1. Prohibited Concomitant Medication

Medications specifically prohibited in the exclusion criteria are not allowed during the Active Study period (Section 5.2 prior/concurrent therapy), unless deemed medically necessary by the Investigator.

6.6. Intervention after the End of the Study

No additional intervention is planned beyond the end of the study.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT WITHDRAWAL FROM STUDY

7.1. 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).

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 follow-up visits.

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
- 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.

7.2. Early Termination Visit (Active or Follow-Up Period)

If a participant is removed from the study or declines further participation during the study Active Period, the Early Termination (ET) visit should be the next visit completed as shown in the SoA per Cohort Assignment. Participants will enter the follow-up period to be monitored for safety and immunogenicity even if they discontinue study drug prematurely unless they withdraw consent.

If a subject withdraws from the study after entering the follow-up period (i.e., after completed their Active Phase participation) the subject will be called for final assessments, per the End of Study Visit assessments as outlined in the SoA (0).

7.3. 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 (Table 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 submit a written request of destruction

of any samples taken and not tested, and the investigator must document this in the site study records.

7.4. 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. Consultation with the Sponsor is required if the new visit date is more than 7 days during each Cohort's Active Period.
- 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.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 2). 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 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 AEs or any event of concern 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.

8.1. Immunogenicity Assessments

Immunogenicity will be evaluated using cellular and humoral immune function assays from blood and mucosal (saliva and nasal swab) samples. Samples will be collected from all participants according to the time points specified in the SoA. The following analytes will be measured:

Key Immunogenicity assessments:

- VP1 specific IgA ASC by ELISpot
- HBGA blocking antibodies by BT50
- VP1 specific serum IgG MSD assay Exploratory Immunogenicity

assessments:

- VP1 specific IgG ASC
- VP1 specific serum IgA
- Ad5 neutralizing antibodies
- VP1 specific IgG and IgA memory B cells
- B cell immunophenotyping
- Saliva VP1 IgA
- Nasal VP1 IgA

Additional exploratory immunogenicity assays may also be performed to further evaluate the activity of the VXA-G1.1-NN vaccine candidate. Note that not all sample timepoints may be relevant for some of the analysis, so not all assays may be performed at all timepoints.

Sample collection, processing and shipping details are provided within the General and Immunogenicity Laboratory Manuals.

8.2. Safety Assessments

The safety of the VXA-G1.1-NN will be evaluated through the reporting of solicited symptoms of reactogenicity for 1 week following each study drug dose, unsolicited AEs for 4 weeks following each study drug dose, SAEs (including AESIs and NOCIs) for 6 months following the last study drug dose. The occurrence of these events should be reported to the Sponsor in an expedited manner, similarly to SAEs as described in Table 9. AESIs are listed in Appendix 5 (Section 10.5).

Planned time points for all safety assessments are provided in the SoA (Table 2).

8.2.1 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) will be measured at site visits as specified in the SoA.

8.3 Vital Signs

Blood pressure, oral temperature, 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.

8.3.1. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and 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.
- Hematology or serum chemistry parameters will be graded according to the FDA toxicity grading scale (Section 10.3.1.1.2) and will be adjusted according to local laboratory reference ranges. Participants have the ability to rescreen once should screening values fall outside of the allowed eligibility criteria, per the discretion of the Investigator.

8.4. Adverse Events and Serious Adverse Events

The definitions of any AE (solicited and unsolicited), SAE and AESIs/NOCIs can be found in Appendix 3 (Section 10.3).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of any AE (solicited and unsolicited), or SAE. Investigators remain responsible for following up AEs, SAEs and other reportable safety events for outcome.

8.4.1. Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs (solicited and unsolicited), 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 5 below summarizes the different reporting timelines for AEs (unsolicited and solicited), 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, as indicated in Appendix 3 (Table 17). The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Table 5 Adverse Event Reporting Timelines to the Sponsor

Type of Event	AE (unsolicited)	AE (solicited)	SAE / AESI / NOCI	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 end of Follow-Up Period/ EOS	From first dose until end of Follow-Up Period/ 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
Reporting Method	AE eCRF	Solicited Symptom Diary	AE eCRF or SAER Form	Pregnancy form

AE, Adverse event; SAE, Serious adverse event; SUSAR, serious unexpected suspected adverse reaction.

8.4.2. Method of Detecting AEs and SAEs

Appendix 3 (Section 10.3) provides the method of recording (Table 10), evaluating severity (Table 11), and assessing causality (Table 16) of AEs and SAEs and the procedures for completing and transmitting SAE reports (Table 17).

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and non-leading questioning of participants is the preferred method to inquire for AE occurrences.

8.4.3. Follow-Up of AEs 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 or SAE as fully as possible. This may include laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The investigator will submit updated SAE data to Sponsor within 24 hours of receipt of the information. AEs and pregnancy will be followed by the investigator as specified in Appendix 4.

8.4.4. 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 (IRB) and investigators.
- 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 IB and will notify the IRB, if appropriate, according to local requirements.

8.4.5. 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.

8.4.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected as outlined in Appendix 4 (Section 10.4).
- 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 10.4.3).

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

The sample size was determined based on experience of a typical Phase 1 vaccine study, therefore there are no sample size calculations utilized for this study. Thirty subjects (30) will be enrolled in each cohort arm for a total planned enrollment of 30 subjects. The numbers of participants per scheduling group are predicted to yield meaningful safety and immunogenicity results in order to plan for future clinical trials.

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 dsDNA adjuvant), the vaccine was well tolerated at total doses up to $2x10^{11}$ IU.

In this study we will observe the difference in IgA ASC responses of VXA-G1.1-NN given at multiple scheduled timepoints. In a prior Phase 1 study, for VXA-GI.1- NN at a dose of 10^{11} IU (N=23), the average IgA ASC count was 560 per 10^6 PBMCs with a standard deviation (SD) of 740. Under the current protocol, immune responses with the initial vaccination at Day 1 versus with the second vaccination at will also be evaluated at each dose level in comparison to the multiple dosing schedules for the boost vaccination.

Populations for Analyses

Analysis Population	Description
Screened	All subjects who enter screening (assigned a screening number)
Dose 1 evaluable immunogenicity	All enrolled participants who receive the study intervention to which they are 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 enrolled participants who receive 2 doses of the study intervention to which they are 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 enrolled participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Safety	All enrolled participants who receive at least 1 dose of the study drug.

9.2. 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.

9.2.1. Safety Analysis

Safety will be summarized for each cohort:

Cohort 1: (4-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 4

Cohort 2: (8-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 8

Cohort 3: (12-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 12

Solicited symptoms of reactogenicity, unsolicited AEs, SAEs, clinical laboratory (blood chemistry, hematology, and urinalysis) test results, physical examination, and vital signs will be summarized descriptively by study visit.

All analyses will be performed separately for each cohort.

Endpoint	Statistical Analysis Methods
Primary (measured from Day 1 through end of Active Period)	VP1 specific IgA ASC by enzyme-linked immunospot (ELISpot) Norovirus G1.1 histo-blood group antigen (HBGA) blocking antibodies (BT50) VP1 specific serum IgG by Mesoscale Discovery (MSD) assay Descriptive statistics will be provided for each reactogenicity endpoint for each dose and treatment group. Local reactions and systemic events from Day 1 through Day 8 after each dose will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint.
Secondary (measured from Day 1 through end of Active Period)	Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each dose of study drug Frequency, duration, and severity of unsolicited adverse events (AEs) and serious AEs (SAEs) through each Study Period (4 weeks post each vaccination) AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. Descriptive summary statistics (counts and percentages) will be provided for any AEs for each vaccine group. SAEs will be categorized according to MedDRA terms. The safety analyses are based on the safety population. Participants will be summarized by cohort. Missing reactogenicity diary data will not be imputed; missing AE dates will be handled according to the rules determined in the SAP.
Exploratory	Occurrence of clinically significant abnormalities in laboratory parameters (chemistry, hematology and urinalysis) at 1 week after each study drug dose and in vital signs immediately following each dose. Frequency, duration, and severity of all SAEs, AESIs and NOCIs through 6 months after last vaccination. Descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at each time point as appropriate for each cohort, including grading shifts in hematology and chemistry laboratory assessments between baseline and each subsequent measurement. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint.

9.2.2. Immunogenicity Analysis

Immunogenicity will be summarized according to the treatment group to which the subject was assigned.

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose. The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations. An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population.

Immunogenicity will be summarized for each cohort:

Cohort 1: (4-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 4

Cohort 2: (8-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 8

Cohort 3: (12-week boost vaccination) 10 subjects will receive two doses of $1x10^{10}$ IU± 0.5 log at Day 1 and Week 12

Endpoint	Statistical Analysis Methods
Exploratory (Key Immunogenicity Endpoints)	VP1 specific IgG ASC VP1 specific serum IgA Ad5 neutralizing antibodies VP1 specific IgG and IgA memory B cells B cell immunophenotyping Saliva VP1 IgA Nasal Swab VP1 IgA All measures will be summarized descriptively for each cohort, for all timepoints where measured. The Dose 1 and Dose 2 evaluable immunogenicity populations will be used for these analyses.

9.3. Safety Oversight

9.3.1. 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 raises concern regarding a participant's safety.

The 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 become and 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 a safety review which can suspend the study, recommend amendments to the protocol, and/or to request further information.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. 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

10.1.2. 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.

10.1.3. 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.

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

This clinical study will include women and men who are 18-55 years of age, inclusive, and volunteers of all races and ethnicities who meet the inclusion/exclusion criteria, regardless of religion, sex, or ethnic background.

10.1.5. 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.

10.1.6. 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.

10.1.7. 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 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.

10.1.8. 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 eCRF 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.

10.1.9. 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.

10.2. Appendix 2: Safety Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory, unless otherwise specified.
- All safety laboratory samples including hematology, serum chemistry and serology are to be drawn by standard phlebotomy techniques, into 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 5.
- 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 6 Protocol-Required Safety Laboratory Assessments

Hematology	Hemoglobin, lymphocytes, hematocrit, neutrophils, eosinophils, platelet count, and complete white blood cell count
Serum Chemistry	Alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, BUN, CPK, creatinine, random glucose, calcium, potassium, sodium, phosphorous, albumin, magnesium, amylase and total protein
Urinalysis	Protein, glucose ketones, bilirubin, urobilinogen, hemoglobin, pH, specific gravity, appearance, color, leukocyte esterase, nitrite
Urine drug screen	Amphetamines, methamphetamines, methadone, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine, phencyclidine, tetrahydrocannabinol
Other laboratory assessments	Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody types 1 and 2 (Screening only) Female participants of child-bearing potential: urine or serum pregnancy tests

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

Table 7 Definition of AE (Unsolicited and Solicited)

AE Definition
• An AE 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: An AE 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 AE
• Unsolicited AEs are any AEs 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 AEs (all AEs not collected in the Solicited Symptom Diary during the first week following each study drug administration) will be monitored and collected from the time of each dose through 4 weeks post each dose. • Solicited AEs 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 study drug administration to record solicited AE daily for the 1 week following each dose.

Table 8 Events Meeting Definition of AE

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., vital signs measurements) that worsen from baseline and are 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.
Events <u>NOT</u> Meeting the AE 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.

Table 9 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.
4. Results in persistent or significant disability/incapacity
An SAE is defined as any serious adverse event that, at any dose:
• 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. 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. o 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.

Table 10 Definition of AESI and NOCI

New Onset of Chronic Illness (NOCI)
• A New Onset of Chronic Illness (NOCI) is defined as diagnosis post-enrollment and vaccination of a new medical condition which is chronic in nature, including those potentially controllable by medication (e.g. diabetes, asthma).
Adverse Events of Special Interest (AESI)
• A Significant Event of Special Interest (AESI) is not necessarily ordinarily considered to be a SAE, even though the event may be of clinical significance. They are events where Vaxart wishes to be promptly informed and to collect information relevant to the event. The same process used for reporting SAEs (see Section **8.4.4. Regulatory Reporting Requirements for SAEs**) should be followed. Adverse Events of Special Interest are listed within Appendix 5, Section 10.5.

Table 11 Recording of AE and/or SAE

AE and SAE Recording
• When an AE/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 AE/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.

Table 12 Grading the Severity of AEs

Assessment of Severity
All AEs 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.

Grading of Solicited Adverse Events

Participants 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 12.

Table 13 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.

10.3.1. Grading of Laboratory Abnormalities

In accordance with the FDA's Guidance on the toxicity grading scale for vaccine studies, new or worsening abnormalities in laboratory values for tests performed and listed in the guidance should be graded based on the severity scale presented in Table 13 (serum chemistry), Table 14 (hematology) and Table 15 (urinalysis).

Table 14 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 UL N	> 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.

Table 15 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.

Table 16 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.

Table 17 Assessment of Causality

Assessment of Causality	
• For all solicited symptoms and unsolicited AEs and SAEs , the Investigator will make a judgment regarding the relationship of the AE to the study vaccine. All AEs 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 AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/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 AE;
Possibly Related:	The AE 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 AE 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 AE 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.

Table 18 Reporting of SAEs

SAE Reporting to Sponsor (or designee) via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the Sponsor (or designee) will be the electronic data collection tool. • 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 (or equivalent).

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

10.4.1. 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.

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.

10.4.2. Contraception Guidance

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).

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)

10.4.3. 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.

10.5. Appendix 5: Adverse Events of Special Interest (AESIs)

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 throughout the entire study period and reported to the Sponsor in an expedited manner as outlined in Section 10.3.

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

10.6. Appendix 6: Abbreviations

Term	Description
Ad5	Adenovirus type 5
AE	Adverse event
AESI	Adverse event of special interest
ANCA	Anti-neutrophil cytoplasmic antibody
ASC	Antibody secreting cells
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research – FDA
CIOMS	Council for International Organizations of Medical Sciences
DP	Drug product
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI.1	Norovirus genogroup I.1
GII.4	Norovirus genogroup II.4
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMP	Good Manufacturing Practice
GMT	Geometric mean titer
HBGA	Histo-blood group antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed Consent
ICH	International Council for Harmonisation
SMC	Safety Monitoring Committee
IEC	Independent Ethics Committee

IgA	Immunoglobulin A
IgG	Immunoglobulin G
IND	Investigational new drug
IRB	Institutional Review Board
IU	International units
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
NOCI	New Onset of Chronic Illness
NoV	Norovirus
PBMC	Peripheral blood mononuclear cells
PF4 Antibody ELISA	Platelet Factor 4 antibody ELISA
PT/INR	Prothrombin time and international normalized ratio
RBD	Receptor binding domain
RCA	Replication-competent Ad5
RCC	Radio-Controlled Capsules
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
SUSAR	Serious unexpected suspected adverse reaction
TLR3	Toll-like receptor 3
TTS	Thrombolytic and thrombocytopenic syndrome
VAAST	Vector adjuvant antigen standard technology
VP1	Vaccine Protein 1, major capsid protein of norovirus
WOCBP	Women of childbearing potential

10.6 Appendix 7: Summary of Changes to Protocol

PROTOCOL VXA-NVV-105 HISTORY:	
Document	**Date**
Protocol Amendment 1; Version 2.0	25 August 2021
Original Protocol; Version 1.0	31 March 2021

Overall Rationale for the Amendment:

Per a request received from the FDA, Vaxart has amended this clinical protocol to incorporate information on the risk of Thrombosis with Thrombocytopenia Syndrome (TTS) that has been observed with administration of two injected adenovirus-vectored COVID-19 vaccines being used under EUA. Enrollment under this protocol has completed, however subjects are currently in safety follow-up. All subjects will be reconsented with an updated informed consent form with updated risk information incorporating TTP at their next site visit. This requirement for updatd risk information has necessitated the modifications listed in the table below within protocol amendment 1 (Ver. 2.0). Additional minor changes incorporated into the amendment for added consistency/clarity are also summarized below.

Section No. & Title	Description of Change	Brief Rationale
Table 1.2: Schedule of Activities	Table 1 has 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 should be collected at baseline and stored for analysis should a participant experience a clotting adverse event.
2.3 Benefit/ Risk Assessment	The risk section has been updated to include language describing the adverse events 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-G1.1-NN 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 2.1 of the protocol.
Appendix 5: Adverse Events of Special Interest (AESIs)	The List of Adverse Events of Special Interest (AESIs) has been updated to include events to be monitored under the category of Coagulopathy	Per the guidance received from FDA, the list of AEs of special interest (AESIs) has been updated to require sites to monitor study participants for the occurrence of TTS events.

Protocol Clarifications

The following additional modifications have been incorporated within the current amendment to provide increased clarity and consistency:

Section No. & Title	Description of Change
Inclusion Criteria #5 and 6.1. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Clarification added to inform that a pregnancy test should be conducted on all female participants and therefore the follicle-stimulating hormone (FSH) testing will not be required. The women of childbearing potential category will no longer be utilized as a differential marker for pregnancy testing
Inclusion Criteria #2	Inclusion criterion #2 which refers to subjects "without significant medical" was revised to be worded consistent with exclusion criterion #1 which states subjects with "significant uncontrolled medical" should be excluded
Section 1.1 Overall Design	There was language present in error on page 8 of the original protocol which states that "absence of acute illness or new medical condition as confirmed by negative for SARS-CoV-2 if symptomatic". SARS-CoV-2 negative testing is not a defining criterion for absence of acute illness or new medical condition and is not included elsewhere in the protocol. This erroneous language has been removed in the current amendment.
Table 1.2: Schedule of Activities	A serum or urine pregnancy test is acceptable prior to both the first and second vaccinations. This has been clarified within the amendment.
Section 8.3 Vital Signs	Oral temperature will be collected as part of the Vital Sign procedures
Table 1.2: Schedule of Activities	For Day 57 vaccination day (Cohort 2) the super script has been corrected to "e" from "3", which was in error.
Table 1.2: Schedule of Activities	Alcohol testing, required to evaluate the associated exclusion criteria, was included in the protocol however not listed out as a separate assessment within the Schedule of activities. It has been added there for consistency and added clarity.
Exclusion Criteria #14	Exclusion criterion #14 has been modified to clarify that subjects who test positive for THC use at screening will be allowed to participate in the trial if they commit to not using THC for the duration of the study, meet all other criteria and have a negative drug test at their Day 1 visit.
Section 10.1.3 Informed Consent Process	Language regarding the use of a second ICF has been deleted as a separate consent for future use is not applicable to this protocol. The current ICF form already addresses storage of samples for future use.

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