Protocol Number: VXA-NVV-108

Official Title: A Phase I, Multicenter, Randomized, Double-blind, Placebo-controlled Single Dose, Dose-ranging Study to Evaluate the Safety, Tolerability, and Immunogenicity of Orally Administered Bivalent GI.1/GII.4 Norovirus Vaccine in Healthy Lactating Females ≥ 18 years Old and Their Breast-feeding Infants

NCT Number: NCT07254728

Document Date: 17 February 2023

Clinical Study Protocol

Protocol Title:	A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants
Brief Title:	Evaluating Vaxart's oral bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females and their nursing infants
Protocol Number:	VXA-NVV-108
Product Name:	Bivalent GI.1 and GII.4 vaccines (VXA-G1.1-NN plus VXA GII.4-NS)
Indication:	Prevention of Norovirus Infection
Sponsor:	Vaxart, Inc. 170 Harbor Way, Suite 300 South San Francisco, CA 94080
Sponsor Contact:	[redacted]
Sponsor Medical Monitor:	[redacted]
Chief Medical Officer:	[redacted]
Protocol Version; Date:	1.0; 17 February 2023

Protocol Title: A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants

Brief Title: Evaluating Vaxart's oral bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females and their nursing infants

Protocol Number: VXA-NVV-108

Amendment Number: Not applicable

Date of Amendment (Optional): Not applicable

Investigational Product Name: Bivalent GI.1 and GII.4 vaccines (VXA-G1.1-NN plus VXA GII.4-NS)

Phase: I

Sponsor: Vaxart, Inc.
170 Harbor Way, Suite 300
South San Francisco, CA 94080

Funding Sponsor: Vaxart, Inc and Bill & Melinda Gates Foundation

SIGNATURE PAGE

PROTOCOL TITLE: A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants

PROTOCOL NUMBER: VXA-NVV-108

PROTOCOL VERSION (Amendment): Not applicable

Signature of Sponsor's authorized representative(s):

[redacted]

17 FEB 2023

Date

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), the ethical principles that have their origin in the Declaration of Helsinki and the Code of Federal Regulations on the Protection of Human Participants (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial Subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training per country requirements.

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

Principal Investigator: _____ _____
Signature Date

Name: _____

Address: _____

_____

_____
(Full Address, Landmark, State, Country, Phone: Fax:)

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LIST OF IN-TEXT FIGURE

LIST OF ABBREVIATIONS [AND DEFINITIONS OF TERMS]

Term	Description
AE	Adverse event
AESI	Adverse event of special interest
AEFI	Adverse events following immunization
AGE	Acute gastroenteritis
ANCA	Anti-neutrophil cytoplasmic antibody
ASC	Antibody secreting cells
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research – FDA
DP	Drug product
eCRF	Electronic case report form
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
CMP	Clinical Monitoring Plan
CSR	Clinical Study Report
DCC	Data Coordinating Center
EOS	End of Study
ET	Early Termination
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI.1	Norovirus genogroup I.1
GII.4	Norovirus genogroup II.4
GMP	Good Manufacturing Practice
GRAS	Generally recognized as safe
HBsAg	Hepatitis B surface antigen
HBGA	Histo-blood group 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 Conference on Harmonisation
IP	Investigational Product

ITT	Intent to treat
SMC	Safety Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IND	Investigational new drug
IRB	Institutional Review Board
IU	Infectious units
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSD	Meso Scale Discovery
NOCI	New Onset of Chronic Illness
NoV	Norovirus
OHRP	Office for Human Research Protections
PBMC	Peripheral blood mononuclear cells
PVP	Polyvinyl pyrrolidone
PI	Principal investigator
RNA	Ribonucleic acid
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
TEAE	Treatment-emergent adverse event
VP1	Viral Protein 1, major capsid protein of norovirus
WHO	World Health Organization

1. PROTOCOL SYNOPSIS

Title of Study: A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants.

Sponsor: Vaxart Biosciences, Inc.
170 Harbor Way, Suite 300
South San Francisco, CA 94080

Contract Research Organization: TBD

Protocol number:	VXA-NVV-108	**IND Number:**	
Trial Blinding scheme:	Double-Blind	**Phase of the study:**	Phase I

Study Arms:

A total of 76 healthy lactating female participants will be enrolled and randomized into three Arms (medium dose, high dose, and placebo), as described below:

- Arm 1: Bivalent GII.4/GI.1 medium dose vaccine (VXA-GII.4-NS plus VXA-G1.1-NN) 5×10^{10} tablets; total dose is 1×10^{11} IU/dose (N=30)
- Arm 2: Bivalent GII.4/GI.1 high dose vaccine (VXA-GII.4-NS plus VXA-G1.1-NN) 1×10^{11} tablets; total dose is 2×10^{11} IU/dose (N=30)
- Arm 3: Placebo tablets (N=16)

Study Rationale:

Noroviruses (NoV) are a genetically diverse group of small, non-enveloped, single-stranded positive-sense RNA viruses belonging to the *Caliciviridae* family and currently, it is the main viral cause of acute gastroenteritis (AGEs) in most countries worldwide. After adoption of the rotavirus vaccine throughout the world, norovirus infection has been one of three major causes of infant diarrheal disease. It was estimated that each year NoVs cause 64,000 episodes of diarrhea requiring hospitalization and 900,000 clinic visits among children in industrialized countries, and up to 200,000 deaths of children <5 years of age in developing countries (Patel, *et al*). Hence, there is an urgent public health need for the rapid development of novel interventions to prevent the spread of this disease.

Vaxart's norovirus oral tablet vaccine uses Vaxart's non-replicating adenoviral-based oral vaccine platform. The platform has been assessed to be well tolerated and safe in over 600 healthy adult subjects who have been enrolled in studies to evaluate the safety, tolerability, and immunogenicity of the platform. Notably, Vaxart's norovirus oral tablet vaccine is highly immunogenic in humans, inducing serum antibodies and potent mucosal responses at both in the intestine and in more distal mucosal sites such as the saliva and the nose (Kim, *et al*, JCI Insights, 2018 and unpublished data).

Norovirus gastroenteritis is a contagious disease that can affect all age groups, and infants aged 6 to 23 months have the highest norovirus disease burden in children. Breastmilk antibodies to norovirus have been shown to be inhibitory to severe disease in breast milk fed children (Labayo, *et al*). Vaxart and collaborators Dr. Stephanie Langel and colleagues at Duke University have shown that oral immunization of lactating ferrets can provide substantial breast milk antibodies to the vaccine candidate (Langel, et al, unpublished data). In this study, we will evaluate the immunogenicity effect of orally administered bivalent GI.1/GII.4 norovirus vaccine in the breast milk of lactating females and fecal samples in their infants.

This trial is not powered as an efficacy study and any cases of norovirus acute gastroenteritis during the study period will be evaluated as exploratory.

Description of Sites/Facilities:

This will be a multi-center trial conducted at (approximately) 7 sites in South Africa. The name of the Investigators and sites are provided within the "List of Investigators and Centers Involved in the Trial" document.

Description of Investigational Product:

Name of Vaccine: Bivalent GI.1/GII.4 norovirus vaccine

- Norovirus GI.1 Norwalk VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant (VXA-G1.1-NN)
- Norovirus GII.4 Sydney VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant (VXA-G2.4-NS)

Dose Regimen: 5×10^{10} IU (medium dose) and 1×10^{11} IU (high dose) per strain per dose at Day 1.

Route: Oral administration

Dosage Form: Enteric coated tablet

Study Design

This study will investigate the safety, tolerability, and immunogenicity of two distinct monovalent norovirus oral vaccine products given together as a single bivalent dose. Both vaccine drug products (DP) will be supplied in the form of small white enteric-coated tablets containing VXA-G1.1-NN or VXA-G2.4-NS.

VXA-G1.1-NN and VXA-G2.4-NS are E1/E3-deleted, replication-incompetent, serotype 5 adenovirus vaccine vectors designed for use as vaccines for the prevention of NoV infection. These non-replicating vectors encode for a full-length VP1 gene of either Norwalk virus (VXA-G1.1-NN vaccine) or Sydney virus (VXA-G2.4-NS vaccine). In addition to the transgene cassette, the rAd5 vector also contains a dsRNA hairpin following a second hCMVie promoter, thereby expressing both vaccine antigen and adjuvant in the same cell. These rAd5 vectors are designed to deliver both NoV VP1 antigen and adjuvant to the same target cells in the intestinal ileum.

A matching number of placebo tablets will be dispensed to maintain the study blinding.

Objectives and Endpoints:

Primary Objective	Primary Endpoints
• To evaluate the safety and tolerability of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants.	• Frequency, duration, and severity of solicited symptoms of reactogenicity (local and systemic) for 1 week following study drug dose. • Frequency, duration, and severity of unsolicited treatment-emergent adverse events (TEAEs), serious AEs (SAEs), adverse events of special interest (AESIs), and new onset of chronic illness (NOCIs) through the active period (4 weeks post dose).
• To assess the short-term immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and its association	• Serum VP1 specific (GI.1 and GII.4) IgA on Day 1 (baseline), Day 8, and Day 29 (4 weeks post last dose). • Breastmilk VPI specific (GI.1 and GII.4) IgA on Day 1 (baseline), Day 8,

with the immunogenicity response in breastmilk.	Day 15, and Day 29 (4 weeks post last dose).
Secondary Objective	**Secondary Endpoints**
• To assess the long-term safety of bivalent GI.1/GII.4 norovirus vaccine through 12 months after the last vaccination.	• Frequency, duration, and severity of all SAEs, AESIs, and NOCIs through 12 months after study drug dose
• To assess the immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and its association with the immunogenicity response in breastmilk.	• Serum VP1 specific (GI.1 and GII.4) IgA on Day 180 after study drug dose • Breastmilk VP1 specific (GI.1 and GII.4) IgA on Day 60, Day 120, and Day 180 after study drug dose • Serum VP1 specific (GI.1 and GII.4) IgG on Day 1 (baseline), Day 8, Day 29, and Day 180 after study drug dose • Serum BT50 (GI.1 and GII.4) on D1 (baseline), on Day 8, Day 29, and Day 180 after study drug dose
Exploratory Objective	**Exploratory Endpoints**
• To assess additional immunogenicity parameters of bivalent GI.1/GII.4 norovirus vaccine including immunogenicity response in breastfed infants.	• Nasal and saliva VP1 specific (GI.1 and GII.4) IgA from lactating mother on D1 (baseline), on Day 8, Day 29, Day 60, and Day 180 • Infant stool VP1 specific (GI.1 and GII.4) IgA on Day 1 (baseline), Day 29, and Day 60 • Breastmilk BT50 (GI.1 and GII.4) at various, critical timepoints if feasible, and with samples that have high probability of significant responses • Breastmilk Enterocyte culture neutralizing antibodies (GI.1 and GII.4) at various timepoints, if feasible, and with samples that have a high probability of significant responses.
• To assess clinical effects in subjects presenting with acute gastroenteritis symptoms during the study period	• Occurrence of norovirus acute gastroenteritis

Study Population:

76 healthy adult lactating female participants aged 18 years or greater and their breastfed infants aged >30 days to 11 months of age

Planned Number of Subjects:

A total of 76 healthy lactating female participants aged ≥18 years and their breastfed infants aged >30 days to 11 months of age will be enrolled and randomized during this trial.

Eligibility Criteria:

Inclusion Criteria:

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

1. Lactating females aged ≥ 18 years at the time of enrolment and their breastfed infants aged >30 days to 11 months of age at the time of the participants' study drug administration.
2. In stable and good general health, without significant medical illness, based on medical history, physical examination (including vital signs), and clinical judgment of the investigator.
3. Lactating females willing and able to provide informed consent which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
4. Lactating females who are willing to provide consent for their breastfed infant.
5. Negative pregnancy tests at screening and prior to dose on Day 1
6. Available for all planned visits and tele-health appointments, and ability to comply with all study-related evaluations (including but not limited to having the ability and willingness to swallow multiple small enteric-coated tablets per study dose, express/pump breastmilk, and collect infant stool samples)
7. Plan to continue breastfeeding as the main source of the infant's nutrition for at least 1 month (longer is preferred with goal of 6 months post dose if possible) from the time of study drug administration. Exclusive breastfeeding is acceptable but not necessary.
8. The nursing infant is the product of a singleton pregnancy AND does not have any of the following:
    a. Any abnormality that may interfere with breastfeeding or milk absorption
    b. Active infection (may be included if the infection resolves and the subject is re-assessed during the screening period)
    c. Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's appropriate inclusion in this study including interference with the interpretation of study results (such as malabsorption)
    d. One or more documented brief resolved unexplained events (BRUE)

e. Extreme prematurity (infants who were born at less than 28 weeks gestation)
f. 30 days of age or less at the participant's study drug administration OR greater than 11 months of age at the participant's study drug administration
g. Prior hospitalization that is not exclusively for hyperbilirubinemia requiring phototherapy
h. Any genetic/metabolic disease
i. Any chronic illness requiring long term medication

9. Subjects must be willing to use a highly effective form of contraception for 30 days prior to vaccination and until 60 days after the vaccination. Acceptable forms are oral, implantable, intrauterine, transdermal, intravaginal, injectable, double barrier or abstinence (subjects using diaphragms must also use condom). The form of contraception must be approved by the investigator.

Subject Exclusion Criteria:

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

1. Presence of a fever ≥ 38.0ºC measured orally at baseline, on Day 1 prior to vaccination. (Assessment may be repeated once during screening period).
2. 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 once during screening period).
3. Participants who have received antipyretic/analgesic medications within 24 hours prior to the intended vaccine administration.
4. Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) tests at the screening visit.
5. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin.
6. History of serious reactions to vaccination such as anaphylaxis, respiratory problems, hives, or abdominal pain.
7. Presence of significant uncontrolled medical or psychiatric illness (acute or chronic) including the 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.
8. History of significant pregnancy-related complications during this pregnancy, including but not limited to pre-eclampsia, eclampsia, or gestational diabetes unless a full resolution is documented.
9. Cancer, or treatment for cancer, within the past 3 years (excluding fully treated and resolved basal cell carcinoma or squamous cell carcinoma).

10. Presence of immunosuppression or medical condition possibly associated with impaired immune responsiveness, including diabetes mellitus type 1 or 2.
11. 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. Any history of:
        i. Malignancy
        ii. Malabsorption
        iii. Pancreatobiliary disorders
        iv. Inflammatory bowel disease
        v. Irritable bowel disease
        vi. Hiatal hernia
        vii. Surgical resection
    b. History of diagnosis or treatment in past 5 years of:
        i. Esophageal or gastric motility disorder
        ii. Gastroesophageal reflux disease (GERD) - Will allow for subjects with a history of pregnancy-related GERD if fully resolved for >3 months and no other history of GERD diagnosis
        iii. Peptic ulcer
        iv. Cholecystectomy
12. Any condition that resulted in the absence or removal of the spleen
13. History of any form of angioedema
14. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic
15. History of GI bleeding including hematochezia (blood in stool) or melena (black stool)
16. Any significant hospitalization within the last year which in the opinion of the investigator or sponsor could interfere with study participation
17. Any of the following history or conditions that may lead to a higher risk of clotting events and/or thrombocytopenia:
    a. Family or personal history of bleeding or thrombosis
    b. History of heparin-related thrombotic events, and/or receiving heparin treatments
    c. History of autoimmune or inflammatory disease
    d. Presence of any of the following conditions known to increase the risk of thrombosis within 6 months prior to screening:
        i. Recent surgery other than fully healed cesarean delivery or excision/ biopsy of cutaneous lesions
        ii. Immobility (confined to bed or wheelchair for 3 or more successive days)

iii. Head trauma with loss of consciousness or documented brain injury
iv. Receipt of anticoagulants for prophylaxis of thrombosis
v. Recent clinically significant infection including hospitalization for COVID-19 related illness

18. 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
19. Receipt of a licensed vaccine (including any COVID-19 vaccines under Emergency Use Authorization) within 14 days prior to study drug dose or planned administration during the study active period
20. 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
21. Use of medications known to affect the immune function (including but not limited to systemic corticosteroids, leukotriene modifiers, and JAK inhibitors) within 2 weeks before study drug administration or planned use during the active study period
22. Daily use of nonsteroidal anti-inflammatory drugs within 7 days prior to study drug administration or planned use during the active study period
23. Donation or receipt of blood or blood products within 30 days prior to study drug administration or planned donation during the active study period
24. Participating in any clinical trial with another investigational product within 30 days prior to the first trial visit or intend to participate in another clinical trial at any time during the conduct of this trial
25. Are first-degree relatives of individuals involved in trial conduct
26. Positive urine drug screen for drugs of abuse at screening
27. Positive alcohol test at screening or baseline
28. History of drug, alcohol, or chemical abuse within 1 year of screening

Study Duration Criteria for Individual Subject:

The total duration of the study will be 365 days.

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

Screening period:	Up to 45 days
Active study period:	29 days
Follow-up period for safety and duration of immune response, SAEs, AESIs, NOCIs	12 months (from the study dose at Day 1)
Total duration:	12 months from study dose at Day 1

Summary of Statistical Analysis:

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.

Analyses will be performed for the total population.

Sample Size Justification:

Overall, 76 healthy lactating female subjects from 18 years of age or greater and their breastfed infants aged >30 days to 11 months of age will be enrolled and randomly assigned to the three cohorts. The sample size chosen is based on clinical judgment consultation with physicians and a biostatistician, and no formal sample size or power calculation was conducted.

Interim Analysis:

No interim analysis will be conducted for this study.

Safety Monitoring Committee:

A Safety Monitoring Committee (SMC) will be assigned by the Sponsor prior to the beginning of the study and will provide oversight of the study throughout the duration of the study period (Day 1 through Day 365) as needed. Ad hoc meetings will be convened if any predefined stopping rules are met, or any serious vaccine-related events or trends are observed.

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

1.1. Schedule of Trial Activities

Table 1: Schedule of Activities

	Screening	Active Study Period				Follow-up Period					
Study Day	**Day -45 to Day -1**	**Day 1**	**Day 8 (ET)[f]**	**Day 15**	**Day 29 (ET)[f]**	**Month 2 Day 60**	**Month 4 Day 120**	**Month 6 Day 180**	**Month 8 Day 240**	**Month 10 Day 300**	**Month 12 Day 365**
Telephone call visit				📞			📞		📞	📞	📞
Visit Window (days)			**+ 2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed consent	X										
Inclusion/Exclusion	X	X									
Demographics	X										
Medical history	X	X									
Serology[a]	X										
Urine drug screen	X										
Alcohol test	X	X									
Pregnancy Test [b]	X	X									
Physical examination	X	X[c]	X[c]		X[c]						
Vital Signs[d]	X	X	X		X						
Study Drug Administration		X									
Distribute Solicited Symptom Diary		X									
Review Solicited Symptom Diary[e]			X[f]								
Review prior & concomitant medication	X	X	X	X	X						
Query for AEs, SAEs, AESIs and NOCIs		X	X	X	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]

	Screening	Active Study Period				Follow-up Period					
Study Day	**Day -45 to Day -1**	**Day 1**	**Day 8 (ET)[f]**	**Day 15**	**Day 29 (ET)[f]**	**Month 2 Day 60**	**Month 4 Day 120**	**Month 6 Day 180**	**Month 8 Day 240**	**Month 10 Day 300**	**Month 12 Day 365**
Telephone call visit				📞			📞		📞	📞	📞
Visit Window (days)			**+ 2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Sample Collection for Immunogenicity Assessments											
Serum sample - BT50, VP1 specific IgA and IgG		X	X		X			X			
Nasal Swab (SAM™ Device) - VP1 specific IgA		X	X		X	X		X			
Saliva Sample - VP1 specific IgA		X	X		X	X		X			
Breastmilk - VP1 specific IgA, Enterocyte culture neutralizing antibodies, and BT50[h]		X	X	X	X	X	X	X			
Infant Stool - VP1 specific IgA		X			X	X					

Notes:

Tele-health appointment (by phone)

a Serology- human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) or Hepatitis C virus (HCV)

b Serum pregnancy tests will be done at screening. Point-of-Care urine pregnancy test will be performed before dosing on Day 1 and women found positive with urine pregnancy test will not be enrolled during this study.

c Targeted exam: at a minimum, assessments of the skin, respiratory system, cardiovascular system, and GI (abdomen, liver, and spleen) will be included.

d Blood pressure, heart rate, and respiratory rate will be measured after the subject has been resting in a sitting position for 5 minutes.

e At the discretion of PI and/or per subject request to evaluate any of the expected reactogenicity symptoms or any unexpected symptoms of concern, a contact must occur as soon as possible between the subject and the Investigator, or a medically qualified member of the study site staff, to assess if an unscheduled visit is required.

f Early termination assessments. Review of solicited symptoms should be included if the subject drops out before Day 8. Day 29 procedures should be performed if the subject drops out before Day 29 on the day of early termination.

g TEAEs will only be collected during the Active Study period (from time of first dose through 4 weeks post dose). Only SAEs, AESIs and NOCIs will be collected during the Follow-up Period.

h Breastmilk VP1 specific IgA will be tested at the indicated intervals in the table. Breastmilk enterocyte culture neutralizing antibodies and BT50 will be tested at various time points if feasible.

2. INTRODUCTION

2.1. Indication

Bivalent GI.1 and GII.4 vaccines are being investigated for the prevention of noroviral gastroenteritis caused by norovirus GI.1 and GII.4.

2.2. Background

2.2.1. Background of Disease

Norovirus (NoV) infection remains a leading cause of Acute gastroenteritis (AGEs) globally, with a prevalence of 16% (Liao *et al*., 2021). Noroviruses are a genetically diverse group of small, non-enveloped, single-stranded positive sense (RNA) viruses belonging to the Caliciviridae family (Bresee *et al*., 2002). Genogroups I, II and IV are human-transmitted. Genogroup I and II account for the majority of norovirus outbreaks. Each genogroup is further divided into genotypes based on the similarity of the amino acid sequence of the major viral capsid protein, VP1 (Atmar and Estes, 2012). Genogroup I and II account for the majority of norovirus outbreaks (Vega *et al*., 2014). The classic symptoms of NoV infection include sudden onset of vomiting, abdominal cramps, watery diarrhea, and other clinical symptoms such as headache, chills, and myalgias. Currently, there is no specific treatment modality for NoV infection. The standard treatment is oral rehydration with fluids and electrolytes (Glass *et al*., 2009). In 2016, the World Health Organization (WHO) stated that the development of a NoV vaccine should be considered an absolute priority. It is important to develop prevention methods like vaccines considering the NoV-associated risk (Esposito and Principi, 2020). Despite a large medical need and years of development, no vaccine is licensed for use in any population for NoV infection.

2.2.2 Non-clinical experience with Monovalent and Bivalent GI.1 and GII.4 vaccine

Vaxart has conducted multiple preclinical studies of our norovirus vaccine candidate in mice and ferrets, further details are available in the Investigator's Brochure. The preclinical and clinical data on VXA-G1.1-NN and on influenza HA (with the same exact vector backbone) demonstrates a 29-fold increase in neutralizing antibody responses after single dose enteric-coated tablet administration (Liebowitz *et al*., 2020), confirming that VXA-G1.1-NN and VXA-GII.4-NS are capable of eliciting robust antibody responses to VP1 following oral tablet delivery.

2.2.3 Clinical experience with Monovalent and Bivalent GI.1 and GII.4 vaccine

Vaxart has completed four Phase 1 studies in over 200 healthy volunteers with our monovalent tableted norovirus GI.1 oral tablet vaccine candidate and one Phase 1b study with our bivalent tableted vaccine candidate (co-administration of GI.1 and GII.4 vaccines). In all studies, the primary endpoint was safety, and the secondary endpoint was immunogenicity. In the bivalent study, potential interference with co-administration was also evaluated. These studies indicate that the vaccine was safe and generally well tolerated, and there have been no severe adverse events

(SAEs) attributed to vaccine. The vaccine has generated robust immune responses including systemic and mucosal antibodies as well as immunoglobulin A + (IgA) and immunoglobulin G (IgG) + memory B cells. 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 *et al*., 2018).

During the Phase 1 dose-ranging study VXA-NVV-104, a total of 65 healthy older adult volunteers ages 55-80 (in two age cohorts) were evaluated for immunogenicity, safety, and tolerability at three dosing levels of monovalent GI.1-NN: low, medium, and high. Preliminary results of this Phase 1 study indicate this oral norovirus vaccine candidate was safe, well-tolerated, and induced similar immune responses in this older population compared to previous results in younger volunteers.

In an open label Phase 1b boost optimization study (VXA-NVV-105), immunogenicity, safety, and tolerability of repeat-dose administration with varying boost schedules were evaluated in 30 healthy adults (18-55 years). VXA-GI.1 was found to be safe and generally well-tolerated in 4-week, 8-week and 12-week boost schedules. All solicited symptoms were graded as mild or moderate severity, and none required treatment or study discontinuation. During the active period there were no related unsolicited AEs and no related SAEs, AESI or NOCIs. There were no SAEs, AESIs, or NOCIs reported during the safety follow-up period. There were no deaths during the study. Clinical laboratory data, vital signs data, and physical examination findings were within normal ranges and those reporting deviations were mild and transient. No clinically significant abnormal physical examination findings were noted.

2.3 Trial Rationale

Noroviruses are a genetically diverse group of small, non-enveloped, single-stranded positive-sense RNA viruses belonging to the *Caliciviridae* family, and currently, it is the main viral cause of acute gastroenteritis (AGEs) in most countries worldwide. After adoption of the rotavirus vaccine throughout the world, norovirus infection has been one of three major causes of infant diarrheal disease. It was estimated that each year NoVs cause 64,000 episodes of diarrhea requiring hospitalization and 900,000 clinic visits among children in industrialized countries, and up to 200,000 deaths of children <5 years of age in developing countries (Patel, *et al*). Hence, there is an urgent public health need for the rapid development of novel interventions to prevent the spread of this disease.

An effective NoV vaccine must prevent the two most common NoV genotypes, GI.1 and GII.4, and Vaxart's bivalent norovirus vaccine consists of VXA-G1.1-NN and VXA-GII.4-NS. Vaxart's norovirus oral tablet vaccine uses Vaxart's non-replicating adenoviral-based oral vaccine platform (vector adjuvant antigen standard technology (VAAST)), which has been studied to be well tolerated and safe in over 600 healthy adult subjects who have been enrolled in studies to evaluate the safety, tolerability, and immunogenicity of vaccines built on the VAAST platform. Notably, Vaxart's norovirus oral tablet vaccine is highly immunogenic in humans, inducing serum antibodies and potent mucosal responses.

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 GI.1/GII.4 bivalent oral vaccine may enable higher degrees of mucosal protection against infection when compared to a parenteral immunization method.

Presently, norovirus gastroenteritis is a contagious disease that can affect all age groups, and infants aged 6 to 23 months have the highest norovirus disease burden in children. A study published by Labayo and colleagues demonstrated the passive transfer of IgA in breastfeeding moms infected with NoV may inhibit norovirus diarrheal disease in their nursing infants (Labayo *et al,* 2020). Although several phase 1 norovirus studies have shown a robust immune response in healthy subjects when given Vaxart's norovirus G1.1 and G2.4 monovalent and bivalent vaccines, the immune response to orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy, lactating females is still unknown.

Unpublished data from Vaxart in collaboration with Stephanie Langel and colleagues show promising results for inducible breastmilk immunogenicity after receipt of a Vaxart vaccine construct in animal models. Pregnant/postpartum ferrets were orally administered Vaxart influenza vaccine and subsequently produced IgG and IgA antibodies to influenza in their breast milk. Breast milk from mucosally immunized ferret mothers was found to be capable of neutralizing influenza H1N1 by microneutralization assay. The bivalent GI.1/GII.4 norovirus vaccine uses the same VAAST platform as Vaxart influenza vaccine, thus there is a potential for lactating women to induce immunogenicity towards NoV in their breastmilk. Besides directly neutralizing pathogens, IgA has other functional activity, which may greatly underestimate IgA protective responses. Following immunization of lactating, postpartum mothers with Vaxart's oral tablet, it is hypothesized that nursing infant incidence of norovirus diarrheal disease will be significantly lower due to the passive transfer of norovirus breast milk IgA antibodies, which may also reduce further viral transmission and thus disease burden within the family.

Therefore, in this phase 1 study, we will evaluate the immunogenicity effect of orally administered bivalent GI.1/GII.4 norovirus vaccine in the breast milk of healthy, lactating female volunteers and fecal samples (exploratory) in their infants. Additionally, the study will evaluate the safety and tolerability of the norovirus bivalent vaccine in lactating females; the dose of the vaccine will be 5×10^{10} IU or 1×10^{11} IU per strain given as a single bivalent dose.

This trial is not powered as an efficacy study and any cases of norovirus acute gastroenteritis during the study period will be evaluated as exploratory.

2.4 Risk / Benefit Assessment

2.4.1 Known Potential Risks to the Subjects

More detailed information about the known and expected risks and reasonably expected adverse events of Bivalent GI.1/GII.4 NoV vaccine may be found in the Investigator's Brochure (IB). Below are the expected treatment emergent adverse events (TEAEs) with Grade 1-3 symptoms:

1. Diarrhea
2. Nausea
3. Abdominal pain
4. Malaise/fatigue
5. Headache
6. Fever
7. Vomiting
8. Anorexia
9. Myalgia (muscle pain)

2.4.2 Known Potential Benefits to the Subject

Benefits to individual subjects may include receipt of a potentially efficacious NoV vaccine. Clinical data from Phase 1 studies demonstrated that VXA-G1.1-NN and VXA-G2.4-NS generated robust immune responses.

Since these are experimental vaccines against NoV, there are no proven benefits to the subjects for their participation in this research study. This vaccine may successfully be developed to address a common and sometimes serious gastrointestinal infection.

2.4.3 Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with Bivalent GI.1/GII.4 NoV vaccine are justified by the anticipated benefits that may be afforded to subjects and potentially their infants with noroviral gastroenteritis caused by NoV GI.1 and GII.4.

3. TRIAL OBJECTIVE AND END POINTS

3.1. Objectives

3.1.1. Primary Objectives

- **Safety**
    - To determine the safety and tolerability of oral bivalent dosing regimen of GI.1 and GII.4 norovirus vaccine administration in healthy lactating female participants.

- **Immunogenicity**
    - To determine the short-term immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and most critically, the association with vaccine specific antibody responses in breastmilk.

3.1.2. Secondary Objectives

- **Safety**
  - To determine the long-term safety of bivalent GI.1/GII.4 norovirus vaccine through 12 months after the last vaccination.

- **Immunogenicity**
  - To assess the immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and most critically, the association with vaccine specific antibody responses in breastmilk.

3.1.3. Exploratory Objectives

- **Immunogenicity**
  - To determine the additional immunogenicity parameters of bivalent GI.1/GII.4 norovirus vaccine including immunogenicity response in breastfed infants.
  - To determine the clinical effects in subjects presenting with acute gastroenteritis symptoms during the study period.

3.2. End Points

3.2.1. Primary End Points

- **Safety**
  - 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 treatment-emergent adverse events (TEAEs), serious AEs (SAEs), adverse events of special interest (AESIs), and new onset of chronic illness (NOCIs) through the active period (4 weeks post last dose).

- **Immunogenicity**
  - Serum VP1 specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8 and Day 29
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 29
  - Breastmilk VPI specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 15, and Day 29
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 15, and from Day 1 to Day 29

- The number of subjects in each dose group that had a 2-fold GMC rise or greater in breast milk VP1 specific IgA (GI.1 and GII.4) between Day 1 and any other timepoint.

3.2.2. Secondary End Points

- **Safety**
  - Frequency, duration, and severity of all SAEs, AESIs, and NOCIs through 12 months after last study drug dose

- **Immunogenicity**
  - Serum VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 180
  - Breastmilk VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) by dose level
    - Geometric mean concentration (GMC) at Day 60, Day 120, and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 60, from Day 1 to Day 120, and from Day 1 to Day 180
  - Serum VP1 specific (GI.1 and GII.4) IgG through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, and from Day 1 to Day 180
  - Serum Blocking titers 50 (BT50) (GI.1 and GII.4) through 6 months after study drug dose measured by Histo-blood group antigen (HBGA) assay by dose level
    - Geometric mean titer (GMT) at Day 1, Day 8, Day 29, and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, and from Day 1 to Day 180

3.2.3. Exploratory End Points

- **Efficacy**
  - Occurrence of norovirus acute gastroenteritis

- **Immunogenicity**
  - Saliva VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Enzyme-linked immunosorbent assay (ELISA) by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, from Day 1 to Day 60, and from Day 1 to Day 180
  - Nasal VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Meso Scale Discovery (MSD) by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, from Day 1 to Day 60, and from Day 1 to Day 180
  - Infant stool VP1 specific (GI.1 and GII.4) IgA measured by Enzyme-linked immunosorbent assay (ELISA) by dose level
    - Geometric mean concentration (GMC) Day 1, Day 29, and Day 60
    - Geometric mean fold rise (GMFR) from Day 1 to Day 29 and from Day 1 to Day 60
  - Breastmilk Blocking titers 50 (BT50) (GI.1 and GII.4) measured by Histo-blood group antigen (HBGA) assay by dose level
    - Individual subject titers on samples and some timepoints that have a high likelihood of success, assuming the assay works in breast milk samples
  - Breastmilk Enterocyte culture neutralizing antibody titers (GI.1 and GII.4) measured by norovirus neutralization in enterocyte culture
    - Individual subject titers on samples and some timepoints that have a high likelihood of success, under the assumption that the assay works in breast milk samples. At the date of this protocol, only serum GII.4 neutralizing antibodies have been successfully measured.

4. TRIAL DESIGN

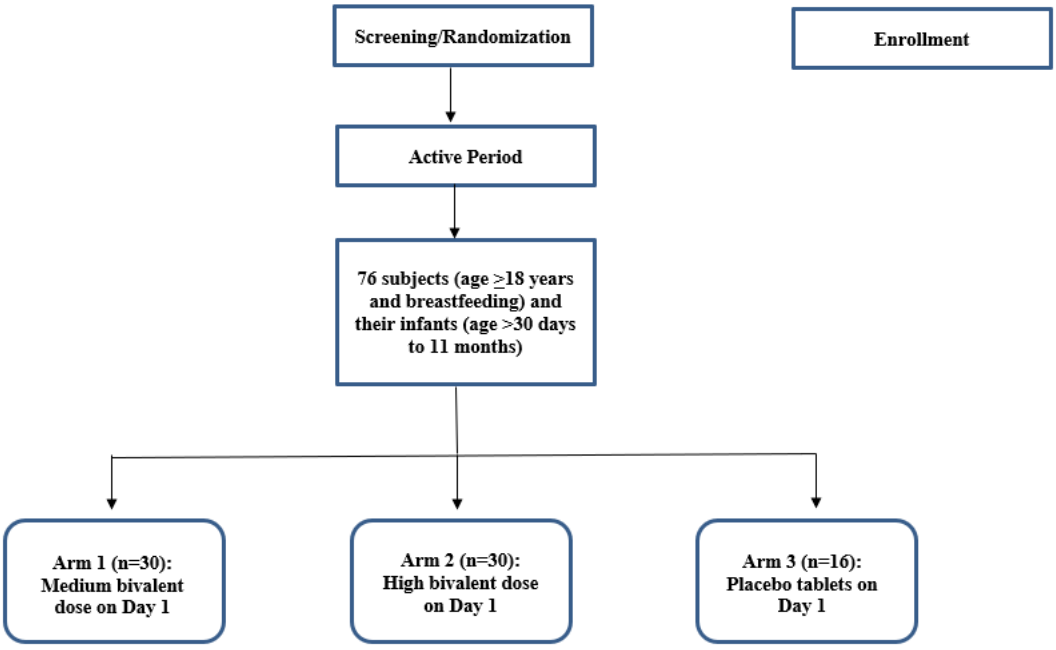
4.1. Overall Description of Trial Design

This is a multi-center, double-blind, randomized, placebo-controlled, single dose, dose ranging study in healthy, breastfeeding, female volunteers (≥18 years). The study will randomize 76 subjects and their breastfed infants aged >30 days to 11 months of age into three arms.

After reviewing and signing an informed consent, the subjects will undergo screening assessments to determine study eligibility up to a 45-day Screening Period.

On Day 1 of the randomized portion, subjects will be randomized in a 2:2:1 ratio to one of the three treatment arms to receive active vaccine at medium dose or high dose or placebo, as follows (Figure 1):

Figure 1



All subjects will be monitored for Solicited Symptoms of Reactogenicity (GI and systemic) for 1 week following the study drug dose and unsolicited AEs for 28 days post study drug dose (until Day 29) during the Active Period. Subjects will then enter the Follow-up period after Day 29 and will be monitored for specified unsolicited adverse events (SAEs, AESIs, and NOCIs) through Day 365 (Month 12) for safety and durability of immune response. Subjects will have samples (nasal, saliva, and serum) collected at the site, and will also self-collect samples (breastmilk and infant stool) at home for evaluation of immunogenicity as specified in the SoA (Table 1).

Table 2 Study Design

Treatment Group	Study Drug	Per Strain Dose (IU) +/- 0.5 log	Total Dose (IU/dose)	Dosing Schedule	No of Subjects
Arm 1 (n=30)	Bivalent GII.4/GI.1 vaccine	5×10^{10}	1×10^{11}	Day 1	30
Arm 2 (n=30)	Bivalent GII.4/GI.1 vaccine	1×10^{11}	2×10^{11}	Day 1	30
Arm 3 (n=16)	Placebo	N/A	N/A	Day 1	16
Total					76

Abbreviations: IU=infectious units

After vaccination on Day 1, the study will include an Active Study Period that runs through 4 weeks after administration (Day 29), and a Follow-up Period of one year for safety and duration of immune response. Study assessments will be conducted as shown in the SoA (Table 1). In addition, subjects will be contacted by phone between site visits to monitor for safety as specified in the SoA (Table 1).

A subject is considered to have completed the study if she completes the study active period at Day 29 (End of Study Active Period). Following completion of the Day 29 visit by all subjects the database will be cleaned and locked and the study unblinded. The Clinical Study Report (CSR) will be written based on the Day 29 dataset.

A subject is considered to have completed the Follow-up Period if she remains in the study through Day 365 (Month 12). Following completion of the Day 365 tele-health appointment for all subjects, the safety database will be cleaned and locked, and data collected during the Follow-up Period will be included in a CSR addendum.

All subjects will be monitored for Solicited Symptoms of Reactogenicity (GI and systemic) for 1 week following the study drug dose and unsolicited AEs for 28 days post study drug dose (until Day 29) during the active period. The subjects will then enter the Follow-Up Period after Day 29 and will be monitored for SAEs, AESIs, and NOCIs through Day 365 (Month 12) for safety. Subjects will also have samples collected for evaluation of immunogenicity and durability of immune response as specified in the SoA (Table 1).

Planned Number of Subjects:

A total of 76 healthy, lactating, female subjects aged ≥18 years and their breastfed infants aged >30 days to 11 months of age will be randomized and assigned to the three cohorts: placebo, medium dose (total 1×10^{11} IU/dose), or high dose (total 2×10^{11} IU/dose).

Study Duration:

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

Table 3: Study Duration

Screening period:	Up to 45 days
Active study period:	29 days
Follow-up period for safety and duration of immune response, SAEs, AESIs, NOCIs	12 months (from the study dose at Day 1)
Total duration:	Approximately 14 months from Screening to Month 12/Day 365 post vaccination

4.2 Scientific Rationale of Trial Design

This study is designed as a standard double-blind placebo-controlled single administration, dose-ranging study to evaluate the effect of 2 different doses (high and medium dose) of VXA-GII.4-NS plus VXA-G1.1-NN in the target population, compared with placebo.

4.3 Justification for Dose Selection

Vaxart has previously completed dose escalation (Protocol VXA-G11-101) and dose optimization (Protocol VXA-G11-102) studies in its initial Phase 1 NoV vaccine studies to demonstrate the safety, tolerability, and immunogenicity of the VXA-G1.1-NN vaccine candidate. A Phase 1b, double-blind, placebo-controlled study (Protocol VXA-NVV-103) with VXA-G1.1-NN and VXA-GII.4-NS with monovalent or bivalent dosing have also been completed. Additionally, dose ranging studies from 1×10^{8} IU – 1×10^{11} IU (2 doses) have been studied across multiple studies with the same vaccine platform.

Safety results from these completed oral tablet vaccine studies support investigations of bivalent administration of the VXA-G1.1-NN and VXA-GII.4-NS vaccine candidates at single total dose of 1×10^{11} IU per vaccine or 2×10^{11} IU per administration.

4.4 End of the Study Definition

A subject is considered to have completed the study if he/she completes the study active period at Day 29 (End of Study Active Period). Following completion of the Day 29 visit by all subjects the database will be cleaned and locked, and the study unblinded. The CSR will be written based on the Day 29 dataset.

A subject is considered to have completed the Safety Follow-up Period if he/she remains in the study Day 365 (Month 12). Following completion of the Day 365 tele-health appointment of all subjects, the safety database will be cleaned and locked, and data collected during the Follow-Up Period will be used to generate a CSR addendum.

4.5 Premature Termination or Suspension of Trial

The Sponsor or designee reserves the right to terminate the study at any time for any reason at the sole discretion of the Sponsor. This trial may be temporarily suspended, or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for trial suspension or termination, will be provided by the suspending, or terminating party to study subjects, Investigators, funding agency, the Investigational New Drug (IND) Sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the site Principal Investigator (PI) will promptly inform study subjects, the site Institutional Review Board (IRB) (if applicable) and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes if any, to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB/IEC, Food and Drug Administration (FDA) and/or South African Health Products Regulatory Authority.

4.6 Trial and Site Start and Close-Out

4.6.1 First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of subjects. The first act of recruitment is the first site open and will be the study start date.

4.6.2 Study/Site Termination

The Sponsor or designee reserves the right to close the study site at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given to Sponsor and subjects in advance of the intended termination.
Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor’s procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator.

- Total number of subjects included is achieved earlier than expected.

The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

5. SELECTION OF TRIAL POPULATION

5.1. Inclusion Criteria

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

Age

1. ≥18 years old at the time of signing the Informed Consent Form (ICF) and her infant will be aged >30 days to 11 months of age at the time of the participants' study drug administration

Type of Subjects

2. In stable and good general health, without significant medical illness, based on medical history, physical examination (including vital signs), and clinical judgment of the investigator.
3. Lactating females willing and able to provide informed consent which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
4. Lactating females who are willing to provide consent for their breastfed infant will be enrolled in the study
5. Negative pregnancy test prior to dose
6. Available for all planned visits and tele-health appointments, and ability to comply with all study-related evaluations (including ability and willingness to swallow multiple small enteric-coated tablets per study dose).
7. Plan to continue breastfeeding as the main source of the infant's nutrition for at least 1 month (longer is preferred with goal of 6 months post dose if possible) from the time of study drug administration. Exclusive breastfeeding is acceptable but not necessary.
8. The nursing infant is the product of a singleton pregnancy AND does not have any of the following:
    a. Any abnormality that may interfere with breastfeeding or milk absorption
    b. Active infection (may be included if the infection resolves and the subject is re-assessed during the screening period)
    c. Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's appropriate inclusion in this study including interference with the interpretation of study results (such as malabsorption)
    d. One or more documented brief resolved unexplained events (BRUE)
    e. Extreme prematurity (infants who were born at less than 28 weeks gestation)

f. 30 days of age or less at the participant's study drug administration OR greater than 11 months of age at the participant's study drug administration
g. Prior hospitalization that is not exclusively for hyperbilirubinemia requiring phototherapy
h. Any genetic/metabolic disease
i. Any chronic illness requiring long term medication

9. Subjects must be willing to use a highly effective form of contraception for 30 days prior to vaccination and until 60 days after the vaccination. Acceptable forms are oral, implantable, intrauterine, transdermal, intravaginal, injectable, double barrier or abstinence (subjects using diaphragms must also use condom). The form of contraception must be approved by the investigator.

Subject Exclusion Criteria:

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

1. Presence of a fever ≥ 38ºC measured orally at baseline, on Day 1 prior to vaccination. (Assessment may be repeated once during screening period)
2. Acute disease within 72 hours prior to vaccination is 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 once during screening period.)
3. Who have received antipyretic/analgesic medications within 24 hours prior to the intended vaccine administration
4. Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) tests at the screening visit
5. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin
6. History of serious reactions to vaccination such as anaphylaxis, respiratory problems, hives, or abdominal pain
7. Presence of significant uncontrolled medical or psychiatric illness (acute or chronic) including the 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
8. History of significant pregnancy-related complications during this pregnancy, including but not limited to pre-eclampsia, eclampsia, or gestational diabetes unless a full resolution is documented.
9. Cancer, or treatment for cancer, within the past 3 years (excluding fully treated and resolved basal cell carcinoma or squamous cell carcinoma)
10. Presence of immunosuppression or medical condition possibly associated with impaired immune responsiveness, including diabetes mellitus

11. 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. Any history of:
        i. Malignancy
        ii. Malabsorption
        iii. Pancreatobiliary disorders
        iv. Inflammatory bowel disease
        v. Irritable bowel disease
        vi. Hiatal hernia
        vii. Surgical resection

    b. History of diagnosis or treatment in past 5 years of:
        v. Esophageal or gastric motility disorder
        vi. GERD (Will allow for subjects with a history of pregnancy-related GERD if fully resolved for >3 months and no other history of GERD diagnosis
        vii. Peptic ulcer
        viii. Cholecystectomy

12. Any condition that resulted in the absence or removal of the spleen

13. History of any form of angioedema

14. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic

15. History of GI bleeding including hematochezia (blood in stool) or melena (black stool)

16. Any significant hospitalization within the last year which in the opinion of the investigator or sponsor could interfere with study participation.

17. Any of the following history or conditions that may lead to a higher risk of clotting events and/or thrombocytopenia:
    a. Family or personal history of bleeding or thrombosis
    b. History of heparin-related thrombotic events, and/or receiving heparin treatments
    c. History of autoimmune or inflammatory disease
    d. Presence of any of the following conditions known to increase the risk of thrombosis within 6 months prior to screening:
        i. Recent surgery other than fully healed cesarean delivery or excision/ biopsy of cutaneous lesions
        ii. Immobility (confined to bed or wheelchair for 3 or more successive days)
        iii. Head trauma with loss of consciousness or documented brain injury
        iv. Receipt of anticoagulants for prophylaxis of thrombosis
        v. Recent clinically significant infection

18. 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

19. Receipt of a licensed vaccine (including any COVID-19 vaccines under Emergency Use Authorization) within 14 days prior to study drug dose or planned administration during the study active period.
20. 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
21. Use of medications known to affect the immune function (including but not limited to systemic corticosteroids, leukotriene modifiers, and JAK inhibitors) within 2 weeks before study drug administration or planned use during the active study period
22. Daily use of nonsteroidal anti-inflammatory drugs within 7 days prior to study drug administration or planned use during the active study period
23. Donation or receipt of blood or blood products within 30 days prior to study drug administration or planned donation during the active study period
24. Participants participating in any clinical trial with another investigational product 30 days prior to the first trial visit or intend to participate in another clinical trial at any time during the conduct of this trial
25. Are first-degree relatives of individuals involved in trial conduct.
26. Positive urine drug screen for drugs of abuse at screening
27. Positive alcohol test at screening or baseline
28. History of drug, alcohol, or chemical abuse within 1 year of screening

5.2. Early Termination/Withdrawal Criteria

All procedures for Day 8 visit should be completed for Early Termination (ET) assessment, including Review Solicited Symptom Diary if ET occurs prior to Day 8 as shown in the SoA (Table 1).

Subjects 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 subject may discontinue/withdraw 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 subject (only for discontinuing study drug, but will remain in study)

The reason for subject discontinuation from study drug will be recorded in the electronic case report form (eCRF).

At the time of withdrawal from the study, the ET visit should be completed, as shown in the SoA (Table 1).

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

5.3. Lost to Follow Up Procedure

A subject 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 subject fails to return to the clinic for a required study visit:

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

5.4. Screening Failure

Screening failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study.

Re-screening outside the screening period will be possible on a case-by-case basis following Sponsor approval. Subjects allowed to be re-screened will be assigned a new screening number and must undergo all screening procedures again. Subjects cannot re-screen more than once and will be determined to be permanent screen failures after the second screening determines a subject is ineligible. Re-assessment of not clinically significant abnormal and/or out of range parameters within the screening period is allowed per Investigators' discretion.

5.5. Classification of Subjects Who Discontinue the Study

For any subject who discontinues the study prior to completion, the most significant reason for early termination will be checked in the eCRF. Reasons are listed below from the most significant to the least significant:

Table 4: Discontinuation Reasons

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.1
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 7.
Protocol Deviation	To be used in case of significant noncompliance with the protocol (e.g., deviation of the Inclusion/Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration).
Withdrawal by Subject	• When the subject indicates unwillingness to continue in the study • When the subject made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (e.g., subject is relocating, inform consent withdrawal, etc.)

6. TRIAL INTERVENTION

6.1. Investigational Product Description

This study will investigate the safety and immunogenicity of bivalent GI.1 and GII.4 vaccine, administered orally at total doses of 1×10^{11} IU/dose and 2×10^{11} IU/dose, for the prevention of NoV infection.

- Norovirus GI.1 Norwalk VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant (VXA-G1.1-NN)
- Norovirus GII.4 Sydney VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant (VXA-GII.4-NS)

VXA-G1.1-NN and VXA-G2.4-NS are E1/E3-deleted, replication-incompetent, adenovirus type 5 vector vaccines. These non-replicating vectors encode for a full-length VP1 gene of either Norwalk virus (VXA-G1.1-NN vaccine) or Sydney virus (VXA-G2.4-NS vaccine). In addition to the transgene cassette, the rAd5 vector also contains a dsRNA hairpin following a second hCMVie promoter, thereby expressing both vaccine antigen and adjuvant in the same cell. These rAd5 vectors are designed to deliver both NoV VP1 antigen and adjuvant to the same target cells in the intestinal ileum.

The VXA-G1.1-NN and VXA-GII.4-NS vaccines are produced in tablet form. The drug substance is formulated as compressed powdered solid material containing [redacted],

[redacted]

All inactive ingredients incorporated into the drug product are generally recognized as safe (GRAS) and all are included in currently approved, US-licensed oral drug products currently listed in the FDA Inactive Ingredients Database. The formulated drug substance is compressed into tablets and enteric coated with an acetone-based solution of methacrylate polymer and talc.

The placebo for this study is manufactured similarly to the active Drug Product (DP) tablets, but without the active drug substance. The placebo tablets are indistinguishable in appearance from the active DP tablets. The number of placebo tablets dispensed to the subject will be matched to the active treatment groups. The placebo will be dispensed by the site's in-house pharmacy in a manner indistinguishable from the active treatment groups.

6.2. Preparation and Dispensing of Investigational Product

Investigational product doses will be prepared at the study sites by an unblinded research pharmacist(s) or designee who will be provided treatment assignment through a randomization schedule.

A trained member of the site study staff will dispense the tablet(s) constituting their assigned dose to the subject.

See the Pharmacy manual for instructions on how to prepare VXA-G1.1-NN and VXA-GII.4-NS vaccines and placebo for administration.

6.3. Dosing and Administration of Investigational Product

This study will investigate the safety and immunogenicity of two monovalent NoV oral tableted vaccine candidates (VXA-G1.1-NN and VXA-GII.4-NS) co-administered (bivalent delivery) against a matching placebo arm. All lots of DP will be provided as small white enteric-coated tablets for oral route of administration.

A single dose comprised of multiple tablets of study drug will be dispensed and a matching number of placebo tablets will be dispensed to maintain the study blinding.

Table 5: Investigational Product Dosing

Intervention Name	**VXA-G1.1-NN**	**VXA-GII.4-NS**	**Placebo**
Type	Biologic	Biologic	Matching placebo
Dose Formulation	Enteric-coated tablets	Enteric-coated tablets	Enteric-coated tablets
Dosing Schedule	Day 1	Day 1	Day 1
Route of Administration	Oral		
Administration instructions	Subjects should fast and refrain from ingesting solid food for at least 4 hours prior to oral dosing. A trained member of the site study staff will dispense the tablet(s) constituting their assigned dose to the subject. The subjects 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 specific Pharmacy Manual.		
Sourcing	Study drug will be provided to the sites by the Sponsor or designated representative.		

Table 6: Study Arm(s)

Arm Title*	**Arm 1**	**Arm 2**	**Arm 3**
Arm Type	Experimental	Experimental	Placebo
Arm Description	Bivalent GII.4/GI.1 vaccine	Bivalent GII.4/GI.1 vaccine	Placebo
Per Strain Dose (IU) +/- 0.5 log	5×10^{10}	1×10^{11}	N/A
Total Dose (IU/dose)	1×10^{11}	2×10^{11}	N/A

6.4. Formulation, Appearance, Packaging, and Labelling

Formulation:

Both the VXA-G1.1-NN and VXA-GII.4-NS are formulated as small enteric-coated tablets.

Packaging and Labelling:

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 product, the concentration of the vaccine, the date of manufacturing or expiration.

Secondary packaging of the study drug upon dispensing from the pharmacy to the clinical staff for subject dosing will be determined with consideration of the site' pharmacy standard operating procedures and outlined in the study pharmacy manual.

The final subject use dispensing container (cup or secondary bottle) will be appropriately labeled with specific requirements for the country and deemed necessary per the site's standard operating procedures (i.e., subject randomization number, total tablet count, dispensing date and time etc.)

6.5. Product Storage and Stability

Storage:

The Investigator will be personally responsible for product management or will designate a study site staff to assume this responsibility.

Both the VXA-G1.1-NN and VXA-GII.4-NS DP should be stored at 2-8 °C. The DP tablets may be kept at room temperature during the dispensation and administration process for a brief period. Please refer to the study specific Pharmacy Manual for detailed information.

Stability:

Stability studies have been performed on similarly formulated tablets prepared from the same or similar adenovirus 5 constructs incorporating different antigens, including, VP1 Norwalk and other influenza antigens (e.g., hemagglutinin H1). The 2-8°C data indicate that drug product potency will remain within release specification prior to retest. Additionally, data from accelerated stability studies indicate that handling at controlled room temperature or brief exposure to temperatures above room temperature (below 37°C) is acceptable for this product.

6.6. Accountability Procedures

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.

Only subjects 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.

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).

At the end of the study active period, the unblinded monitor will conduct a final drug reconciliation for all subjects 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 specific Pharmacy Manual.

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

6.7. Randomization and Blinding

6.7.1. Randomization Procedures

Assignment of a Subject Number:

New subjects once deemed eligible and enrolled in the study will also receive a randomization number and treatment assignment, based on the blinded randomization schedule. The subject number will be used as the primary identifier for the complete duration of the study. After the subject signed the informed consent form (ICF), the Investigator (or designee) will enter the subject into the Screening Log, once randomized or screen failed their data will be entered into the eCRF.

Randomization:

After signing an informed consent, the subjects will undergo screening assessments to determine study eligibility over a 45-day Screening Period. All subjects who sign a study specific informed consent form will have data entered into the EDC. On Day 1, subjects will be randomized in a 2:2:1 ratio to one of the three treatment arms to receive active vaccine or placebo (Table 6: Study Arm(s).

6.7.2. Blinding and Unblinding Procedures

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

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

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

An SMC may convene to review unblinded overall safety if deemed necessary to ensure the safety of study subjects (Section 10.2).

Instructions for breaking the blind will be provided to the study site in case of a medical emergency. The Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. The Investigator must notify the Sponsor's Medical Monitor (or designee) prior to unblinding a subject's treatment assignment. The Investigator(s) must document and report to the Medical Monitor any breaking of the treatment code but must not disclose the result of unblinding. The date and reason that the blind was broken must be recorded in the source documentation.

Appropriate personnel at the Sponsor (or designee) will unblind suspected unexpected serious adverse reactions (SUSARs) for the purpose as required per each local regulation. The Sponsor

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

6.8. Treatment Compliance

Subjects will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study drug and study subject 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.

6.9. Overdose of Treatment

Any overdose of intervention 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.

The effects of acute overdose of VXA-G1.1-NN and VXA-GII.4-NS in human are unknown.

No specific antidote for overdose is known. Study subjects should be managed with appropriate supportive care if overdose occurs.

6.10. Concomitant Medications and Other Therapies

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

Use of concomitant medication from 4 weeks before Day 1 through Day 29 (completion of Active Study period) must be recorded onto the eCRF from the subject'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.

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.

7. SCHEDULE OF TRIAL PROCEDURES AND ASSESSMENTS

7.1. Trial Procedures

A schedule of trial procedures and their timing are summarized in the SoA (Table 1). The day of the first investigational product vaccination is considered to be Day 1.

7.1.1. Procedure to be followed on Screening Period (Day -45 to Day -1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the subject. Each signature on the ICF must be personally dated by the signatory. A copy of the signed and dated ICF must be given to the subject. The source data must reflect that the informed consent was obtained before participation in the study.

After obtaining signed copy of written informed consent from the subject, the subject will undergo screening procedures as mentioned below:

- The demographic information (i.e., age, ethnic origin, race, height (cm), body weight (kg), and body mass index (kg/m^2) will be recorded.
- Obtain history of drug abuse, alcohol abuse, and blood or plasma donation.
- Obtain any medical history of clinical significance and details of any medications currently taken.
- Measure vital signs, including blood pressure, pulse rate and respiratory rate after resting in a sitting position for at least 5 minutes.
- Measure subject's temperature (oral). Oral temperature is preferred for all visits. If unavailable, it is acceptable for clinical study sites to measure subject's temperature according to site usual standard using tympanic thermometer instead of oral and this should be clearly documented. All subjects must use the study-provided thermometer for daily oral temperature checks for solicited symptoms in the week following vaccine dose.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; cardiovascular; respiratory; gastrointestinal (GI); musculoskeletal; extremities; neurological; and lymph nodes.
- Perform a serum pregnancy test for all subjects at screening. At screening all women will have a negative serum HCG. (Prior to dosing all women will have a negative urine HCG.)
- Verify understanding of and compliance with protocol requirements for contraception (see Appendix 4).
- Perform an alcohol test.
- Verify understanding of requirement for breastmilk and infant stool collection.
- Ensure that all inclusion criteria are met and that none of exclusion criteria are met for the subject and her infant.
- Obtain a urine sample for urine drug screen test.

- Collect a blood sample to determine the subject's Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) status.
- If the subject and her infant pass all the inclusion and exclusion criteria at the end of the screening visit:
    1. Provide a manual breast pump set. Teach the subject how to use a manual breast pump properly.
    2. Provide kits with instructions for breastmilk sample collection, storage, and return. Teach the subject how to express breastmilk to provide a total of 10 ml of breastmilk from the right breast for each sample collection. Instruct the subject to consistently collect breastmilk samples from the right breast. Teach the subject how to properly freeze her milk after expression each time until all samples are collected and shipped. (The subject can use a manual breast pump if she does not wish to manually express her breastmilk. If the subject is unable to express or pump breastmilk from the right breast, she can collect breastmilk from the left breast and must consistently collect breastmilk samples from the left breast.)
    3. Provide kits with instructions for infant stool sample collection, storage, and return. Teach the subject how to properly collect the infant stool sample and store it until the samples are ready to be shipped.
    4. Timepoints for breastmilk and infant stool sample collection must be thoroughly discussed with the subject. The subject must collect breastmilk sample and infant stool sample at baseline prior to the first dose (Day -2 to Day 1).

7.1.2. Procedure to be followed during Active Study Period (Day 1 to Day 29)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensuring that procedures listed prior to administration of the vaccine are conducted prior to that administration. The site does not need to wait the full 45 day screening period to start the active study period for the subject.

- The Principal Investigator will ensure that all inclusion criteria and none of the exclusion criteria for the subject and her infant are met on Day1.
- Ensure the subject collected baseline breastmilk sample (5ml-10ml) and infant stool sample between D-2 to D1. Review with the subject how the collection was done and if the samples were properly stored, prior to vaccination. If this was not done, the subject will need to reschedule the dosing visit ASAP and be reminded to collect baseline samples prior to the rescheduled visit.
- A urine pregnancy test will be done for all subjects; site must confirm negative result before dosing.
- Perform an alcohol test and site must confirm negative result before dosing.
- Vital signs will be obtained, including temperature, blood pressure, pulse rate and respiratory rate after resting in a sitting position for at least 5 minutes.

- A targeted, and symptom-directed physical examination will be done for all subjects during the active study period visits. At a minimum, assessments of the skin, respiratory system, cardiovascular system, and GI (abdomen, liver, and spleen) will be included.
- The subject's randomization number will be noted.
- Collect blood, nasal and saliva samples for Immunogenicity assessment prior to study drug administration.
- Site staff member(s) will dispense/administer the investigational product. Please refer to the Pharmacy Manual for further instruction on this process.
- Prior to study drug administration on Day 1, the subject's temperature (oral) will be measured, and a trained member of the site study staff will dispense the tablet(s) constituting the assigned dose to the subject.
- The site staff must observe the subjects for at least 30 minutes after study drug administration for any acute reactions. Any acute reactions are to be recorded in the subject's source documents, on the AE page of the eCRF, as applicable.
- Subjects will be asked to record symptoms of reactogenicity daily for 1 week after study drug administration on Day 1, using the Solicited Symptom Diary; the Solicited Symptom Diary will be collected from the subject on Day 8 and reviewed.
- Subjects will be queried for unsolicited AEs for 28 days following the study drug administration and for SAEs, AESIs and NOCIs for 1 year following the study drug administration.
- Subjects will return to the site on Day 8 and Day 29:

    1. Blood, nasal, and saliva samples will be collected for immunogenicity assessment on Day 8 and Day 29 as specified in the SoA (Table 1).
    2. Ascertain if the subject is still breastfeeding. Ensure the subject has also collected breastmilk sample and infant stool sample during the timepoints specified in the SoA (Table 1), if not then remind the subject. Review with the subject how the collection was done and if the samples were properly stored.
    3. Verify understanding of and compliance with protocol requirements for contraception (see Appendix 4).

- The subject will be asked to contact the site staff or Investigator if an AE (e.g., doctor's visit, emergency room visit) or hospitalization occurs.
- The subject is to be informed that use of prophylactic antipyretic/pain medication, is not permitted on the day of study drug administration. If antipyretic/pain medication is used after study drug dosing, and if clinically appropriate in the judgement of the Investigator, acetaminophen is preferred over other non-steroidal anti-inflammatory drugs.
- Prior and concomitant medications will be reviewed if the subjects took any during the active study period.
- The subject will be asked to bring the completed Diary to the next visit.
- The subject will be reminded that study staff may contact them to obtain additional information on events entered into the Solicited Symptom Diary.
- Source documents will be completed.

- The Investigator or appropriately qualified designee will review the Diary following vaccination, to evaluate subject compliance and as part of the ongoing safety review. Daily review is optimal during the active Diary period. Any solicited symptom marked as Grade 3 should be specifically reviewed with the subject to ensure they meet the detailed solicited AE grading criteria in (Table 10) and to evaluate for potential alternative etiology.
- An appointment will be scheduled for the subject to return for the next study visit.
- The Investigator or an authorized designee completes the eCRFs and an unblinded dispenser/administrator will update the investigational product accountability records.
- The subjects will be contacted by phone between site visits on Day 15 to monitor for safety as specified in the SoA (Table 1) and to remind the subjects to collect and store breastmilk samples. If the study personnel are unable to contact the subject with 3 attempts, the study personnel will follow instructions given in Section 5.4.

7.1.3. Procedure to be followed during follow-up period (Day 30 to Day 365)

- Verify understanding of and compliance with protocol requirements for contraception (see Appendix 4).
- Subjects will return to the site on Day 60 and Day 180:
    1. A blood sample will be collected for immunogenicity assessment on D180 as specified in the SoA (Table 1).
    2. Nasal and saliva samples will be collected for immunogenicity assessment on Day 60 and Day 180 as specified in the SoA (Table 1).
    3. Ascertain if the subject is still breastfeeding. If they are then ensure the subject has also collected breastmilk sample and infant stool sample during the timepoints specified in the SoA (Table 1), if not then remind the subject. Review with the subject how the collection was done and if the samples were properly stored.
- Collect and record SAEs, AESIs and NOCIs.
- Complete the source documents.
- The Investigator or an authorized designee completes the eCRFs.
- Ask the subject to contact the site staff or Investigator if an adverse event (e.g., doctor's visit, emergency room visit) or hospitalization occurs.
- The subjects will be contacted by phone between site visits on Day 120, Day 240, Day 300, and Day 365 to monitor for safety as specified in the SoA (Table 1). For Day 120, determine if the subjects are still breastfeeding; if yes then remind the subjects to collect and store breastmilk samples. If the study personnel are unable to contact the subject with 3 attempts, the study personnel will follow instructions given in Section 5.4.

7.1.4 Follow-up of Subjects with Related AEs or with AEs that Led to Study Discontinuation

Unless the subject refuses further contact, each subject who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the subject's participation in the study) if either of the following is true.

- The AE is considered by the Investigator to be related to the product administered.
- The AE caused the discontinuation of the subject from the study.

7.1.5 Unscheduled Visit

At the discretion of PI and/or per subject request to evaluate any of the expected reactogenicity symptoms or any unexpected symptoms of concern, a contact must occur as soon as possible between the subject and the Investigator, or a medically qualified member of the study site staff, to assess if an unscheduled visit is required.

This contact will be recorded in the subject's eCRF. If the subject is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit. Reactogenicity events should be assessed by the Investigator or a medically qualified member of the site staff, such as a study physician or a study nurse, as applicable, to the Investigator's local practice, who will:

- Measure oral temperature.
- Measure the subject's pulse rate (after five minutes of sitting).
- Measure the subject's blood pressure (after five minutes of sitting).
- Assess any events (specify the events of interest) that are present, in accordance with the reactogenicity grading scale.
- Perform a symptom focused physical examination.
- Ask the subject if she attended an emergency room visit or was hospitalized.
- Complete the source documents.
- The Investigator or an authorized designee will complete the eCRF.

The subject will be instructed to contact the site to report any significant illness, AEs, or hospitalization that occurs during the study period.

7.2. Management of Blood/Saliva/Nasal/Breastmilk/Infant Fecal Samples

7.2.1. Blood/Saliva/Nasal/Breastmilk/Infant Fecal Sample Collection

Blood / saliva samples for the assessment of immunogenicity will be collected from the subjects as specified in the SoA (Table 1). Sample collection, storage, and shipping information can be found in the General and Immunogenicity Laboratory Manuals.

7.2.2 Blood/Saliva/Nasal/Breastmilk/Infant Fecal Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of immune response are contained in the study specific Laboratory Manual provided to the site.

7.2.3 Blood/Saliva/Nasal/Breastmilk/Infant Fecal Sample Storage and Shipment

Detailed instructions on blood sample storage and shipment are contained in the study specific Laboratory Manual provided to the site.

7.2.4 Future Use of Stored Specimens and Data

The current trial is an early phase study in which Vaxart's goal is to understand the mechanism of action of the oral NoV vaccine in the prevention of NoV illness, it is important to have samples available for the full characterization of the vaccine. The Sponsor is planning to store blood, saliva, nasal, breastmilk, and infant stool samples post the completion of the study for possible future testing towards the development of a NoV vaccine. This testing includes evaluation of serum antibody titers to NoV and cell-mediated immune responses to NoV. At this time, the exact tests are not known but this will help to further understand how the oral NoV vaccine works in the body and in the prevention of NoV illness. Other immunological assays may be performed to further elucidate the response to our vaccine. These may include cloning the antibodies that are induced following immunization. All samples will use subject identifiers that are coded and will not include subject initials or demographic information. Only Vaxart staff will have access to the samples and data; they will be responsible for providing access to the samples as needed for assays. Samples will be stored at Vaxart or Vaxart's designee in a secured, access-controlled location for at least 05 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested. Samples may be shared with collaborating researchers, but only in relationship to the NoV program. Any data developed externally will only be displayed in a deidentified form as authorized by Vaxart.

8. TRIAL ASSESSMENTS AND PROCEDURES

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
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 subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Subjects who experience any serious or severe TEAEs, 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 Safety Assessment

The safety of the bivalent GI.1 and GII.4 vaccines will be evaluated through the reporting of Solicited Symptoms of Reactogenicity (GI and systemic) for 1 week following the study drug dose and through reporting of frequency, duration, and severity of unsolicited AEs for the next 28 days following the study drug dose. The subjects will then enter the Follow-Up Period after Day 29 and will be monitored for SAEs, AESIs, and NOCIs through Day 365 (Month 12) for safety and duration of immune response. Each SAE, AESI, and NOCI occurrence must be assessed for causality.

AESIs are listed in Appendix 5, the occurrence of these events should be reported to the Sponsor in an expedited manner, similar to SAEs as described in Section 9.

Planned time points for all safety assessments are provided in the SoA (Table 1)

8.1.1 Physical Examination

A complete physical examination evaluating any clinically significant abnormalities in general appearance and within the following body systems: skin; head, eyes, ears, nose, and throat; cardiovascular; respiratory; gastrointestinal (GI) (abdomen; liver and spleen) musculoskeletal; extremities; neurological; and lymph nodes. Height and weight will also be measured and recorded at screening and BMI will be calculated.

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

8.1.2 Vital Signs

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

8.1.3 Clinical Safety Laboratory Tests

See APPENDIX 1: Clinical Laboratory Tests for the list of clinical laboratory tests to be performed for inclusion and exclusion purposes only.

8.1.4 Pregnancy Testing

- Details of all pregnancies in female subjects, will be tested as outlined in SoA (Table 1).
- 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 Section 9.1.7.

8.2 Immunogenicity Assessment

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

8.2.1 Primary Immunogenicity Assessments:

- Serum VP1 specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level
  - Geometric mean concentration (GMC) at Day 1, Day 8 and Day 29
  - Geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 29
- Breastmilk VPI specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level
  - Geometric mean concentration (GMC) at Day 1, Day 8, Day 15, and Day 29
  - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 15, and from Day 1 to Day 29
- The number of subjects in each dose group that had a 2-fold GMC rise or greater in breast milk VP1 specific IgA (GI.1 and GII.4) between Day 1 and any other timepoint.

8.2.2 Immunogenicity Assessments:

Serum VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level

  - Geometric mean concentration (GMC) at Day 180
  - Geometric mean fold rise (GMFR) from Day 1 to Day 180
- Breastmilk VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) by dose level
  - Geometric mean concentration (GMC) at Day 60, Day 120, and Day 180
  - Geometric mean fold rise (GMFR) from Day 1 to Day 60, from Day 1 to Day 120, and from Day 1 to Day 180
- Serum VP1 specific (GI.1 and GII.4) IgG through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level
  - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, and Day 180

    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, and from Day 1 to Day 180
- Serum Blocking titers 50 (BT50) (GI.1 and GII.4) through 6 months after study drug dose measured by Histo-blood group antigen (HBGA) assay by dose level
    - Geometric mean titer (GMT) at Day 1, Day 8, Day 29, and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, and from Day 1 to Day 180

8.2.3 Exploratory Immunogenicity Assessments:

- Saliva VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Enzyme-linked immunosorbent assay (ELISA) by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, from Day 1 to Day 60, and from Day 1 to Day 180
- Nasal VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Meso Scale Discovery (MSD) by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, from Day 1 to Day 60, and from Day 1 to Day 180
- Infant stool VP1 specific (GI.1 and GII.4) IgA measured by Enzyme-linked immunosorbent assay (ELISA) by dose level:
    - Geometric mean concentration (GMC) Day 1, Day 29, and Day 60
    - Geometric mean fold rise (GMFR) from Day 1 to Day 29 and from Day 1 to Day 60
- Breastmilk Blocking titers 50 (BT50) (GI.1 and GII.4) measured by Histo-blood group antigen (HBGA) assay by dose level
    - Individual subject titers on samples and some timepoints that have a high likelihood of success, assuming the assay works in breast milk samples
- Breastmilk Enterocyte culture neutralizing antibody titers (GI.1 and GII.4) measured by enterocyte culture
    - Individual subject titers on samples and some timepoints that have a high likelihood of success, under the assumption that the assay works in breast milk samples. At the date of this protocol, only serum GII.4 neutralizing antibodies have been successfully measured

Additional exploratory immunogenicity assays may also be performed to further evaluate the activity of the bivalent GI.1 and GII.4 vaccines. Note that not all sample timepoints may be relevant for some of the analysis, so not all assays may be performed at all timepoints. In particular, because it is unclear if the breast milk matrix will inhibit the analysis of neutralizing antibodies or BT50, those assays may not be feasible.

Sample collection, processing and shipping details are provided within the study specific Laboratory Manuals.

9. ADVERSE EVENTS

9.1 Definition of an Adverse Event, Serious Adverse Event, Suspected Unexpected Serious Adverse Reaction, Adverse Event of Special Interest and New Onset of Chronic Illness

Adverse Event Reporting

Adverse event means any untoward medical occurrence associated with the use of an investigational product, whether or not considered intervention related.

Adverse Events Treatment Emergent Adverse Event

Treatment emergent adverse event (TEAE) is an AE that began after the start of an investigational product or an already present event that worsens either in intensity or frequency following the intervention.

Serious Adverse Event (SAE)

a. An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
    i. Death
    ii. A life-threatening adverse event (at the time of the event; not an event that hypothetically might have caused death if it were more severe)
    iii. Inpatient hospitalization or prolongation of existing hospitalization
    iv. A persistent or significant incapacity or disability which results in a substantial disruption of the ability to conduct normal life functions
    v. A congenital anomaly/birth defect
    vi. Important medical events which based upon appropriate medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
        - Examples of such medical events include but are not limited to allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
b. A preplanned/elective procedure and its associated hospitalization for a pre-existing condition that did not worsen from baseline is not considered an AE/SAE. If the procedure is performed early due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction refers to an adverse event which is assessed by the sponsor and or study investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the investigational product.

Adverse Event of Special Interest (AESIs)

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. For this study, AESIs are serious or non-serious adverse events of scientific and medical concern with potential immune-mediated medical conditions as well as events associated with thrombosis and thrombocytopenia as listed in but not limited to Table 11.

New Onset of Chronic Illness (NOCIs)

New Onset of Chronic Illness 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 Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse reactions (AR). (The phrase "responses to an investigational product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.)

Additional Sponsor Definition

a. Solicited Adverse Events-

i. Solicited adverse events (AEs) are predefined signs and symptoms of reactogenicity for which the subject is specifically questioned, and which are noted by the subject 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

ii. Subjects will utilize a Solicited Symptom Diary issued on the day of the vaccination to record solicited any TEAE daily for the one week following that administration.

b. Unsolicited Adverse Events

i. An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the eCRF in terms of diagnosis and/or onset window post-vaccination; this also includes progression of chronic diseases. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AE.

9.2 Grading of Severity of an Adverse Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the subject'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 subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

9.3 Relationship of Adverse Event Following Immunization to Experimental Vaccine/Vaccine Adverse Event Causality Assessment

The principal investigator will use his or her clinical judgment to assess each and every occurrence of an AE/SAE for causality. A 'reasonable possibility' means there is evidence to suggest a causal relationship between the study drug and the adverse event, and the AE is more likely to be explained by the study drug than by another cause.

The investigator is obligated to consider and investigate alternative causes including underlying disease(s), concomitant therapy, and other risk factors, in addition to the temporal sequence of the adverse event to the administration of the study drug.

The investigator will determine biological plausibility and strength of association by consulting the IB and comparators if applicable in his/her assessment. The investigator will also evaluate the course of event including the reproducibility of the adverse event with subsequent study drug administration (in subjects who are allowed to continue with the study).

For more details refer to Causality Assessment of an Adverse Event Following Immunization (AEFI): User Manual for the Revised WHO Classification Second Edition, 2019 Update link: https://www.who.int/publications/i/item/9789241516990.

All adverse events following immunization (AEFIs) must have their relationship to study drug assessed by the Investigator. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug should be clinically plausible.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study drug) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

In situations where an SAE has occurred with minimal information available to the investigator, the investigator is still required to make an assessment of causality for the event with the transmission of the initial report to the sponsor. If the investigator is uncertain about causality, the adverse event will initially be handled as "related to study intervention" for reporting purposes. Once more clinical information is obtained, the investigator can modify the causality assessment to reflect this new knowledge by sending an SAE follow-up report with the updated assessment.

9.4 Monitoring and Follow-up of AEs, NOCIs, and SUSARs during Trial

9.4.1 Monitoring and Follow-up of SAEs from Day 1 to Day 29 after Vaccination

Following AEs/SAEs, could appear during the entire course of the trial after vaccination. The following symptoms will be captured via Solicited Symptoms during Day 1 to Day 8. After Day 8 they will be captured as unsolicited adverse events. SAEs are captured from the first dose of study product.

- Fever/pyrexia
- Diarrhea
- Nausea
- Vomiting
- Abdominal pain
- Malaise/fatigue
- Anorexia
- Headache
- Myalgia (muscle pain)

9.4.2 Time Period and Frequency for Collecting AE, AESI, NOCIs, and SAE Information

All TEAEs, SAEs, AESIs, and NOCIs will be collected from the time of study drug dose until the follow up visit at the timepoints specified in the SoA (Table 1). TEAEs will be collected through Day 29. SAEs, AESIs, and NOCIs will be collected through Day 365.

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs if they do not have a causal relationship with study participation. There are two situations to note as below:

- If the medical occurrence causes the subject to be excluded from the study, then it must be reported by the investigator. This event will then need to be classified as an "AE not related to the study drug."
- If the medical occurrence is the result of a protocol-specified intervention (prior to study drug dose), including but not limited to washout or discontinuation of usual therapy, diet, or a procedure then these must be reported appropriately as an AE (solicited and unsolicited), SAE, AESI, NOCI, and other reportable safety events by the Investigator.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of being available. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and the Investigator considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

9.4.3 Information for Follow-up of AESIS, NOCIS, and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 5.4).

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, AESIs, NOCIs or SAEs as fully as possible. This may include laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

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

9.5 Reporting of AEs, AESIs, NOCIs, SAEs, SUSARs, Pregnancies, and Death Events

All AEs (solicited and unsolicited), AESIs, NOCIs, SAEs and other reportable safety events that occur after the consent form is signed but before study product administration must be reported by the Investigator if the event causes the subject to be excluded from the study (these will be reported as "AE not related to the study drug") or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

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

Table 7 Adverse Event Reporting Timelines to the Sponsor

Type of Event	TEAE (unsolicited)	TEAE (solicited)	AESI/NOCIs	SAE / SUSAR
Reporting period	From first dose until 4 weeks after last dose of study drug	1 week after each study drug administration	From first dose until EOS	From first dose until EOS
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 page of eCRF	Solicited Symptom Diary	AE page of eCRF	AE page of eCRF

Abbreviations: AE = adverse event; eCRF = electronic Case Report Form; EOS = end of study; AESI = Adverse Event of Special Interest; NOCI= New Onset Chronic Illness; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; TEAE = treatment-emergent adverse event

9.5.1 Adverse Event Reporting

All subjects experiencing AEs after the first dose of study drug, until Day 29 (Active Period), whether considered causally related with the use of the investigational vaccine or not, must be

monitored until symptoms subside, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

All findings must be reported on an adverse event page of eCRF and on the SAE form, if applicable. All findings in subjects experiencing AEs must also be documented in the subject's clinical research records.

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date.
- Serious (Y/N)? If yes, appropriate seriousness criteria must be selected on eCRF and SAE Form.
- Severity.
- Investigator's opinion of the causality (relationship) between the event and administration of investigational vaccine(s) ("related" or "not related").
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.
- Action taken with study treatment (investigational vaccine).,
- Outcome of event.
- For Death cases provide all applicable details (e.g., date and cause of death etc., including autopsy results if available).

9.5.2 Serious Adverse Events Reporting

The Investigator or designee will within 24 hours report to the Sponsor any serious adverse event, whether or not considered study drug related, including those listed in the protocol or Investigator Brochure and must include an assessment of whether there is a reasonable possibility that the study drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must within 24 hours report the event to the Sponsor.

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to

the Sponsor within 24 hours of it being available. The information should be completed as fully as possible and contain the following information at the minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and submit it within 24 hours of receipt. The timelines and procedure for follow-up reports are the same as those for the initial report.

9.5.3 Suspected Unexpected Serious Adverse Reaction Reporting

Suspected unexpected serious adverse reactions (SUSARs) are subject to expedited reporting. The study Sponsor will be responsible for notifying both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation including the Food and Drug Administration (FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, the Sponsor must notify FDA and all participating Investigators in an Investigational New Drug (IND safety report of potential serious risks, from

clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs 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 for the study and will notify the IRB/EC, if appropriate according to local requirements.

9.5.4 Pregnancy Reporting

Details of all pregnancies in female subjects will be collected after the start of study drug as per SoA (Table 1).

- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form (pregnancy form) and submit it to the Sponsor within 24 hours of learning of the female subject pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate up to one month post-partum, and the information will be forwarded to the Sponsor.
- 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 subjects) beyond the resolution of the pregnancy, he or she may learn of an SAE through spontaneous reporting.

Should a female subject become pregnant during the course of the study after dosing, she will continue to be followed for safety and pregnancy outcomes. Subjects who have a positive pregnancy test at Day 1, prior to randomization, will be considered screen failures.

If a subject is found pregnant post study drug administration, the subject will only be monitored for safety.

9.5.5 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.

10. SAFETY OVERSIGHT

10.1. Internal Sponsor Review

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

The lead Medical Monitor will be a physician experienced in the conduct of research clinical studies whose primary responsibility will be to monitor subject safety. The Medical Monitor will be responsible for reviewing the cumulative safety data, including a review of safety laboratory test results and adverse event reporting. The Medical Monitor will be familiar with study-specific data as well as relevant background information about the disease, investigational drug, and target population under study. The Medical Monitor(s) will be empowered to request a SMC safety review which can suspend the study, recommend amendments to the protocol, and/or to request further information.

10.2. Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will be created to provide oversight of the conduct of the trial to ensure the safety of subjects. The committee will consist of independent physicians and/or scientists with vaccine clinical trials experience or expertise, and the Medical Monitor, who does not enroll subjects into the study.

The SMC will be assigned by the Sponsor prior to the beginning of the study and will provide oversight of the study throughout the duration of the study period (Day 1 through Day 365) as needed. Ad hoc meetings will be convened if any predefined stopping rules are met, or any serious vaccine-related events or trends are observed.

The SMC will function in accordance with the following provisions: (1) United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 312.55 and 312.56. (2) ICH E6 and 62 Federal Register 25691 (1997): Good Clinical Practice (GCP) Consolidated Guideline.

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

11. STATISTICAL CONSIDERATION

A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to locking the database. The full details of data presentation and analyses will be provided in SAP.

Additional statistical analyses other than these described in this section may be performed if deemed appropriate and included in the SAP. Any deviations from the final SAP or from what is outlined in the protocol will be discussed in the final study report (CSR).

11.1 Sample Size Determination

A sample size of 76 randomized subjects (30 each in medium and high dose levels and 16 in placebo) is not based on formal statistical testing but rather based on clinical judgement and predicted to yield meaningful safety and immunogenicity results. Placebo was added for safety comparison.

11.2 Multiplicity Adjustment

No multiplicity adjustment will be implemented for this study.

11.3 Population for Analysis

For purposes of analysis, the following analysis sets are defined:

Table 8: Populations for Analyses

Analysis Population	Description
Screened	All subjects who enter screening (assigned a screening number)
Intent to Treat (ITT)	All subjects who are randomized. The analyses using ITT will be based upon the randomization group allocated.
Per Protocol	All subjects in the ITT set who receive one dose and who have not violated any inclusion/exclusion criteria and / or deviated in a way that could influence their Immunogenicity assessments.
Safety	All randomized subjects who receive at least 1 dose of the study drug. Subjects will be analyzed according to the treatment (vaccine) they actually received. All safety analyses will be conducted based on the Safety set.
Immunogenicity	All randomized subjects who receive at least 1 dose of the study drug and have at least one valid immunogenicity result after Day 1. Subjects will be analyzed according to the treatment (vaccine) they actually received. All immunogenicity analyses will be conducted based on the Immunogenicity set.

11.4 Statistical Analysis Plan

11.4.1 General Approach

The SAP will be developed and finalized before database lock and breaking the blind for any of the planned analyses. It will describe the subject sets 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 endpoints.

11.4.2 Analysis of the Primary and Secondary Safety End Points

Safety will be summarized for the safety set (active vs. placebo). Solicited Symptoms of Reactogenicity, unsolicited AEs, SAEs, physical examination, and vital signs will be summarized descriptively by treatment group and study visit.

Analyses will be performed for the total set (active vs. placebo). All results will be presented descriptively and summarized by treatment groups.

Endpoint	Statistical Analysis Methods
Primary (measured from Day 1 through Day 29)	Frequency, duration, and severity of Solicited Symptoms of Reactogenicity (local, systemic) measured daily for 1 week following vaccination. Frequency, duration, and severity of unsolicited AEs, and SAEs through the active period (4 weeks post dose). Descriptive statistics will be provided for each reactogenicity endpoint for each dose. 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 subjects with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA®) terms. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any TEAEs for each vaccine group as well as the placebo group. SAEs will be categorized according to MedDRA® terms. The safety analyses are based on the safety set. Subjects will be summarized by vaccine group and placebo according to the study drug they actually received. Missing reactogenicity Diary data will not be imputed; missing TEAE dates will be handled according to the rules determined in the SAP.
Secondary (measured through Day 365)	Frequency, duration, and severity of SAEs, AESIs and NOCIs for 1 year following the study drug dose.

11.4.3 Analysis of Primary, Secondary, and Exploratory Immunogenicity and Endpoints

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

Immunogenicity samples will be drawn for all subjects and their infants. 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 sets.

An additional analysis will be performed based on the all-available sets if there is a large enough difference in sample size between the all-available immunogenicity set and the evaluable immunogenicity set.

Immunogenicity will be summarized by the total set (active vs. placebo). For all endpoints, all measures will be analyzed comparing the two active vaccine groups. The immunogenicity set will be used for this analysis. All results will be presented descriptively and summarized by treatment groups.

Endpoint	**Statistical Analysis Methods**
Primary (Key Immunogenicity Endpoints measured from Day 1 through Day 29)	Serum and breastmilk VP1 specific IgA for both GI.1 and GII.4 by Meso Scale Discovery will be summarized descriptively through the active period (4 weeks post dose).
Secondary (measured through Day 180)	Serum VP1 specific IgA and IgG for both GI.1 and GII.4 by Meso Scale Discovery will be summarized descriptively through 6 months post dose. Serum Blocking titers 50 (BT50) (GI.1 and GII.4) by Histo-blood group antigen (HBGA) assay will be summarized descriptively through 6 months post dose. Breastmilk VP1 specific IgA for both GI.1 and GII.4 by Meso Scale Discovery will be summarized descriptively through 6 months post dose.
Exploratory	For specific exploratory immunogenicity endpoints please refer to Section 8.2-Immunogenicity Assessments- Exploratory Immunogenicity Assessments.

11.4.4 Baseline Descriptive Statistics

Demographic data, baseline characteristics, physical examination, concomitant medications, medical history data and study medication exposure will be summarized by treatment group.

11.4.5 Tabulation of Individual Subject Data

By subjects listing will be produced for each variable by treatment group and study visit.

12. ETHICAL CONSIDERATIONS

12.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences [CIOMS] 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.2 Institutional Review Board

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/EC should be retained in the Investigator file.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/IEC and Sponsor in writing immediately after the implementation.

They should also be informed of any event likely to affect the safety of the subjects or the continued conduct of the clinical study, in particular any change in safety. All updates to the IB will be sent to the IRB/IEC and to Health Authorities (Competent Regulatory Authority), as required by local regulation. A progress report is sent to the IRB/IEC at least annually and a summary of the study's outcome at the end of the clinical study.

12.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the subject will be asked to read and review the document. The Investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent documents for herself and her infant prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the forms signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to

them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If the trial is involving vulnerable population, video recording of entire informed consent process should be ensured depending on the norms of respective country's regulatory authorities.

12.4 Insurance Compensation

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IRB/IEC or regulatory authorities in countries requiring this document.

12.5 Stipends/Rewards/Compensation for Participation

Subjects may be provided with a stipend according to local practice to compensate for the time and travel required for study visits and procedures. Participating subjects will be given a manual breast pump set.

12.6 Subject Confidentiality

Subject confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor. All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the Subjects in this study. The clinical study site will permit access to such records.
The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at sponsors designated vendor. This will not include the subject's contact or identifying information. Rather, individual Subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by designated vendor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

12.7 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable regulatory authority in any area of the world, or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Sponsor should be informed immediately.

In addition, the Investigator will inform Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

13. DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for validation of the clinical data. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. All information on the CRF will be traceable to these source documents, which are generally maintained in the subject's study file.

The source documents will include a copy of the signed Informed Consent/ Health Insurance Portability and Accountability Act (HIPAA) authorization. The source document data collection forms for screening. Outpatient visits and AEs will also serve as CRF data collection instruments.

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Source documents are maintained for recording data for each subject enrolled in this clinical trial. Study subjects' data collected on the CRF during the trial will only be identified by subject number. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both the Sponsor and the Investigator are bound to keep this information confidential.

13.2 Case Report Forms (CRF)

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Vaxart and should not be made available in any form to third parties, except for authorized representatives of Vaxart or appropriate regulatory authorities, without written permission from Vaxart.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents)

and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required.

The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

13.3 Data Collection and Management Responsibility

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each subject enrolled in the study.

Data recorded in the eCRF/CRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a data capture system that is 21 CFR Part 11-compliant. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.4 Record Retention

Study documents should be retained for a minimum of 10 years after the last approval of a marketing application in an International Conference on Harminosation (ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 10 years have elapsed since the formal discontinuation of clinical development of the study drug.

These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

13.5 Property Rights and Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that their 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

subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that their 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.

All information, data and documents including results and investigational products provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Early Safety Data Review AND/OR Committee

Subject safety will be continuously monitored by the Sponsor or designee, which includes safety signal detection during the study.

All safety data collected will be summarized and reviewed by the sponsor's internal/external safety monitoring committee for agreement of next steps.

In particular, data will be reviewed by the sponsor for identification of the following events that would potentially contribute to a requirement to [pause/stop] the study.

- One or more subjects experiences a treatment-related serious adverse event (SAE) of any grade
- Two or more subjects experience the same treatment-related grade ≥3 solicited symptom within one week following vaccination.
- Two or more subjects experience the same treatment-related unsolicited grade ≥3 AE between Day 1 and Day 29 (Active Period).

Enrollment will be paused during the review. If a pausing/stopping rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume. If no dose-related toxicities are observed, and upon the recommendation of the SMC following review of safety data, enrollment of the remaining subjects will be initiated.

14.2 Clinical Trial Site Monitoring

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

- Monitoring for this study will be performed by the Sponsor or designee

- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- If needed, independent audits will be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

14.3 Audit and Inspection

The trial site also may be subject to quality assurance audits by the Sponsor or designees.

For the purpose of ensuring compliance with the clinical study protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on behalf of the Sponsor and inspection by regulatory authorities.

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

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified, and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.4 Responsibility of Investigator

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all trial procedures provided by the Sponsor (including security rules).

The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, discrepancy resolution form, or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to the Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the subject's data to be transferred. The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical study in accordance with the clinical trial protocol.

All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

To 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.

To notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Signed copy of Investigator's undertaking should be provided as an appendix.

14.5 Responsibility of Sponsor

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical study as regards ethics, clinical study protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical study.

At regular intervals during the clinical study, the site will be contacted, through monitoring visits, letters, or electronically, by a representative of the monitoring team to review study progress, Investigator and subject compliance with clinical study protocol requirements, and any emergent problems.

These monitoring visits will include but not be limited to review of the following aspects: subject's informed consent, subject recruitment and follow-up, SAE documentation and reporting, AE documentation, IP allocation, IP accountability, concomitant therapy use, and quality of data.

14.6 Protocol Deviation

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Details can be found in the study specific Protocol Deviation Plan or the Clinical Monitoring Plan.

15. PUBLICATION AND DATA SHARING 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.

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Appendix 1: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory, unless otherwise specified.
- Protocol-specific requirements for inclusion or exclusion of subject 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 9 Protocol-Required Laboratory Assessments

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 subjects serum pregnancy tests at screening Female subjects Point-of-Care urine pregnancy tests prior to dosing at Day 1 Alcohol test at screening and prior to dosing on Day 1

Appendix 2: Country-specific Requirements

Not applicable.

Appendix 3: Adverse Events Grading

Grading of Solicited Adverse Events

Subjects should be instructed to rate Solicited Symptoms of Reactogenicity that are collected within their Solicited Symptom Diary based on the severity scale presented in Table 10.

Table 10 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 (muscle pain)	None	AE easily tolerated, causing minimal discomfort and does not interfere with everyday activities[a]	Adverse event sufficiently discomforting to interfere with everyday activities	Adverse event 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	None	No interference with activity or 1 to 2 episodes	Some interference with activity or >2 episodes	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Vomiting	None	No interference with activity or 24 hours	Some interference with activity or 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 activity include attendance at work, school, and usual habits of the subjects.

Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A negative pregnancy test will be required for all female subjects prior to study drug administration, as outlined in the SoA (Table 1).

Collection of Pregnancy Information

Female subjects or Male subjects with partners who become pregnant:

- The investigator will attempt to collect pregnancy information on any female subjects or male subject's female partner who becomes pregnant while the male subject is in this study.

After obtaining the necessary signed ICF from the pregnant female subject or male subject's 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 pregnancy. The Sponsor will attempt to follow the female subject or 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 subject or 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.

Appendix 5: ADVERSE EVENTS OF SPECIAL INTEREST

An Adverse event of special interest (AESI) is a serious or non-serious adverse events of scientific and medical concern for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is indicated. The following adverse events (AEs) for potential immune-mediated medical conditions as well as events associated with thrombosis and thrombocytopenia are AEs of special interest (AESIs) and include new onset of chronic illness (NOCIs). These events should be monitored for actively and reported to the Sponsor in an expedited manner as outlined in *Section 9.*

Table 11: Adverse Events of Special Interest

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 angitits), 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

PROTOCOL VERSION HISTORY

Name of the Document with Version Number	Date	Summary of Changes and Rationale
VERSION 1.0	12 OCT 2022	INITIAL VERSION

Clinical Study Protocol

Protocol Title:	A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants
Brief Title:	Evaluating Vaxart's oral bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females and their nursing infants
Protocol Number:	VXA-NVV-108
Product Name:	Bivalent GI.1 and GII.4 vaccines (VXA-G1.1-NN plus VXA GII.4-NS)
Indication:	Prevention of Norovirus Infection
Sponsor:	Vaxart, Inc. 170 Harbor Way, Suite 300 South San Francisco, CA 94080
Sponsor Contact:	[redacted]
Sponsor Medical Monitor:	[redacted]
Chief Medical Officer:	[redacted]
Protocol Version; Date:	2.0 ; 25 Jul 2023

Protocol Title: A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants

Brief Title: Evaluating Vaxart's oral bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females and their nursing infants

Protocol Number: VXA-NVV-108

Amendment Number: Not applicable

Date of Amendment (Optional): Not applicable

Investigational Product Name: Bivalent GI.1 and GII.4 vaccines (VXA-G1.1-NN plus VXA GII.4-NS)

Phase: I

Sponsor: Vaxart, Inc.
170 Harbor Way, Suite 300
South San Francisco, CA 94080

Funding Sponsor: Vaxart, Inc and Bill & Melinda Gates Foundation

SIGNATURE PAGE

PROTOCOL TITLE: A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants

PROTOCOL NUMBER: VXA-NVV-108

PROTOCOL VERSION (Amendment): 1.0 (Version 2.0)

Signature of Sponsor's authorized representative(s):

[redacted]

7/28/2023

Date

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), the ethical principles that have their origin in the Declaration of Helsinki and the Code of Federal Regulations on the Protection of Human Participants (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial Subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training per country requirements.

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

Principal Investigator: _____ _____
Signature Date

Name: _____

Address: _____

_____

_____
(Full Address, Landmark, State, Country, Phone: Fax:)

TABLE OF CONTENTS

LIST OF IN-TEXT TABLE

LIST OF IN-TEXT FIGURE

LIST OF ABBREVIATIONS [AND DEFINITIONS OF TERMS]

Term	Description
AE	Adverse event
AESI	Adverse event of special interest
AEFI	Adverse events following immunization
AGE	Acute gastroenteritis
ANCA	Anti-neutrophil cytoplasmic antibody
ASC	Antibody secreting cells
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research – FDA
DP	Drug product
eCRF	Electronic case report form
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
CMP	Clinical Monitoring Plan
CSR	Clinical Study Report
DCC	Data Coordinating Center
EOS	End of Study
ET	Early Termination
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI.1	Norovirus genogroup I.1
GII.4	Norovirus genogroup II.4
GMP	Good Manufacturing Practice
GRAS	Generally recognized as safe
HBsAg	Hepatitis B surface antigen
HBGA	Histo-blood group 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 Conference on Harmonisation
IP	Investigational Product

ITT	Intent to treat
SMC	Safety Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IND	Investigational new drug
IRB	Institutional Review Board
IU	Infectious units
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSD	Meso Scale Discovery
NOCI	New Onset of Chronic Illness
NoV	Norovirus
OHRP	Office for Human Research Protections
PBMC	Peripheral blood mononuclear cells
PVP	Polyvinyl pyrrolidone
PI	Principal investigator
RNA	Ribonucleic acid
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
TEAE	Treatment-emergent adverse event
VP1	Viral Protein 1, major capsid protein of norovirus
WHO	World Health Organization

1. PROTOCOL SYNOPSIS

Title of Study: A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants.

Sponsor: Vaxart Biosciences, Inc.
170 Harbor Way, Suite 300
South San Francisco, CA 94080

Contract Research Organization:

[redacted]

Protocol number:	VXA-NVV-108	**IND Number:**	
Trial Blinding scheme:	Double-Blind	**Phase of the study:**	Phase I

Study Arms:

A total of 76 healthy lactating female participants will be enrolled and randomized into three Arms (medium dose, high dose, and placebo), as described below:

- Arm 1: Bivalent GII.4/GI.1 medium dose vaccine (VXA-GII.4-NS plus VXA-G1.1-NN) 5×10^{10} tablets; total dose is 1×10^{11} IU/dose (N=30)
- Arm 2: Bivalent GII.4/GI.1 high dose vaccine (VXA-GII.4-NS plus VXA-G1.1-NN) 1×10^{11} tablets; total dose is 2×10^{11} IU/dose (N=30)
- Arm 3: Placebo tablets (N=16)

Study Rationale:

Noroviruses (NoV) are a genetically diverse group of small, non-enveloped, single-stranded positive-sense RNA viruses belonging to the *Caliciviridae* family and currently, it is the main viral cause of acute gastroenteritis (AGEs) in most countries worldwide. After adoption of the rotavirus vaccine throughout the world, norovirus infection has been one of three major causes of infant diarrheal disease. It was estimated that each year NoVs cause 64,000 episodes of diarrhea requiring hospitalization and 900,000 clinic visits among children in industrialized countries, and up to 200,000 deaths of children <5 years of age in developing countries (Patel, *et al*). Hence, there is an urgent public health need for the rapid development of novel interventions to prevent the spread of this disease.

Vaxart's norovirus oral tablet vaccine uses Vaxart's non-replicating adenoviral-based oral vaccine platform. The platform has been assessed to be well tolerated and safe in over 600 healthy adult subjects who have been enrolled in studies to evaluate the safety, tolerability, and immunogenicity of the platform. Notably, Vaxart's norovirus oral tablet vaccine is highly immunogenic in humans, inducing serum antibodies and potent mucosal responses at both in the intestine and in more distal mucosal sites such as the saliva and the nose (Kim, *et al*, JCI Insights, 2018 and unpublished data).

Norovirus gastroenteritis is a contagious disease that can affect all age groups, and infants aged 6 to 23 months have the highest norovirus disease burden in children. Breastmilk antibodies to norovirus have been shown to be inhibitory to severe disease in breast milk fed children (Labayo, *et al*). Vaxart and collaborators Dr. Stephanie Langel and colleagues at Duke University have shown that oral immunization of lactating ferrets can provide substantial breast milk antibodies to the vaccine candidate (Langel, et al, unpublished data). In this study, we will evaluate the immunogenicity effect of orally administered bivalent GI.1/GII.4 norovirus vaccine in the breast milk of lactating females and fecal samples in their infants.

This trial is not powered as an efficacy study and any cases of norovirus acute gastroenteritis during the study period will be evaluated as exploratory.

Description of Sites/Facilities:

This will be a multi-center trial conducted at (approximately) 7 sites in South Africa. The name of the Investigators and sites are provided within the "List of Investigators and Centers Involved in the Trial" document.

Description of Investigational Product:

Name of Vaccine: Bivalent GI.1/GII.4 norovirus vaccine

- Norovirus GI.1 Norwalk VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant (VXA-G1.1-NN)
- Norovirus GII.4 Sydney VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant (VXA-G2.4-NS)

Dose Regimen: 5×10^{10} IU (medium dose) and 1×10^{11} IU (high dose) per strain per dose at Day 1.

Route: Oral administration

Dosage Form: Enteric coated tablet

Study Design

This study will investigate the safety, tolerability, and immunogenicity of two distinct monovalent norovirus oral vaccine products given together as a single bivalent dose. Both vaccine drug products (DP) will be supplied in the form of small white enteric-coated tablets containing VXA-G1.1-NN or VXA-G2.4-NS.

VXA-G1.1-NN and VXA-G2.4-NS are E1/E3-deleted, replication-incompetent, serotype 5 adenovirus vaccine vectors designed for use as vaccines for the prevention of NoV infection. These non-replicating vectors encode for a full-length VP1 gene of either Norwalk virus (VXA-G1.1-NN vaccine) or Sydney virus (VXA-G2.4-NS vaccine). In addition to the transgene cassette, the rAd5 vector also contains a dsRNA hairpin following a second hCMVie promoter, thereby expressing both vaccine antigen and adjuvant in the same cell. These rAd5 vectors are designed to deliver both NoV VP1 antigen and adjuvant to the same target cells in the intestinal ileum.

A matching number of placebo tablets will be dispensed to maintain the study blinding.

Objectives and Endpoints:

Primary Objective	Primary Endpoints
• To evaluate the safety and tolerability of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants.	• Frequency, duration, and severity of solicited symptoms of reactogenicity (local and systemic) for 1 week following study drug dose. • Frequency, duration, and severity of unsolicited treatment-emergent adverse events (TEAEs), serious AEs (SAEs), adverse events of special interest (AESIs), and new onset of chronic illness (NOCIs) through the active period (4 weeks post dose).
• To assess the short-term immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and its association	• Serum VP1 specific (GI.1 and GII.4) IgA on Day 1 (baseline), Day 8, and Day 29 (4 weeks post last dose). • Breastmilk VPI specific (GI.1 and GII.4) IgA on Day 1 (baseline), Day 8, , and Day 29 (4 weeks post last dose).

with the immunogenicity response in breastmilk.	
Secondary Objective	**Secondary Endpoints**
• To assess the long-term safety of bivalent GI.1/GII.4 norovirus vaccine through 12 months after the last vaccination.	• Frequency, duration, and severity of all SAEs, AESIs, and NOCIs through 12 months after study drug dose
• To assess the immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and its association with the immunogenicity response in breastmilk.	• Serum VP1 specific (GI.1 and GII.4) IgA on Day 180 after study drug dose • Breastmilk VP1 specific (GI.1 and GII.4) IgA on Day 60, , and Day 180 after study drug dose • Serum VP1 specific (GI.1 and GII.4) IgG on Day 1 (baseline), Day 8, Day 29, and Day 180 after study drug dose • Serum BT50 (GI.1 and GII.4) on D1 (baseline), on Day 8, Day 29, and Day 180 after study drug dose
Exploratory Objective	**Exploratory Endpoints**
• To assess additional immunogenicity parameters of bivalent GI.1/GII.4 norovirus vaccine including immunogenicity response in breastfed infants.	• Nasal and saliva VP1 specific (GI.1 and GII.4) IgA from lactating mother on D1 (baseline), on Day 8, Day 29, Day 60, and Day 180 • Infant stool VP1 specific (GI.1 and GII.4) IgA on Day 1 (baseline), Day 29, and Day 60 • Breastmilk BT50 (GI.1 and GII.4) at various, critical timepoints if feasible, and with samples that have high probability of significant responses • Breastmilk Enterocyte culture neutralizing antibodies (GI.1 and GII.4) at various timepoints, if feasible, and with samples that have a high probability of significant responses.
• To assess clinical effects in subjects presenting with acute gastroenteritis symptoms during the study period	• Occurrence of norovirus acute gastroenteritis

Study Population:

76 healthy adult lactating female participants aged 18 years or greater and their breastfed infants aged >30 days to 11 months of age

Planned Number of Subjects:

A total of 76 healthy lactating female participants aged ≥18 years and their breastfed infants aged >30 days to 11 months of age will be enrolled and randomized during this trial.

Eligibility Criteria:

Inclusion Criteria:

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

1. Lactating females aged ≥ 18 years at the time of enrolment and their breastfed infants aged >30 days to 11 months of age at the time of the participants' study drug administration.
2. In stable and good general health, without significant medical illness, based on medical history, physical examination (including vital signs), and clinical judgment of the investigator.
3. Lactating females willing and able to provide informed consent which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
4. Lactating females who are willing to provide consent for their breastfed infant.
5. Negative pregnancy tests at screening and prior to dose on Day 1
6. Available for all planned visits and tele-health appointments, and ability to comply with all study-related evaluations (including but not limited to having the ability and willingness to swallow multiple small enteric-coated tablets per study dose, express/pump breastmilk, and collect infant stool samples)
7. Plan to continue breastfeeding as the main source of the infant's nutrition for at least 1 month (longer is preferred with goal of 6 months post dose if possible) from the time of study drug administration. Exclusive breastfeeding is acceptable but not necessary.
8. The nursing infant is the product of a singleton pregnancy AND does not have any of the following (therefore, subjects must be willing to provide the infant's medical record at screening and Day 1 and the infant's updated vaccine record at Day 60 or later):
    a. Any abnormality that may interfere with breastfeeding or milk absorption
    b. Active infection (may be included if the infection resolves and the subject is re-assessed during the screening period)
    c. Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's appropriate

inclusion in this study including interference with the interpretation of study results (such as malabsorption)
   d. One or more documented brief resolved unexplained events (BRUE)
   e. Extreme prematurity (infants who were born at less than 28 weeks gestation)
   f. 30 days of age or less at the participant's study drug administration OR greater than 11 months of age at the participant's study drug administration
   g. Prior hospitalization that is not exclusively for hyperbilirubinemia requiring phototherapy
   h. Any genetic/metabolic disease
   i. Any chronic illness requiring long term medication

9. Subjects must be willing to use a highly effective form of contraception for 30 days prior to vaccination and until 60 days after the vaccination. Acceptable forms are oral, implantable, intrauterine, transdermal, intravaginal, injectable, double barrier or abstinence (subjects using diaphragms must also use condom). The form of contraception must be approved by the investigator.

Subject reac Criteria:

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

1. Presence of a fever ≥ 38.0ºC measured orally at baseline, on Day 1 prior to vaccination. (Assessment may be repeated once during screening period).
2. 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 once during screening period).
3. Participants who have received antipyretic/analgesic medications within 24 hours prior to the intended vaccine administration.
4. Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) tests at the screening visit.
5. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin.
6. History of serious reactions to vaccination such as anaphylaxis, respiratory problems, hives, or abdominal pain.
7. Presence of significant uncontrolled medical or psychiatric illness (acute or chronic) including the 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.
8. History of significant pregnancy-related complications during this pregnancy, including but not limited to pre-eclampsia, eclampsia, or gestational diabetes unless a full resolution is documented.

9. Cancer, or treatment for cancer, within the past 3 years (excluding fully treated and resolved basal cell carcinoma or squamous cell carcinoma).
10. Presence of immunosuppression or medical condition possibly associated with impaired immune responsiveness, including diabetes mellitus type 1 or 2.
11. 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. Any history of:
        i. Malignancy
        ii. Malabsorption
        iii. Pancreatobiliary disorders
        iv. Inflammatory bowel disease
        v. Irritable bowel disease
        vi. Hiatal hernia
        vii. Surgical resection
    b. History of diagnosis or treatment in past 5 years of:
        i. Esophageal or gastric motility disorder
        ii. Gastroesophageal reflux disease (GERD) - Will allow for subjects with a history of pregnancy-related GERD if fully resolved for >3 months and no other history of GERD diagnosis
        iii. Peptic ulcer
        iv. Cholecystectomy
12. Any condition that resulted in the absence or removal of the spleen
13. History of any form of angioedema
14. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic
15. History of GI bleeding including hematochezia (blood in stool) or melena (black stool)
16. Any significant hospitalization within the last year which in the opinion of the investigator or sponsor could interfere with study participation
17. Any of the following history or conditions that may lead to a higher risk of clotting events and/or thrombocytopenia:
    a. Family or personal history of bleeding or thrombosis
    b. History of heparin-related thrombotic events, and/or receiving heparin treatments
    c. History of autoimmune or inflammatory disease
    d. Presence of any of the following conditions known to increase the risk of thrombosis within 6 months prior to screening:
        i. Recent surgery other than fully healed cesarean delivery or excision/ biopsy of cutaneous lesions

ii. Immobility (confined to bed or wheelchair for 3 or more successive days)
iii. Head trauma with loss of consciousness or documented brain injury
iv. Receipt of anticoagulants for prophylaxis of thrombosis
v. Recent clinically significant infection including hospitalization for COVID-19 related illness

18. 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
19. Receipt of a licensed vaccine (including any COVID-19 vaccines under Emergency Use Authorization) within 14 days prior to study drug dose or planned administration during the study active period
20. 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
21. Use of medications known to affect the immune function (including but not limited to systemic corticosteroids, leukotriene modifiers, and JAK inhibitors) within 2 weeks before study drug administration or planned use during the active study period. Ophthalmic, inhaled, and intranasal steroids should follow these restrictions.
22. Daily use of nonsteroidal anti-inflammatory drugs within 7 days prior to study drug administration or planned use during the active study period
23. Donation or receipt of blood or blood products within 30 days prior to study drug administration or planned donation during the active study period
24. Participating in any clinical trial with another investigational product within 30 days prior to the first trial visit or intend to participate in another clinical trial at any time during the conduct of this trial
25. Are first-degree relatives of individuals involved in trial conduct
26. Positive urine drug screen for drugs of abuse at screening
27. Positive alcohol test at screening or baseline
28. History of drug, alcohol, or chemical abuse within 1 year of screening

Study Duration Criteria for Individual Subject:

The total duration of the study will be 365 days.

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

Screening period:	Up to 45 days
Active study period:	29 days
Follow-up period for safety and duration of immune response, SAEs, AESIs, NOCIs	12 months (from the study dose at Day 1)
Total duration:	12 months from study dose at Day 1

Summary of Statistical Analysis:

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.

Analyses will be performed for the total population.

Sample Size Justification:

Overall, 76 healthy lactating female subjects from 18 years of age or greater and their breastfed infants aged >30 days to 11 months of age will be enrolled and randomly assigned to the three cohorts. The sample size chosen is based on clinical judgment consultation with physicians and a biostatistician, and no formal sample size or power calculation was conducted.

Interim Analysis:

No interim analysis will be conducted for this study.

Safety Monitoring Committee:

A Safety Monitoring Committee (SMC) will be assigned by the Sponsor prior to the beginning of the study and will provide oversight of the study throughout the duration of the study period (Day 1 through Day 365) as needed. Ad hoc meetings will be convened if any predefined stopping rules are met, or any serious vaccine-related events or trends are observed.

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

1.1. Schedule of Trial Activities

Table 1: Schedule of Activities

	Screening	Active Study Period				Follow-up Period					
Study Day	**Day -45 to Day -1**	**Day 1**	**Day 8 (ET)[f]**	**Day 15**	**Day 29 (ET)[f]**	**Month 2 Day 60[*]**	**Month 4 Day 120**	**Month 6 Day 180**	**Month 8 Day 240**	**Month 10 Day 300**	**Month 12 Day 365**
Telephone call visit				📞			📞		📞	📞	📞
Visit Window (days)			**+ 2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed consent	X										
Inclusion/Exclusion	X	X									
Demographics	X										
Medical history[*]	X	X									
Serology[a]	X										
Urine drug screen	X										
Alcohol test	X	X									
Pregnancy Test[b]	X	X									
Physical examination	X	X[c]	X[c]		X[c]						
Vital Signs[d]	X	X	X		X						
Study Drug Administration		X									
Distribute Solicited Symptom Diary		X									
Review Solicited Symptom Diary[e]			X[f]								
Review prior & concomitant medication	X	X	X	X	X						
Query for AEs, SAEs, AESIs and NOCIs		X	X	X	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]

	Screening	Active Study Period				Follow-up Period					
Study Day	**Day -45 to Day -1**	**Day 1**	**Day 8 (ET)[f]**	**Day 15**	**Day 29 (ET)[f]**	**Month 2 Day 60***	**Month 4 Day 120**	**Month 6 Day 180**	**Month 8 Day 240**	**Month 10 Day 300**	**Month 12 Day 365**
Telephone call visit				📞			📞		📞	📞	📞
Visit Window (days)			**+ 2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Sample Collection for Immunogenicity Assessments											
Serum sample - BT50, VP1 specific IgA and IgG		X	X		X			X			
Nasal Swab (SAM™ Device) - VP1 specific IgA		X	X		X	X		X			
Saliva Sample - VP1 specific IgA		X	X		X	X		X			
Breastmilk - VP1 specific IgA, Enterocyte culture neutralizing antibodies, and BT50[h]		X	X		X	X		X			
Infant Stool - VP1 specific IgA		X			X	X					

Notes:
Tele-health appointment (by phone)
a F- human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) or Hepatitis C virus (HCV)
b Serum pregnancy tests will be done at screening. Point-of-Care urine pregnancy test will be performed before dosing on Day 1 and women found positive with urine pregnancy test will not be enrolled during this study.
c Targeted exam: at a minimum, assessments of the skin, respiratory system, cardiovascular system, and GI (abdomen, liver, and spleen) will be included.
d Blood pressure, heart rate, and respiratory rate will be measured after the subject has been resting in a sitting position for 5 minutes.
e At the discretion of PI and/or per subject request to evaluate any of the expected reactogenicity symptoms or any unexpected symptoms of concern, a contact must occur as soon as possible between the subject and the Investigator, or a medically qualified member of the study site staff, to assess if an unscheduled visit is required.
f Early termination assessments. Review of solicited symptoms should be included if the subject drops out before Day 8. Day 29 procedures should be performed if the subject drops out before Day 29 on the day of early termination.
g TEAEs will only be collected during the Active Study period (from time of first dose through 4 weeks post dose). Only SAEs, AESIs and NOCIs will be collected during the Follow-up Period.
h Breastmilk VP1 specific IgA will be tested at the indicated intervals in the table. Breastmilk enterocyte culture neutralizing antibodies and BT50 will be tested at various time points if feasible.
* Also collect the infant's medical record at screening and day 1 and the infant's updated vaccine record at D60 or later

2. INTRODUCTION

2.1. Indication

Bivalent GI.1 and GII.4 vaccines are being investigated for the prevention of noroviral gastroenteritis caused by norovirus GI.1 and GII.4.

2.2. Background

2.2.1. Background of Disease

Norovirus (NoV) infection remains a leading cause of Acute gastroenteritis (AGEs) globally, with a prevalence of 16% (Liao *et al*., 2021). Noroviruses are a genetically diverse group of small, non-enveloped, single-stranded positive sense (RNA) viruses belonging to the Caliciviridae family (Bresee *et al*., 2002). Genogroups I, II and IV are human-transmitted. Genogroup I and II account for the majority of norovirus outbreaks. Each genogroup is further divided into genotypes based on the similarity of the amino acid sequence of the major viral capsid protein, VP1 (Atmar and Estes, 2012). Genogroup I and II account for the majority of norovirus outbreaks (Vega *et al*., 2014). The classic symptoms of NoV infection include sudden onset of vomiting, abdominal cramps, watery diarrhea, and other clinical symptoms such as headache, chills, and myalgias. Currently, there is no specific treatment modality for NoV infection. The standard treatment is oral rehydration with fluids and electrolytes (Glass *et al*., 2009). In 2016, the World Health Organization (WHO) stated that the development of a NoV vaccine should be considered an absolute priority. It is important to develop prevention methods like vaccines considering the NoV-associated risk (Esposito and Principi, 2020). Despite a large medical need and years of development, no vaccine is licensed for use in any population for NoV infection.

2.2.2 Non-clinical experience with Monovalent and Bivalent GI.1 and GII.4 vaccine

Vaxart has conducted multiple preclinical studies of our norovirus vaccine candidate in mice and ferrets, further details are available in the Investigator's Brochure. The preclinical and clinical data on VXA-G1.1-NN and on influenza HA (with the same exact vector backbone) demonstrates a 29-fold increase in neutralizing antibody responses after single dose enteric-coated tablet administration (Liebowitz *et al*., 2020), confirming that VXA-G1.1-NN and VXA-GII.4-NS are capable of eliciting robust antibody responses to VP1 following oral tablet delivery.

2.2.3 Clinical experience with Monovalent and Bivalent GI.1 and GII.4 vaccine

Vaxart has completed four Phase 1 studies in over 200 healthy volunteers with our monovalent tableted norovirus GI.1 oral tablet vaccine candidate and one Phase 1b study with our bivalent tableted vaccine candidate (co-administration of GI.1 and GII.4 vaccines). In all studies, the primary endpoint was safety, and the secondary endpoint was immunogenicity. In the bivalent study, potential interference with co-administration was also evaluated. These studies indicate that the vaccine was safe and generally well tolerated, and there have been no severe adverse events

(SAEs) attributed to vaccine. The vaccine has generated robust immune responses including systemic and mucosal antibodies as well as immunoglobulin A + (IgA) and immunoglobulin G (IgG) + memory B cells. 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 *et al*., 2018).

During the Phase 1 dose-ranging study VXA-NVV-104, a total of 65 healthy older adult volunteers ages 55-80 (in two age cohorts) were evaluated for immunogenicity, safety, and tolerability at three dosing levels of monovalent GI.1-NN: low, medium, and high. Preliminary results of this Phase 1 study indicate this oral norovirus vaccine candidate was safe, well-tolerated, and induced similar immune responses in this older population compared to previous results in younger volunteers.

In an open label Phase 1b boost optimization study (VXA-NVV-105), immunogenicity, safety, and tolerability of repeat-dose administration with varying boost schedules were evaluated in 30 healthy adults (18-55 years). VXA-GI.1 was found to be safe and generally well-tolerated in 4-week, 8-week and 12-week boost schedules. All solicited symptoms were graded as mild or moderate severity, and none required treatment or study discontinuation. During the active period there were no related unsolicited AEs and no related SAEs, AESI or NOCIs. There were no SAEs, AESIs, or NOCIs reported during the safety follow-up period. There were no deaths during the study. Clinical laboratory data, vital signs data, and physical examination findings were within normal ranges and those reporting deviations were mild and transient. No clinically significant abnormal physical examination findings were noted.

2.3 Trial Rationale

Noroviruses are a genetically diverse group of small, non-enveloped, single-stranded positive-sense RNA viruses belonging to the *Caliciviridae* family, and currently, it is the main viral cause of acute gastroenteritis (AGEs) in most countries worldwide. After adoption of the rotavirus vaccine throughout the world, norovirus infection has been one of three major causes of infant diarrheal disease. It was estimated that each year NoVs cause 64,000 episodes of diarrhea requiring hospitalization and 900,000 clinic visits among children in industrialized countries, and up to 200,000 deaths of children <5 years of age in developing countries (Patel, *et al*). Hence, there is an urgent public health need for the rapid development of novel interventions to prevent the spread of this disease.

An effective NoV vaccine must prevent the two most common NoV genotypes, GI.1 and GII.4, and Vaxart's bivalent norovirus vaccine consists of VXA-G1.1-NN and VXA-GII.4-NS. Vaxart's norovirus oral tablet vaccine uses Vaxart's non-replicating adenoviral-based oral vaccine platform (vector adjuvant antigen standard technology (VAAST)), which has been studied to be well tolerated and safe in over 600 healthy adult subjects who have been enrolled in studies to evaluate the safety, tolerability, and immunogenicity of vaccines built on the VAAST platform. Notably, Vaxart's norovirus oral tablet vaccine is highly immunogenic in humans, inducing serum antibodies and potent mucosal responses.

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 GI.1/GII.4 bivalent oral vaccine may enable higher degrees of mucosal protection against infection when compared to a parenteral immunization method.

Presently, norovirus gastroenteritis is a contagious disease that can affect all age groups, and infants aged 6 to 23 months have the highest norovirus disease burden in children. A study published by Labayo and colleagues demonstrated the passive transfer of IgA in breastfeeding moms infected with NoV may inhibit norovirus diarrheal disease in their nursing infants (Labayo *et al,* 2020). Although several phase 1 norovirus studies have shown a robust immune response in healthy subjects when given Vaxart's norovirus G1.1 and G2.4 monovalent and bivalent vaccines, the immune response to orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy, lactating females is still unknown.

Unpublished data from Vaxart in collaboration with Stephanie Langel and colleagues show promising results for inducible breastmilk immunogenicity after receipt of a Vaxart vaccine construct in animal models. Pregnant/postpartum ferrets were orally administered Vaxart influenza vaccine and subsequently produced IgG and IgA antibodies to influenza in their breast milk. Breast milk from mucosally immunized ferret mothers was found to be capable of neutralizing influenza H1N1 by microneutralization assay. The bivalent GI.1/GII.4 norovirus vaccine uses the same VAAST platform as Vaxart influenza vaccine, thus there is a potential for lactating women to induce immunogenicity towards NoV in their breastmilk. Besides directly neutralizing pathogens, IgA has other functional activity, which may greatly underestimate IgA protective responses. Following immunization of lactating, postpartum mothers with Vaxart's oral tablet, it is hypothesized that nursing infant incidence of norovirus diarrheal disease will be significantly lower due to the passive transfer of norovirus breast milk IgA antibodies, which may also reduce further viral transmission and thus disease burden within the family.

Therefore, in this phase 1 study, we will evaluate the immunogenicity effect of orally administered bivalent GI.1/GII.4 norovirus vaccine in the breast milk of healthy, lactating female volunteers and fecal samples (exploratory) in their infants. Additionally, the study will evaluate the safety and tolerability of the norovirus bivalent vaccine in lactating females; the dose of the vaccine will be 5×10^{10} IU or 1×10^{11} IU per strain given as a single bivalent dose.

This trial is not powered as an efficacy study and any cases of norovirus acute gastroenteritis during the study period will be evaluated as exploratory.

2.4 Risk / Benefit Assessment

2.4.1 Known Potential Risks to the Subjects

More detailed information about the known and expected risks and reasonably expected adverse events of Bivalent GI.1/GII.4 NoV vaccine may be found in the Investigator's Brochure (IB). Below are the expected treatment emergent adverse events (TEAEs) with Grade 1-3 symptoms:

1. Diarrhea
2. Nausea
3. Abdominal pain
4. Malaise/fatigue
5. Headache
6. Fever
7. Vomiting
8. Anorexia
9. Myalgia (muscle pain)

2.4.2 Known Potential Benefits to the Subject

Benefits to individual subjects may include receipt of a potentially efficacious NoV vaccine. Clinical data from Phase 1 studies demonstrated that VXA-G1.1-NN and VXA-G2.4-NS generated robust immune responses.

Since these are experimental vaccines against NoV, there are no proven benefits to the subjects for their participation in this research study. This vaccine may successfully be developed to address a common and sometimes serious gastrointestinal infection.

2.4.3 Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with Bivalent GI.1/GII.4 NoV vaccine are justified by the anticipated benefits that may be afforded to subjects and potentially their infants with noroviral gastroenteritis caused by NoV GI.1 and GII.4.

3. TRIAL OBJECTIVE AND END POINTS

3.1. Objectives

3.1.1. Primary Objectives

- **Safety**
  - To determine the safety and tolerability of oral bivalent dosing regimen of GI.1 and GII.4 norovirus vaccine administration in healthy lactating female participants.

- **Immunogenicity**
  - To determine the short-term immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and most critically, the association with vaccine specific antibody responses in breastmilk.

3.1.2. Secondary Objectives

- **Safety**
  - To determine the long-term safety of bivalent GI.1/GII.4 norovirus vaccine through 12 months after the last vaccination.

- **Immunogenicity**
  - To assess the immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and most critically, the association with vaccine specific antibody responses in breastmilk.

3.1.3. Exploratory Objectives

- **Immunogenicity**
  - To determine the additional immunogenicity parameters of bivalent GI.1/GII.4 norovirus vaccine including immunogenicity response in breastfed infants.
  - To determine the clinical effects in subjects presenting with acute gastroenteritis symptoms during the study period.

3.2. End Points

3.2.1. Primary End Points

- **Safety**
  - 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 treatment-emergent adverse events (TEAEs), serious AEs (SAEs), adverse events of special interest (AESIs), and new onset of chronic illness (NOCIs) through the active period (4 weeks post last dose).

- **Immunogenicity**
  - Serum VP1 specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8 and Day 29
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 29
  - Breastmilk VPI specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, and Day 29
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 29

- The number of subjects in each dose group that had a 2-fold GMC rise or greater in breast milk VP1 specific IgA (GI.1 and GII.4) between Day 1 and any other timepoint.

3.2.2. Secondary End Points

- **Safety**
  - Frequency, duration, and severity of all SAEs, AESIs, and NOCIs through 12 months after last study drug dose

- **Immunogenicity**
  - Serum VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 180
  - Breastmilk VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) by dose level
    - Geometric mean concentration (GMC) at Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 60 and from Day 1 to Day 180
  - Serum VP1 specific (GI.1 and GII.4) IgG through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, and from Day 1 to Day 180
  - Serum Blocking titers 50 (BT50) (GI.1 and GII.4) through 6 months after study drug dose measured by Histo-blood group antigen (HBGA) assay by dose level
    - Geometric mean titer (GMT) at Day 1, Day 8, Day 29, and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, and from Day 1 to Day 180

3.2.3. Exploratory End Points

- **Efficacy**
  - Occurrence of norovirus acute gastroenteritis

- **Immunogenicity**
  - Saliva VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Enzyme-linked immunosorbent assay (ELISA) by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, from Day 1 to Day 60, and from Day 1 to Day 180
  - Nasal VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Meso Scale Discovery (MSD) by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, from Day 1 to Day 60, and from Day 1 to Day 180
  - Infant stool VP1 specific (GI.1 and GII.4) IgA measured by Enzyme-linked immunosorbent assay (ELISA) by dose level
    - Geometric mean concentration (GMC) Day 1, Day 29, and Day 60
    - Geometric mean fold rise (GMFR) from Day 1 to Day 29 and from Day 1 to Day 60
  - Breastmilk Blocking titers 50 (BT50) (GI.1 and GII.4) measured by Histo-blood group antigen (HBGA) assay by dose level
    - Individual subject titers on samples and some timepoints that have a high likelihood of success, assuming the assay works in breast milk samples
  - Breastmilk Enterocyte culture neutralizing antibody titers (GI.1 and GII.4) measured by norovirus neutralization in enterocyte culture
    - Individual subject titers on samples and some timepoints that have a high likelihood of success, under the assumption that the assay works in breast milk samples. At the date of this protocol, only serum GII.4 neutralizing antibodies have been successfully measured.

4. TRIAL DESIGN

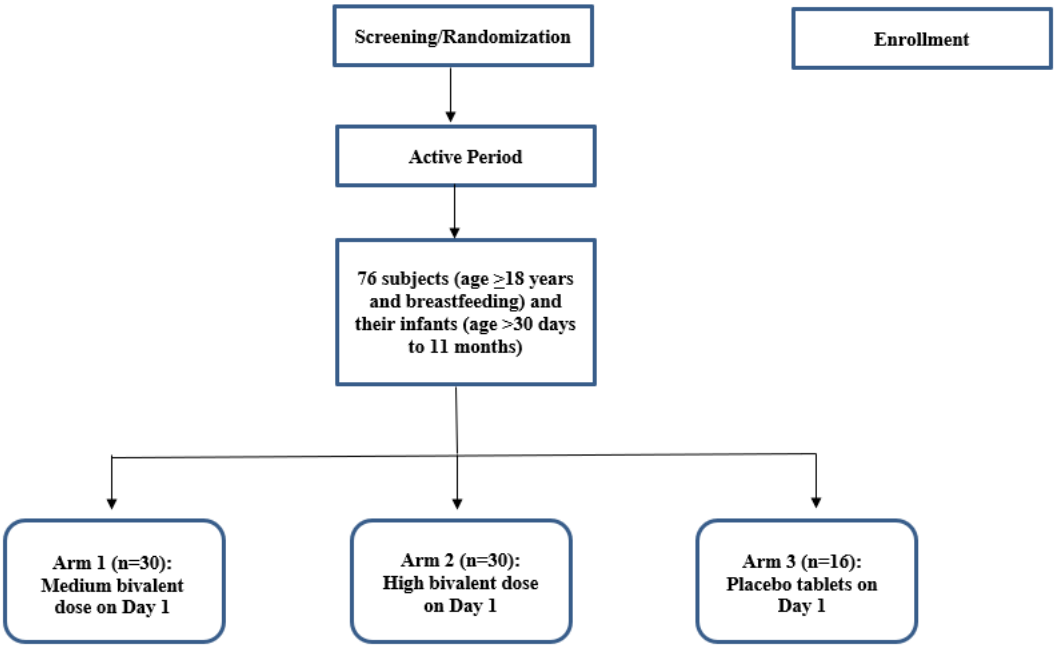
4.1. Overall Description of Trial Design

This is a multi-center, double-blind, randomized, placebo-controlled, single dose, dose ranging study in healthy, breastfeeding, female volunteers (≥18 years). The study will randomize 76 subjects and their breastfed infants aged >30 days to 11 months of age into three arms.

After reviewing and signing an informed consent, the subjects will undergo screening assessments to determine study eligibility up to a 45-day Screening Period.

On Day 1 of the randomized portion, subjects will be randomized in a 2:2:1 ratio to one of the three treatment arms to receive active vaccine at medium dose or high dose or placebo, as follows (Figure 1):

Figure 1



All subjects will be monitored for Solicited Symptoms of Reactogenicity (GI and systemic) for 1 week following the study drug dose and unsolicited AEs for 28 days post study drug dose (until Day 29) during the Active Period. Subjects will then enter the Follow-up period after Day 29 and will be monitored for specified unsolicited adverse events (SAEs, AESIs, and NOCIs) through Day 365 (Month 12) for safety and durability of immune response. Subjects will have samples (nasal, saliva, and serum) collected at the site, and will also self-collect samples (breastmilk and infant stool) at home for evaluation of immunogenicity as specified in the SoA (Table 1).

Table 2 Study Design

Treatment Group	Study Drug	Per Strain Dose (IU) +/- 0.5 log	Total Dose (IU/dose)	Dosing Schedule	No of Subjects
Arm 1 (n=30)	Bivalent GII.4/GI.1 vaccine	5×10^{10}	1×10^{11}	Day 1	30
Arm 2 (n=30)	Bivalent GII.4/GI.1 vaccine	1×10^{11}	2×10^{11}	Day 1	30
Arm 3 (n=16)	Placebo	N/A	N/A	Day 1	16
Total					76

Abbreviations: IU=infectious units

After vaccination on Day 1, the study will include an Active Study Period that runs through 4 weeks after administration (Day 29), and a Follow-up Period of one year for safety and duration of immune response. Study assessments will be conducted as shown in the SoA (Table 1). In addition, subjects will be contacted by phone between site visits to monitor for safety as specified in the SoA (Table 1).

A subject is considered to have completed the study if she completes the study active period at Day 29 (End of Study Active Period). Following completion of the Day 29 visit by all subjects the database will be cleaned and locked and the study unblinded. The Clinical Study Report (CSR) will be written based on the Day 29 dataset.

A subject is considered to have completed the Follow-up Period if she remains in the study through Day 365 (Month 12). Following completion of the Day 365 tele-health appointment for all subjects, the safety database will be cleaned and locked, and data collected during the Follow-up Period will be included in a CSR addendum.

All subjects will be monitored for Solicited Symptoms of Reactogenicity (GI and systemic) for 1 week following the study drug dose and unsolicited AEs for 28 days post study drug dose (until Day 29) during the active period. The subjects will then enter the Follow-Up Period after Day 29 and will be monitored for SAEs, AESIs, and NOCIs through Day 365 (Month 12) for safety. Subjects will also have samples collected for evaluation of immunogenicity and durability of immune response as specified in the SoA (Table 1).

Planned Number of Subjects:

A total of 76 healthy, lactating, female subjects aged ≥18 years and their breastfed infants aged >30 days to 11 months of age will be randomized and assigned to the three cohorts: placebo, medium dose (total 1×10^{11} IU/dose), or high dose (total 2×10^{11} IU/dose).

Study Duration:

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

Table 3: Study Duration

Screening period:	Up to 45 days
Active study period:	29 days
Follow-up period for safety and duration of immune response, SAEs, AESIs, NOCIs	12 months (from the study dose at Day 1)
Total duration:	Approximately 14 months from Screening to Month 12/Day 365 post vaccination

4.2 Scientific Rationale of Trial Design

This study is designed as a standard double-blind placebo-controlled single administration, dose-ranging study to evaluate the effect of 2 different doses (high and medium dose) of VXA-GII.4-NS plus VXA-G1.1-NN in the target population, compared with placebo.

4.3 Justification for Dose Selection

Vaxart has previously completed dose escalation (Protocol VXA-G11-101) and dose optimization (Protocol VXA-G11-102) studies in its initial Phase 1 NoV vaccine studies to demonstrate the safety, tolerability, and immunogenicity of the VXA-G1.1-NN vaccine candidate. A Phase 1b, double-blind, placebo-controlled study (Protocol VXA-NVV-103) with VXA-G1.1-NN and VXA-GII.4-NS with monovalent or bivalent dosing have also been completed. Additionally, dose ranging studies from 1×10^{8} IU – 1×10^{11} IU (2 doses) have been studied across multiple studies with the same vaccine platform.

Safety results from these completed oral tablet vaccine studies support investigations of bivalent administration of the VXA-G1.1-NN and VXA-GII.4-NS vaccine candidates at single total dose of 1×10^{11} IU per vaccine or 2×10^{11} IU per administration.

4.4 End of the Study Definition

A subject is considered to have completed the study if he/she completes the study active period at Day 29 (End of Study Active Period). Following completion of the Day 29 visit by all subjects the database will be cleaned and locked, and the study unblinded. The CSR will be written based on the Day 29 dataset.

A subject is considered to have completed the Safety Follow-up Period if he/she remains in the study Day 365 (Month 12). Following completion of the Day 365 tele-health appointment of all subjects, the safety database will be cleaned and locked, and data collected during the Follow-Up Period will be used to generate a CSR addendum.

4.5 Premature Termination or Suspension of Trial

The Sponsor or designee reserves the right to terminate the study at any time for any reason at the sole discretion of the Sponsor. This trial may be temporarily suspended, or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for trial suspension or termination, will be provided by the suspending, or terminating party to study subjects, Investigators, funding agency, the Investigational New Drug (IND) Sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the site Principal Investigator (PI) will promptly inform study subjects, the site Institutional Review Board (IRB) (if applicable) and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes if any, to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB/IEC, Food and Drug Administration (FDA) and/or South African Health Products Regulatory Authority.

4.6 Trial and Site Start and Close-Out

4.6.1 First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of subjects. The first act of recruitment is the first site open and will be the study start date.

4.6.2 Study/Site Termination

The Sponsor or designee reserves the right to close the study site at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given to Sponsor and subjects in advance of the intended termination.
Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor’s procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator.

- Total number of subjects included is achieved earlier than expected.

The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

5. SELECTION OF TRIAL POPULATION

5.1. Inclusion Criteria

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

Age

1. ≥18 years old at the time of signing the Informed Consent Form (ICF) and her infant will be aged >30 days to 11 months of age at the time of the participants' study drug administration

Type of Subjects

2. In stable and good general health, without significant medical illness, based on medical history, physical examination (including vital signs), and clinical judgment of the investigator.
3. Lactating females willing and able to provide informed consent which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
4. Lactating females who are willing to provide consent for their breastfed infant will be enrolled in the study
5. Negative pregnancy test prior to dose
6. Available for all planned visits and tele-health appointments, and ability to comply with all study-related evaluations (including ability and willingness to swallow multiple small enteric-coated tablets per study dose).
7. Plan to continue breastfeeding as the main source of the infant's nutrition for at least 1 month (longer is preferred with goal of 6 months post dose if possible) from the time of study drug administration. Exclusive breastfeeding is acceptable but not necessary.
8. The nursing infant is the product of a singleton pregnancy AND does not have any of the following (therefore, subjects must be willing to provide the infant's medical record at screening and Day 1 and the infant's updated vaccine record at Day 60 or later):
    a. Any abnormality that may interfere with breastfeeding or milk absorption
    b. Active infection (may be included if the infection resolves and the subject is re-assessed during the screening period)
    c. Infant has any other medical condition or abnormality that, in the opinion of the investigator, could compromise the infant's appropriate inclusion in this study including interference with the interpretation of study results (such as malabsorption)
    d. One or more documented brief resolved unexplained events (BRUE)

e. Extreme prematurity (infants who were born at less than 28 weeks gestation)
f. 30 days of age or less at the participant's study drug administration OR greater than 11 months of age at the participant's study drug administration
g. Prior hospitalization that is not exclusively for hyperbilirubinemia requiring phototherapy
h. Any genetic/metabolic disease
i. Any chronic illness requiring long term medication

9. Subjects must be willing to use a highly effective form of contraception for 30 days prior to vaccination and until 60 days after the vaccination. Acceptable forms are oral, implantable, intrauterine, transdermal, intravaginal, injectable, double barrier or abstinence (subjects using diaphragms must also use condom). The form of contraception must be approved by the investigator.

Subject Exclusion Criteria:

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

1. Presence of a fever ≥ 38ºC measured orally at baseline, on Day 1 prior to vaccination. (Assessment may be repeated once during screening period)
2. Acute disease within 72 hours prior to vaccination is 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 once during screening period.)
3. Who have received antipyretic/analgesic medications within 24 hours prior to the intended vaccine administration
4. Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) tests at the screening visit
5. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin
6. History of serious reactions to vaccination such as anaphylaxis, respiratory problems, hives, or abdominal pain
7. Presence of significant uncontrolled medical or psychiatric illness (acute or chronic) including the 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
8. History of significant pregnancy-related complications during this pregnancy, including but not limited to pre-eclampsia, eclampsia, or gestational diabetes unless a full resolution is documented.
9. Cancer, or treatment for cancer, within the past 3 years (excluding fully treated and resolved basal cell carcinoma or squamous cell carcinoma)

10. Presence of immunosuppression or medical condition possibly associated with impaired immune responsiveness, including diabetes mellitus
11. 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. Any history of:
        i. Malignancy
        ii. Malabsorption
        iii. Pancreatobiliary disorders
        iv. Inflammatory bowel disease
        v. Irritable bowel disease
        vi. Hiatal hernia
        vii. Surgical resection
    b. History of diagnosis or treatment in past 5 years of:
        v. Esophageal or gastric motility disorder
        vi. GERD (Will allow for subjects with a history of pregnancy-related GERD if fully resolved for >3 months and no other history of GERD diagnosis
        vii. Peptic ulcer
        viii. Cholecystectomy
12. Any condition that resulted in the absence or removal of the spleen
13. History of any form of angioedema
14. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic
15. History of GI bleeding including hematochezia (blood in stool) or melena (black stool)
16. Any significant hospitalization within the last year which in the opinion of the investigator or sponsor could interfere with study participation.
17. Any of the following history or conditions that may lead to a higher risk of clotting events and/or thrombocytopenia:
    a. Family or personal history of bleeding or thrombosis
    b. History of heparin-related thrombotic events, and/or receiving heparin treatments
    c. History of autoimmune or inflammatory disease
    d. Presence of any of the following conditions known to increase the risk of thrombosis within 6 months prior to screening:
        i. Recent surgery other than fully healed cesarean delivery or excision/ biopsy of cutaneous lesions
        ii. Immobility (confined to bed or wheelchair for 3 or more successive days)
        iii. Head trauma with loss of consciousness or documented brain injury
        iv. Receipt of anticoagulants for prophylaxis of thrombosis
        v. Recent clinically significant infection

18. 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
19. Receipt of a licensed vaccine (including any COVID-19 vaccines under Emergency Use Authorization) within 14 days prior to study drug dose or planned administration during the study active period.
20. 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
21. Use of medications known to affect the immune function (including but not limited to systemic corticosteroids, leukotriene modifiers, and JAK inhibitors) within 2 weeks before study drug administration or planned use during the active study period. Ophthalmic, inhaled, and intranasal steroids should follow these restrictions.
22. Daily use of nonsteroidal anti-inflammatory drugs within 7 days prior to study drug administration or planned use during the active study period
23. Donation or receipt of blood or blood products within 30 days prior to study drug administration or planned donation during the active study period
24. Participants participating in any clinical trial with another investigational product 30 days prior to the first trial visit or intend to participate in another clinical trial at any time during the conduct of this trial
25. Are first-degree relatives of individuals involved in trial conduct.
26. Positive urine drug screen for drugs of abuse at screening
27. Positive alcohol test at screening or baseline
28. History of drug, alcohol, or chemical abuse within 1 year of screening

5.2. Early Termination/Withdrawal Criteria

All procedures for Day 8 visit should be completed for Early Termination (ET) assessment, including Review Solicited Symptom Diary if ET occurs prior to Day 8 as shown in the SoA (Table 1).

Subjects 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 subject may discontinue/withdraw 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 subject (only for discontinuing study drug, but will remain in study)

The reason for subject discontinuation from study drug will be recorded in the electronic case report form (eCRF).

At the time of withdrawal from the study, the ET visit should be completed, as shown in the SoA (Table 1).

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

5.3. Lost to Follow Up Procedure

A subject 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 subject fails to return to the clinic for a required study visit:

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

5.4. Screening Failure

Screening failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study.

Re-screening outside the screening period will be possible on a case-by-case basis following Sponsor approval. Subjects allowed to be re-screened will be assigned a new screening number and must undergo all screening procedures again. Subjects cannot re-screen more than once and will be determined to be permanent screen failures after the second screening determines a subject is ineligible. Re-assessment of not clinically significant abnormal and/or out of range parameters within the screening period is allowed per Investigators' discretion.

5.5. Classification of Subjects Who Discontinue the Study

For any subject who discontinues the study prior to completion, the most significant reason for early termination will be checked in the eCRF. Reasons are listed below from the most significant to the least significant:

Table 4: Discontinuation Reasons

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.1
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 7.
Protocol Deviation	To be used in case of significant noncompliance with the protocol (e.g., deviation of the Inclusion/Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration).
Withdrawal by Subject	• When the subject indicates unwillingness to continue in the study • When the subject made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (e.g., subject is relocating, inform consent withdrawal, etc.)

6. TRIAL INTERVENTION

6.1. Investigational Product Description

This study will investigate the safety and immunogenicity of bivalent GI.1 and GII.4 vaccine, administered orally at total doses of 1×10^{11} IU/dose and 2×10^{11} IU/dose, for the prevention of NoV infection.

- Norovirus GI.1 Norwalk VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant (VXA-G1.1-NN)
- Norovirus GII.4 Sydney VP1 Vaccine, Oral E1-/E3-Deleted Replication Defective Recombinant Adenovirus 5 with dsRNA Adjuvant (VXA-GII.4-NS)

VXA-G1.1-NN and VXA-G2.4-NS are E1/E3-deleted, replication-incompetent, adenovirus type 5 vector vaccines. These non-replicating vectors encode for a full-length VP1 gene of either Norwalk virus (VXA-G1.1-NN vaccine) or Sydney virus (VXA-G2.4-NS vaccine). In addition to the transgene cassette, the rAd5 vector also contains a dsRNA hairpin following a second hCMVie promoter, thereby expressing both vaccine antigen and adjuvant in the same cell. These rAd5 vectors are designed to deliver both NoV VP1 antigen and adjuvant to the same target cells in the intestinal ileum.

The VXA-G1.1-NN and VXA-GII.4-NS vaccines are produced in tablet form. The drug substance is formulated as compressed powdered solid material containing [redacted]

[redacted]All inactive ingredients incorporated into the drug product are generally recognized as safe (GRAS) and all are included in currently approved, US-licensed oral drug products currently listed in the FDA Inactive Ingredients Database. The formulated drug substance is compressed into tablets and enteric coated with an acetone-based solution of methacrylate polymer and talc.

The placebo for this study is manufactured similarly to the active Drug Product (DP) tablets, but without the active drug substance. The placebo tablets are indistinguishable in appearance from the active DP tablets. The number of placebo tablets dispensed to the subject will be matched to the active treatment groups. The placebo will be dispensed by the site's in-house pharmacy in a manner indistinguishable from the active treatment groups.

6.2. Preparation and Dispensing of Investigational Product

Investigational product doses will be prepared at the study sites by an unblinded research pharmacist(s) or designee who will be provided treatment assignment through a randomization schedule.

A trained member of the site study staff will dispense the tablet(s) constituting their assigned dose to the subject.

See the Pharmacy manual for instructions on how to prepare VXA-G1.1-NN and VXA-GII.4-NS vaccines and placebo for administration.

6.3. Dosing and Administration of Investigational Product

This study will investigate the safety and immunogenicity of two monovalent NoV oral tableted vaccine candidates (VXA-G1.1-NN and VXA-GII.4-NS) co-administered (bivalent delivery) against a matching placebo arm. All lots of DP will be provided as small white enteric-coated tablets for oral route of administration.

A single dose comprised of multiple tablets of study drug will be dispensed and a matching number of placebo tablets will be dispensed to maintain the study blinding.

Table 5: Investigational Product Dosing

Intervention Name	**VXA-G1.1-NN**	**VXA-GII.4-NS**	**Placebo**
Type	Biologic	Biologic	Matching placebo
Dose Formulation	Enteric-coated tablets	Enteric-coated tablets	Enteric-coated tablets
Dosing Schedule	Day 1	Day 1	Day 1
Route of Administration	Oral		
Administration instructions	Subjects should fast and refrain from ingesting solid food for at least 4 hours prior to oral dosing. A trained member of the site study staff will dispense the tablet(s) constituting their assigned dose to the subject. The subjects 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 specific Pharmacy Manual.		
Sourcing	Study drug will be provided to the sites by the Sponsor or designated representative.		

Table 6: Study Arm(s)

Arm Title*	**Arm 1**	**Arm 2**	**Arm 3**
Arm Type	Experimental	Experimental	Placebo
Arm Description	Bivalent GII.4/GI.1 vaccine	Bivalent GII.4/GI.1 vaccine	Placebo
Per Strain Dose (IU) +/- 0.5 log	5×10^{10}	1×10^{11}	N/A
Total Dose (IU/dose)	1×10^{11}	2×10^{11}	N/A

6.4. Formulation, Appearance, Packaging, and Labelling

Formulation:

Both the VXA-G1.1-NN and VXA-GII.4-NS are formulated as small enteric-coated tablets.

Packaging and Labelling:

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 product, the concentration of the vaccine, the date of manufacturing or expiration.

Secondary packaging of the study drug upon dispensing from the pharmacy to the clinical staff for subject dosing will be determined with consideration of the site' pharmacy standard operating procedures and outlined in the study pharmacy manual.

The final subject use dispensing container (cup or secondary bottle) will be appropriately labeled with specific requirements for the country and deemed necessary per the site's standard operating procedures (i.e., subject randomization number, total tablet count, dispensing date and time etc.)

6.5. Product Storage and Stability

Storage:

The Investigator will be personally responsible for product management or will designate a study site staff to assume this responsibility.

Both the VXA-G1.1-NN and VXA-GII.4-NS DP should be stored at 2-8 °C. The DP tablets may be kept at room temperature during the dispensation and administration process for a brief period. Please refer to the study specific Pharmacy Manual for detailed information.

Stability:

Stability studies have been performed on similarly formulated tablets prepared from the same or similar adenovirus 5 constructs incorporating different antigens, including, VP1 Norwalk and other influenza antigens (e.g., hemagglutinin H1). The 2-8°C data indicate that drug product potency will remain within release specification prior to retest. Additionally, data from accelerated stability studies indicate that handling at controlled room temperature or brief exposure to temperatures above room temperature (below 37°C) is acceptable for this product.

6.6. Accountability Procedures

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.

Only subjects 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.

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).

At the end of the study active period, the unblinded monitor will conduct a final drug reconciliation for all subjects 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 specific Pharmacy Manual.

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

6.7. Randomization and Blinding

6.7.1. Randomization Procedures

Assignment of a Subject Number:

New subjects once deemed eligible and enrolled in the study will also receive a randomization number and treatment assignment, based on the blinded randomization schedule. The subject number will be used as the primary identifier for the complete duration of the study. After the subject signed the informed consent form (ICF), the Investigator (or designee) will enter the subject into the Screening Log, once randomized or screen failed their data will be entered into the eCRF.

Randomization:

After signing an informed consent, the subjects will undergo screening assessments to determine study eligibility over a 45-day Screening Period. All subjects who sign a study specific informed consent form will have data entered into the EDC. On Day 1, subjects will be randomized in a 2:2:1 ratio to one of the three treatment arms to receive active vaccine or placebo (Table 6: Study Arm(s).

6.7.2. Blinding and Unblinding Procedures

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

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

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

An SMC may convene to review unblinded overall safety if deemed necessary to ensure the safety of study subjects (Section 10.2).

Instructions for breaking the blind will be provided to the study site in case of a medical emergency. The Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. The Investigator must notify the Sponsor's Medical Monitor (or designee) prior to unblinding a subject's treatment assignment. The Investigator(s) must document and report to the Medical Monitor any breaking of the treatment code but must not disclose the result of unblinding. The date and reason that the blind was broken must be recorded in the source documentation.

Appropriate personnel at the Sponsor (or designee) will unblind suspected unexpected serious adverse reactions (SUSARs) for the purpose as required per each local regulation. The Sponsor

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

6.8. Treatment Compliance

Subjects will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study drug and study subject 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.

6.9. Overdose of Treatment

Any overdose of intervention 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.

The effects of acute overdose of VXA-G1.1-NN and VXA-GII.4-NS in human are unknown.

No specific antidote for overdose is known. Study subjects should be managed with appropriate supportive care if overdose occurs.

6.10. Concomitant Medications and Other Therapies

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

Use of concomitant medication from 4 weeks before Day 1 through Day 29 (completion of Active Study period) must be recorded onto the eCRF from the subject'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.

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.

7. SCHEDULE OF TRIAL PROCEDURES AND ASSESSMENTS

7.1. Trial Procedures

A schedule of trial procedures and their timing are summarized in the SoA (Table 1). The day of the first investigational product vaccination is considered to be Day 1.

7.1.1. Procedure to be followed on Screening Period (Day -45 to Day -1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the subject. Each signature on the ICF must be personally dated by the signatory. A copy of the signed and dated ICF must be given to the subject. The source data must reflect that the informed consent was obtained before participation in the study.

After obtaining signed copy of written informed consent from the subject, the subject will undergo screening procedures as mentioned below:

- The demographic information (i.e., age, ethnic origin, race, height (cm), body weight (kg), and body mass index (kg/m^2) will be recorded.
- Obtain history of drug abuse, alcohol abuse, and blood or plasma donation.
- Obtain any medical history of clinical significance and details of any medications currently taken.
- Measure vital signs, including blood pressure, pulse rate and respiratory rate after resting in a sitting position for at least 5 minutes.
- Measure subject's temperature (oral). Oral temperature is preferred for all visits. If unavailable, it is acceptable for clinical study sites to measure subject's temperature according to site usual standard using tympanic thermometer instead of oral and this should be clearly documented. All subjects must use the study-provided thermometer for daily oral temperature checks for solicited symptoms in the week following vaccine dose.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; cardiovascular; respiratory; gastrointestinal (GI); musculoskeletal; extremities; neurological; and lymph nodes.
- Perform a serum pregnancy test for all subjects at screening. At screening all women will have a negative serum HCG. (Prior to dosing all women will have a negative urine HCG.)
- Verify understanding of and compliance with protocol requirements for contraception (see Appendix 4).
- Perform an alcohol test.
- Verify understanding of requirement for breastmilk and infant stool collection.
- Ensure that all inclusion criteria are met and that none of exclusion criteria are met for the subject and her infant.
- Obtain a urine sample for urine drug screen test.

- Collect a blood sample to determine the subject's Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) status.
- If the subject and her infant pass all the inclusion and exclusion criteria at the end of the screening visit:
    1. Provide a manual breast pump set. Teach the subject how to use a manual breast pump properly.
    2. Provide kits with instructions for breastmilk sample collection, storage, and return. Teach the subject how to express breastmilk to provide a total of 10 ml of breastmilk from the right breast for each sample collection. Instruct the subject to consistently collect breastmilk samples from the right breast. (The subject can use a manual or electric breast pump if she does not wish to manually express her breastmilk. If the subject is unable to express or pump breastmilk from the right breast, she can collect breastmilk from the left breast and must consistently collect breastmilk samples from the left breast.)
    3. Provide kits with instructions for infant stool sample collection, storage, and return. Teach the subject how to properly collect the infant stool sample and store it until the samples are ready to be shipped.
    4. Timepoints for breastmilk and infant stool sample collection must be thoroughly discussed with the subject. The subject must collect breastmilk sample and infant stool sample (15ml) at baseline prior to the first dose (Day -2 to Day 1).

7.1.2. Procedure to be followed during Active Study Period (Day 1 to Day 29)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensuring that procedures listed prior to administration of the vaccine are conducted prior to that administration. The site does not need to wait the full 45 day screening period to start the active study period for the subject.

- The Principal Investigator will ensure that all inclusion criteria and none of the exclusion criteria for the subject and her infant are met on Day1.
- Ensure the subject collected baseline breastmilk sample (10ml) and infant stool sample between D-2 to D1. Review with the subject how the collection was done and if the samples were properly stored, prior to vaccination. If this was not done, the subject will need to reschedule the dosing visit ASAP and be reminded to collect baseline samples prior to the rescheduled visit.
- A urine pregnancy test will be done for all subjects; site must confirm negative result before dosing.
- Perform an alcohol test and site must confirm negative result before dosing.
- Vital signs will be obtained, including temperature, blood pressure, pulse rate and respiratory rate after resting in a sitting position for at least 5 minutes.
- A targeted, and symptom-directed physical examination will be done for all subjects during the active study period visits. At a minimum, assessments of the skin, respiratory system, cardiovascular system, and GI (abdomen, liver, and spleen) will be included.
- The subject's randomization number will be noted.

- Collect blood, nasal and saliva samples for Immunogenicity assessment prior to study drug administration.
- Site staff member(s) will dispense/administer the investigational product. Please refer to the Pharmacy Manual for further instruction on this process.
- Prior to study drug administration on Day 1, the subject's temperature (oral) will be measured, and a trained member of the site study staff will dispense the tablet(s) constituting the assigned dose to the subject.
- The site staff must observe the subjects for at least 30 minutes after study drug administration for any acute reactions. Any acute reactions are to be recorded in the subject's source documents, on the AE page of the eCRF, as applicable.
- Subjects will be asked to record symptoms of reactogenicity daily for 1 week after study drug administration on Day 1, using the Solicited Symptom Diary; the Solicited Symptom Diary will be collected from the subject on Day 8 and reviewed.
- Subjects will be queried for unsolicited AEs for 28 days following the study drug administration and for SAEs, AESIs and NOCIs for 1 year following the study drug administration.
- Subjects will return to the site on Day 8 and Day 29:

    1. Blood, nasal, and saliva samples will be collected for immunogenicity assessment on Day 8 and Day 29 as specified in the SoA (Table 1).
    2. Ascertain if the subject is still breastfeeding. Ensure the subject has also collected breastmilk sample and infant stool sample during the timepoints specified in the SoA (Table 1), if not then remind the subject. Review with the subject how the collection was done and if the samples were properly stored.
    3. Verify understanding of and compliance with protocol requirements for contraception (see Appendix 4).

- The subject will be asked to contact the site staff or Investigator if an AE (e.g., doctor's visit, emergency room visit) or hospitalization occurs.
- The subject is to be informed that use of prophylactic antipyretic/pain medication, is not permitted on the day of study drug administration. If antipyretic/pain medication is used after study drug dosing, and if clinically appropriate in the judgement of the Investigator, acetaminophen is preferred over other non-steroidal anti-inflammatory drugs.
- Prior and concomitant medications will be reviewed if the subjects took any during the active study period.
- The subject will be asked to bring the completed Diary to the next visit.
- The subject will be reminded that study staff may contact them to obtain additional information on events entered into the Solicited Symptom Diary.
- Source documents will be completed.
- The Investigator or appropriately qualified designee will review the Diary following vaccination, to evaluate subject compliance and as part of the ongoing safety review. Daily review is optimal during the active Diary period. Any solicited symptom marked as Grade 3 should be specifically reviewed with the subject to ensure they meet the

detailed solicited AE grading criteria in (Table 10) and to evaluate for potential alternative etiology.

- An appointment will be scheduled for the subject to return for the next study visit.
- The Investigator or an authorized designee completes the eCRFs and an unblinded dispenser/administrator will update the investigational product accountability records.
- The subjects will be contacted by phone between site visits on Day 15 to monitor for safety as specified in the SoA (Table 1). If the study personnel are unable to contact the subject with 3 attempts, the study personnel will follow instructions given in Section 5.4.

7.1.3. Procedure to be followed during follow-up period (Day 30 to Day 365)

- Verify understanding of and compliance with protocol requirements for contraception (see Appendix 4).
- Subjects will return to the site on Day 60 and Day 180:
    1. A blood sample will be collected for immunogenicity assessment on D180 as specified in the SoA (Table 1).
    2. Nasal and saliva samples will be collected for immunogenicity assessment on Day 60 and Day 180 as specified in the SoA (Table 1).
    3. Ascertain if the subject is still breastfeeding. If they are then ensure the subject has also collected breastmilk sample and infant stool sample during the timepoints specified in the SoA (Table 1), if not then remind the subject. Review with the subject how the collection was done and if the samples were properly stored.
    4. Collect the most current infant vaccine record on Day 60 or any time after.
- Collect and record SAEs, AESIs and NOCIs.
- Complete the source documents.
- The Investigator or an authorized designee completes the eCRFs.
- Ask the subject to contact the site staff or Investigator if an adverse event (e.g., doctor's visit, emergency room visit) or hospitalization occurs.
- The subjects will be contacted by phone between site visits on Day 120, Day 240, Day 300, and Day 365 to monitor for safety as specified in the SoA (Table 1). If the study personnel are unable to contact the subject with 3 attempts, the study personnel will follow instructions given in Section 5.4.

7.1.4 Follow-up of Subjects with Related AEs or with AEs that Led to Study Discontinuation

Unless the subject refuses further contact, each subject who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or

becomes chronic (even after the end of the subject's participation in the study) if either of the following is true.

- The AE is considered by the Investigator to be related to the product administered.
- The AE caused the discontinuation of the subject from the study.

7.1.5 Unscheduled Visit

At the discretion of PI and/or per subject request to evaluate any of the expected reactogenicity symptoms or any unexpected symptoms of concern, a contact must occur as soon as possible between the subject and the Investigator, or a medically qualified member of the study site staff, to assess if an unscheduled visit is required.

This contact will be recorded in the subject's eCRF. If the subject is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit. Reactogenicity events should be assessed by the Investigator or a medically qualified member of the site staff, such as a study physician or a study nurse, as applicable, to the Investigator's local practice, who will:

- Measure oral temperature.
- Measure the subject's pulse rate (after five minutes of sitting).
- Measure the subject's blood pressure (after five minutes of sitting).
- Assess any events (specify the events of interest) that are present, in accordance with the reactogenicity grading scale.
- Perform a symptom focused physical examination.
- Ask the subject if she attended an emergency room visit or was hospitalized.
- Complete the source documents.
- The Investigator or an authorized designee will complete the eCRF.

The subject will be instructed to contact the site to report any significant illness, AEs, or hospitalization that occurs during the study period.

7.2. Management of Blood/Saliva/Nasal/Breastmilk/Infant Fecal Samples

7.2.1. Blood/Saliva/Nasal/Breastmilk/Infant Fecal Sample Collection

Blood / saliva samples for the assessment of immunogenicity will be collected from the subjects as specified in the SoA (Table 1). Sample collection, storage, and shipping information can be found in the General and Immunogenicity Laboratory Manuals.

7.2.2 Blood/Saliva/Nasal/Breastmilk/Infant Fecal Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of immune response are contained in the study specific Laboratory Manual provided to the site.

7.2.3 Blood/Saliva/Nasal/Breastmilk/Infant Fecal Sample Storage and Shipment

Detailed instructions on blood sample storage and shipment are contained in the study specific Laboratory Manual provided to the site.

7.2.4 Future Use of Stored Specimens and Data

The current trial is an early phase study in which Vaxart's goal is to understand the mechanism of action of the oral NoV vaccine in the prevention of NoV illness, it is important to have samples available for the full characterization of the vaccine. The Sponsor is planning to store blood, saliva, nasal, breastmilk, and infant stool samples post the completion of the study for possible future testing towards the development of a NoV vaccine. This testing includes evaluation of serum antibody titers to NoV and cell-mediated immune responses to NoV. At this time, the exact tests are not known but this will help to further understand how the oral NoV vaccine works in the body and in the prevention of NoV illness. Other immunological assays may be performed to further elucidate the response to our vaccine. These may include cloning the antibodies that are induced following immunization. All samples will use subject identifiers that are coded and will not include subject initials or demographic information. Only Vaxart staff will have access to the samples and data; they will be responsible for providing access to the samples as needed for assays. Samples will be stored at Vaxart or Vaxart's designee in a secured, access-controlled location for at least 05 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested. Samples may be shared with collaborating researchers, but only in relationship to the NoV program. Any data developed externally will only be displayed in a deidentified form as authorized by Vaxart.

8. TRIAL ASSESSMENTS AND PROCEDURES

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
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 subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Subjects who experience any serious or severe TEAEs, 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 Safety Assessment

The safety of the bivalent GI.1 and GII.4 vaccines will be evaluated through the reporting of Solicited Symptoms of Reactogenicity (GI and systemic) for 1 week following the study drug dose and through reporting of frequency, duration, and severity of unsolicited AEs for the next 28 days following the study drug dose. The subjects will then enter the Follow-Up Period after Day 29 and will be monitored for SAEs, AESIs, and NOCIs through Day 365 (Month 12) for safety and duration of immune response. Each SAE, AESI, and NOCI occurrence must be assessed for causality.

AESIs are listed in Appendix 5, the occurrence of these events should be reported to the Sponsor in an expedited manner, similar to SAEs as described in Section 9.

Planned time points for all safety assessments are provided in the SoA (Table 1)

8.1.1 Physical Examination

A complete physical examination evaluating any clinically significant abnormalities in general appearance and within the following body systems: skin; head, eyes, ears, nose, and throat; cardiovascular; respiratory; gastrointestinal (GI) (abdomen; liver and spleen) musculoskeletal; extremities; neurological; and lymph nodes. Height and weight will also be measured and recorded at screening and BMI will be calculated.

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

8.1.2 Vital Signs

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

8.1.3 Clinical Safety Laboratory Tests

See APPENDIX 1: Clinical Laboratory Tests for the list of clinical laboratory tests to be performed for inclusion and exclusion purposes only.

8.1.4 Pregnancy Testing

- Details of all pregnancies in female subjects, will be tested as outlined in SoA (Table 1).
- 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 Section 9.5.4.

8.2 Immunogenicity Assessment

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

8.2.1 Primary Immunogenicity Assessments:

- Serum VP1 specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8 and Day 29
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 29
- Breastmilk VPI specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, , and Day 29
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, to, and from Day 1 to Day 29
- The number of subjects in each dose group that had a 2-fold GMC rise or greater in breast milk VP1 specific IgA (GI.1 and GII.4) between Day 1 and any other timepoint.

8.2.2 Secondary Immunogenicity Assessments:

Serum VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level

    - Geometric mean concentration (GMC) at Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 180
- Breastmilk VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) by dose level
    - Geometric mean concentration (GMC) at Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 60 and from Day 1 to Day 180
- Serum VP1 specific (GI.1 and GII.4) IgG through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, and from Day 1 to Day 180
- Serum Blocking titers 50 (BT50) (GI.1 and GII.4) through 6 months after study drug dose measured by Histo-blood group antigen (HBGA) assay by dose level
    - Geometric mean titer (GMT) at Day 1, Day 8, Day 29, and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, and from Day 1 to Day 180

8.2.3 Exploratory Immunogenicity Assessments:

- Saliva VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Enzyme-linked immunosorbent assay (ELISA) by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, from Day 1 to Day 60, and from Day 1 to Day 180
- Nasal VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Meso Scale Discovery (MSD) by dose level
    - Geometric mean concentration (GMC) at Day 1, Day 8, Day 29, Day 60 and Day 180
    - Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 29, from Day 1 to Day 60, and from Day 1 to Day 180
- Infant stool VP1 specific (GI.1 and GII.4) IgA measured by Enzyme-linked immunosorbent assay (ELISA) by dose level:
    - Geometric mean concentration (GMC) Day 1, Day 29, and Day 60
    - Geometric mean fold rise (GMFR) from Day 1 to Day 29 and from Day 1 to Day 60
- Breastmilk Blocking titers 50 (BT50) (GI.1 and GII.4) measured by Histo-blood group antigen (HBGA) assay by dose level
    - Individual subject titers on samples and some timepoints that have a high likelihood of success, assuming the assay works in breast milk samples
- Breastmilk Enterocyte culture neutralizing antibody titers (GI.1 and GII.4) measured by enterocyte culture
    - Individual subject titers on samples and some timepoints that have a high likelihood of success, under the assumption that the assay works in breast milk samples. At the date of this protocol, only serum GII.4 neutralizing antibodies have been successfully measured

Additional exploratory immunogenicity assays may also be performed to further evaluate the activity of the bivalent GI.1 and GII.4 vaccines. Note that not all sample timepoints may be relevant for some of the analysis, so not all assays may be performed at all timepoints. In particular, because it is unclear if the breast milk matrix will inhibit the analysis of neutralizing antibodies or BT50, those assays may not be feasible.

Sample collection, processing and shipping details are provided within the study specific Laboratory Manuals.

9. ADVERSE EVENTS

9.1 Definition of an Adverse Event, Serious Adverse Event, Suspected Unexpected Serious Adverse Reaction, Adverse Event of Special Interest and New Onset of Chronic Illness

Adverse Event Reporting

Adverse event means any untoward medical occurrence associated with the use of an investigational product, whether or not considered intervention related.

Adverse Events Treatment Emergent Adverse Event

Treatment emergent adverse event (TEAE) is an AE that began after the start of an investigational product or an already present event that worsens either in intensity or frequency following the intervention.

Serious Adverse Event (SAE)

a. An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
   i. Death
   ii. A life-threatening adverse event (at the time of the event; not an event that hypothetically might have caused death if it were more severe)
   iii. Inpatient hospitalization or prolongation of existing hospitalization
   iv. A persistent or significant incapacity or disability which results in a substantial disruption of the ability to conduct normal life functions
   v. A congenital anomaly/birth defect
   vi. Important medical events which based upon appropriate medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
      - Examples of such medical events include but are not limited to allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

b. A preplanned/elective procedure and its associated hospitalization for a pre-existing condition that did not worsen from baseline is not considered an AE/SAE. If the procedure is performed early due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction refers to an adverse event which is assessed by the sponsor and or study investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the investigational product.

Adverse Event of Special Interest (AESIs)

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. For this study, AESIs are serious or non-serious adverse events of scientific and medical concern with potential immune-mediated medical conditions as well as events associated with thrombosis and thrombocytopenia as listed in but not limited to Table 11.

New Onset of Chronic Illness (NOCIs)

New Onset of Chronic Illness 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 Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse reactions (AR). (The phrase "responses to an investigational product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.)

Additional Sponsor Definition

a. Solicited Adverse Events-

i. Solicited adverse events (AEs) are predefined signs and symptoms of reactogenicity for which the subject is specifically questioned, and which are noted by the subject 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

ii. Subjects will utilize a Solicited Symptom Diary issued on the day of the vaccination to record solicited any TEAE daily for the one week following that administration.

b. Unsolicited Adverse Events

i. An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the eCRF in terms of diagnosis and/or onset window post-vaccination; this also includes progression of chronic diseases. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AE.

9.2 Grading of Severity of an Adverse Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the subject'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 subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

9.3 Relationship of Adverse Event Following Immunization to Experimental Vaccine/Vaccine Adverse Event Causality Assessment

The principal investigator will use his or her clinical judgment to assess each and every occurrence of an AE/SAE for causality. A 'reasonable possibility' means there is evidence to suggest a causal relationship between the study drug and the adverse event, and the AE is more likely to be explained by the study drug than by another cause.

The investigator is obligated to consider and investigate alternative causes including underlying disease(s), concomitant therapy, and other risk factors, in addition to the temporal sequence of the adverse event to the administration of the study drug.

The investigator will determine biological plausibility and strength of association by consulting the IB and comparators if applicable in his/her assessment. The investigator will also evaluate the course of event including the reproducibility of the adverse event with subsequent study drug administration (in subjects who are allowed to continue with the study).

For more details refer to Causality Assessment of an Adverse Event Following Immunization (AEFI): User Manual for the Revised WHO Classification Second Edition, 2019 Update link: https://www.who.int/publications/i/item/9789241516990.

All adverse events following immunization (AEFIs) must have their relationship to study drug assessed by the Investigator. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug should be clinically plausible.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study drug) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

In situations where an SAE has occurred with minimal information available to the investigator, the investigator is still required to make an assessment of causality for the event with the transmission of the initial report to the sponsor. If the investigator is uncertain about causality, the adverse event will initially be handled as "related to study intervention" for reporting purposes. Once more clinical information is obtained, the investigator can modify the causality assessment to reflect this new knowledge by sending an SAE follow-up report with the updated assessment.

9.4 Monitoring and Follow-up of AEs, NOCIs, and SUSARs during Trial

9.4.1 Monitoring and Follow-up of SAEs from Day 1 to Day 29 after Vaccination

Following AEs/SAEs, could appear during the entire course of the trial after vaccination. The following symptoms will be captured via Solicited Symptoms during Day 1 to Day 8. After Day 8 they will be captured as unsolicited adverse events. SAEs are captured from the first dose of study product.

- Fever/pyrexia
- Diarrhea
- Nausea
- Vomiting
- Abdominal pain
- Malaise/fatigue
- Anorexia
- Headache
- Myalgia (muscle pain)

9.4.2 Time Period and Frequency for Collecting AE, AESI, NOCIs, and SAE Information

All TEAEs, SAEs, AESIs, and NOCIs will be collected from the time of study drug dose until the follow up visit at the timepoints specified in the SoA (Table 1). TEAEs will be collected through Day 29. SAEs, AESIs, and NOCIs will be collected through Day 365.

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs if they do not have a causal relationship with study participation. There are two situations to note as below:

- If the medical occurrence causes the subject to be excluded from the study, then it must be reported by the investigator. This event will then need to be classified as an "AE not related to the study drug."
- If the medical occurrence is the result of a protocol-specified intervention (prior to study drug dose), including but not limited to washout or discontinuation of usual therapy, diet, or a procedure then these must be reported appropriately as an AE (solicited and unsolicited), SAE, AESI, NOCI, and other reportable safety events by the Investigator.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of being available. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and the Investigator considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

9.4.3 Information for Follow-up of AESIS, NOCIS, and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 5.4).

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, AESIs, NOCIs or SAEs as fully as possible. This may include laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

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

9.5 Reporting of AEs, AESIs, NOCIs, SAEs, SUSARs, Pregnancies, and Death Events

All AEs (solicited and unsolicited), AESIs, NOCIs, SAEs and other reportable safety events that occur after the consent form is signed but before study product administration must be reported by the Investigator if the event causes the subject to be excluded from the study (these will be reported as "AE not related to the study drug") or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

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

Table 7 Adverse Event Reporting Timelines to the Sponsor

Type of Event	TEAE (unsolicited)	TEAE (solicited)	AESI/NOCIs	SAE / SUSAR
Reporting period	From first dose until 4 weeks after last dose of study drug	1 week after each study drug administration	From first dose until EOS	From first dose until EOS
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 page of eCRF	Solicited Symptom Diary	AE page of eCRF	AE page of eCRF

Abbreviations: AE = adverse event; eCRF = electronic Case Report Form; EOS = end of study; AESI = Adverse Event of Special Interest; NOCI= New Onset Chronic Illness; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; TEAE = treatment-emergent adverse event

9.5.1 Adverse Event Reporting

All subjects experiencing AEs after the first dose of study drug, until Day 29 (Active Period), whether considered causally related with the use of the investigational vaccine or not, must be

monitored until symptoms subside, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

All findings must be reported on an adverse event page of eCRF and on the SAE form, if applicable. All findings in subjects experiencing AEs must also be documented in the subject's clinical research records.

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date.
- Serious (Y/N)? If yes, appropriate seriousness criteria must be selected on eCRF and SAE Form.
- Severity.
- Investigator's opinion of the causality (relationship) between the event and administration of investigational vaccine(s) ("related" or "not related").
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.
- Action taken with study treatment (investigational vaccine).,
- Outcome of event.
- For Death cases provide all applicable details (e.g., date and cause of death etc., including autopsy results if available).

9.5.2 Serious Adverse Events Reporting

The Investigator or designee will within 24 hours report to the Sponsor any serious adverse event, whether or not considered study drug related, including those listed in the protocol or Investigator Brochure and must include an assessment of whether there is a reasonable possibility that the study drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must within 24 hours report the event to the Sponsor.

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to

the Sponsor within 24 hours of it being available. The information should be completed as fully as possible and contain the following information at the minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and submit it within 24 hours of receipt. The timelines and procedure for follow-up reports are the same as those for the initial report.

9.5.3 Suspected Unexpected Serious Adverse Reaction Reporting

Suspected unexpected serious adverse reactions (SUSARs) are subject to expedited reporting. The study Sponsor will be responsible for notifying both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation including the Food and Drug Administration (FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, the Sponsor must notify FDA and all participating Investigators in an Investigational New Drug (IND safety report of potential serious risks, from

clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs 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 for the study and will notify the IRB/EC, if appropriate according to local requirements.

9.5.4 Pregnancy Reporting

Details of all pregnancies in female subjects will be collected after the start of study drug as per SoA (Table 1).

- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form (pregnancy form) and submit it to the Sponsor within 24 hours of learning of the female subject pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate up to one month post-partum, and the information will be forwarded to the Sponsor.
- 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 subjects) beyond the resolution of the pregnancy, he or she may learn of an SAE through spontaneous reporting.

Should a female subject become pregnant during the course of the study after dosing, she will continue to be followed for safety and pregnancy outcomes. Subjects who have a positive pregnancy test at Day 1, prior to randomization, will be considered screen failures.

If a subject is found pregnant post study drug administration, the subject will only be monitored for safety.

9.5.5 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.

10. SAFETY OVERSIGHT

10.1. Internal Sponsor Review

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

The lead Medical Monitor will be a physician experienced in the conduct of research clinical studies whose primary responsibility will be to monitor subject safety. The Medical Monitor will be responsible for reviewing the cumulative safety data, including a review of safety laboratory test results and adverse event reporting. The Medical Monitor will be familiar with study-specific data as well as relevant background information about the disease, investigational drug, and target population under study. The Medical Monitor(s) will be empowered to request a SMC safety review which can suspend the study, recommend amendments to the protocol, and/or to request further information.

10.2. Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will be created to provide oversight of the conduct of the trial to ensure the safety of subjects. The committee will consist of independent physicians and/or scientists with vaccine clinical trials experience or expertise, and the Medical Monitor, who does not enroll subjects into the study.

The SMC will be assigned by the Sponsor prior to the beginning of the study and will provide oversight of the study throughout the duration of the study period (Day 1 through Day 365) as needed. Ad hoc meetings will be convened if any predefined stopping rules are met, or any serious vaccine-related events or trends are observed.

The SMC will function in accordance with the following provisions: (1) United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 312.55 and 312.56. (2) ICH E6 and 62 Federal Register 25691 (1997): Good Clinical Practice (GCP) Consolidated Guideline.

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

11. STATISTICAL CONSIDERATION

A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to locking the database. The full details of data presentation and analyses will be provided in SAP.

Additional statistical analyses other than these described in this section may be performed if deemed appropriate and included in the SAP. Any deviations from the final SAP or from what is outlined in the protocol will be discussed in the final study report (CSR).

11.1 Sample Size Determination

A sample size of 76 randomized subjects (30 each in medium and high dose levels and 16 in placebo) is not based on formal statistical testing but rather based on clinical judgement and predicted to yield meaningful safety and immunogenicity results. Placebo was added for safety comparison.

11.2 Multiplicity Adjustment

No multiplicity adjustment will be implemented for this study.

11.3 Population for Analysis

For purposes of analysis, the following analysis sets are defined:

Table 8: Populations for Analyses

Analysis Population	Description
Screened	All subjects who enter screening (assigned a screening number)
Intent to Treat (ITT)	All subjects who are randomized. The analyses using ITT will be based upon the randomization group allocated.
Per Protocol	All subjects in the ITT set who receive one dose and who have not violated any inclusion/exclusion criteria and / or deviated in a way that could influence their Immunogenicity assessments.
Safety	All randomized subjects who receive at least 1 dose of the study drug. Subjects will be analyzed according to the treatment (vaccine) they actually received. All safety analyses will be conducted based on the Safety set.
Immunogenicity	All randomized subjects who receive at least 1 dose of the study drug and have at least one valid immunogenicity result after Day 1. Subjects will be analyzed according to the treatment (vaccine) they actually received. All immunogenicity analyses will be conducted based on the Immunogenicity set.

11.4 Statistical Analysis Plan

11.4.1 General Approach

The SAP will be developed and finalized before database lock and breaking the blind for any of the planned analyses. It will describe the subject sets 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 endpoints.

11.4.2 Analysis of the Primary and Secondary Safety End Points

Safety will be summarized for the safety set (active vs. placebo). Solicited Symptoms of Reactogenicity, unsolicited AEs, SAEs, physical examination, and vital signs will be summarized descriptively by treatment group and study visit.

Analyses will be performed for the total set (active vs. placebo). All results will be presented descriptively and summarized by treatment groups.

Endpoint	Statistical Analysis Methods
Primary (measured from Day 1 through Day 29)	Frequency, duration, and severity of Solicited Symptoms of Reactogenicity (local, systemic) measured daily for 1 week following vaccination. Frequency, duration, and severity of unsolicited AEs, and SAEs through the active period (4 weeks post dose). Descriptive statistics will be provided for each reactogenicity endpoint for each dose. 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 subjects with the indicated endpoint and the associated Clopper-Pearson 95% CIs. AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA®) terms. Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any TEAEs for each vaccine group as well as the placebo group. SAEs will be categorized according to MedDRA® terms. The safety analyses are based on the safety set. Subjects will be summarized by vaccine group and placebo according to the study drug they actually received. Missing reactogenicity Diary data will not be imputed; missing TEAE dates will be handled according to the rules determined in the SAP.
Secondary (measured through Day 365)	Frequency, duration, and severity of SAEs, AESIs and NOCIs for 1 year following the study drug dose.

11.4.3 Analysis of Primary, Secondary, and Exploratory Immunogenicity and Endpoints

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

Immunogenicity samples will be drawn for all subjects. 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 sets.

An additional analysis will be performed based on the all-available sets if there is a large enough difference in sample size between the all-available immunogenicity set and the evaluable immunogenicity set.

Immunogenicity will be summarized by the total set (active vs. placebo). For all endpoints, all measures will be analyzed comparing the two active vaccine groups. The immunogenicity set will be used for this analysis. All results will be presented descriptively and summarized by treatment groups.

Endpoint	**Statistical Analysis Methods**
Primary (Key Immunogenicity Endpoints measured from Day 1 through Day 29)	Serum and breastmilk VP1 specific IgA for both GI.1 and GII.4 by Meso Scale Discovery will be summarized descriptively through the active period (4 weeks post dose).
Secondary (measured through Day 180)	Serum VP1 specific IgA and IgG for both GI.1 and GII.4 by Meso Scale Discovery will be summarized descriptively through 6 months post dose. Serum Blocking titers 50 (BT50) (GI.1 and GII.4) by Histo-blood group antigen (HBGA) assay will be summarized descriptively through 6 months post dose. Breastmilk VP1 specific IgA for both GI.1 and GII.4 by Meso Scale Discovery will be summarized descriptively through 6 months post dose.
Exploratory	For specific exploratory immunogenicity endpoints please refer to Section 8.2-Immunogenicity Assessments- Exploratory Immunogenicity Assessments.

11.4.4 Baseline Descriptive Statistics

Demographic data, baseline characteristics, physical examination, concomitant medications, medical history data and study medication exposure will be summarized by treatment group.

11.4.5 Tabulation of Individual Subject Data

By subjects listing will be produced for each variable by treatment group and study visit.

12. ETHICAL CONSIDERATIONS

12.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences [CIOMS] 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.2 Institutional Review Board

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/EC should be retained in the Investigator file.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/IEC and Sponsor in writing immediately after the implementation.

They should also be informed of any event likely to affect the safety of the subjects or the continued conduct of the clinical study, in particular any change in safety. All updates to the IB will be sent to the IRB/IEC and to Health Authorities (Competent Regulatory Authority), as required by local regulation. A progress report is sent to the IRB/IEC at least annually and a summary of the study's outcome at the end of the clinical study.

12.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the subject will be asked to read and review the document. The Investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent documents for herself and her infant prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the forms signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to

them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If the trial is involving vulnerable population, video recording of entire informed consent process should be ensured depending on the norms of respective country's regulatory authorities.

12.4 Insurance Compensation

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IRB/IEC or regulatory authorities in countries requiring this document.

12.5 Stipends/Rewards/Compensation for Participation

Subjects may be provided with a stipend according to local practice to compensate for the time and travel required for study visits and procedures. Participating subjects will be given a manual breast pump set.

12.6 Subject Confidentiality

Subject confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor. All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the Subjects in this study. The clinical study site will permit access to such records.
The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at sponsors designated vendor. This will not include the subject's contact or identifying information. Rather, individual Subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by designated vendor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

12.7 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable regulatory authority in any area of the world, or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Sponsor should be informed immediately.

In addition, the Investigator will inform Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

13. DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for validation of the clinical data. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. All information on the CRF will be traceable to these source documents, which are generally maintained in the subject's study file.

The source documents will include a copy of the signed Informed Consent/ Health Insurance Portability and Accountability Act (HIPAA) authorization. The source document data collection forms for screening. Outpatient visits and AEs will also serve as CRF data collection instruments.

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Source documents are maintained for recording data for each subject enrolled in this clinical trial. Study subjects' data collected on the CRF during the trial will only be identified by subject number. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both the Sponsor and the Investigator are bound to keep this information confidential.

13.2 Case Report Forms (CRF)

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Vaxart and should not be made available in any form to third parties, except for authorized representatives of Vaxart or appropriate regulatory authorities, without written permission from Vaxart.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents)

and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required.

The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

13.3 Data Collection and Management Responsibility

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each subject enrolled in the study.

Data recorded in the eCRF/CRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a data capture system that is 21 CFR Part 11-compliant. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.4 Record Retention

Study documents should be retained for a minimum of 10 years after the last approval of a marketing application in an International Conference on Harminosation (ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 10 years have elapsed since the formal discontinuation of clinical development of the study drug.

These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

13.5 Property Rights and Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that their 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

subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that their 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.

All information, data and documents including results and investigational products provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Early Safety Data Review AND/OR Committee

Subject safety will be continuously monitored by the Sponsor or designee, which includes safety signal detection during the study.

All safety data collected will be summarized and reviewed by the sponsor's internal/external safety monitoring committee for agreement of next steps.

In particular, data will be reviewed by the sponsor for identification of the following events that would potentially contribute to a requirement to [pause/stop] the study.

- One or more subjects experiences a treatment-related serious adverse event (SAE) of any grade
- Two or more subjects experience the same treatment-related grade ≥3 solicited symptom within one week following vaccination.
- Two or more subjects experience the same treatment-related unsolicited grade "severe" AE between Day 1 and Day 29 (Active Period).

Enrollment will be paused during the review. If a pausing/stopping rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume. If no dose-related toxicities are observed, and upon the recommendation of the SMC following review of safety data, enrollment of the remaining subjects will be initiated.

14.2 Clinical Trial Site Monitoring

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

- Monitoring for this study will be performed by the Sponsor or designee

- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- If needed, independent audits will be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

14.3 Audit and Inspection

The trial site also may be subject to quality assurance audits by the Sponsor or designees.

For the purpose of ensuring compliance with the clinical study protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on behalf of the Sponsor and inspection by regulatory authorities.

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

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified, and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.4 Responsibility of Investigator

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all trial procedures provided by the Sponsor (including security rules).

The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, discrepancy resolution form, or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to the Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the subject's data to be transferred. The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical study in accordance with the clinical trial protocol.

All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

To 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.

To notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Signed copy of Investigator's undertaking should be provided as an appendix.

14.5 Responsibility of Sponsor

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical study as regards ethics, clinical study protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical study.

At regular intervals during the clinical study, the site will be contacted, through monitoring visits, letters, or electronically, by a representative of the monitoring team to review study progress, Investigator and subject compliance with clinical study protocol requirements, and any emergent problems.

These monitoring visits will include but not be limited to review of the following aspects: subject's informed consent, subject recruitment and follow-up, SAE documentation and reporting, AE documentation, IP allocation, IP accountability, concomitant therapy use, and quality of data.

14.6 Protocol Deviation

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Details can be found in the study specific Protocol Deviation Plan or the Clinical Monitoring Plan.

15. PUBLICATION AND DATA SHARING 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.

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Appendix 1: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory, unless otherwise specified.
- Protocol-specific requirements for inclusion or exclusion of subject 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 9 Protocol-Required Laboratory Assessments

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 subjects serum pregnancy tests at screening Female subjects Point-of-Care urine pregnancy tests prior to dosing at Day 1 Alcohol test at screening and prior to dosing on Day 1

Appendix 2: Country-specific Requirements

Not applicable.

Appendix 3: Adverse Events Grading

Grading of Solicited Adverse Events

Subjects should be instructed to rate Solicited Symptoms of Reactogenicity that are collected within their Solicited Symptom Diary based on the severity scale presented in Table 10.

Table 10 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 (muscle pain)	None	AE easily tolerated, causing minimal discomfort and does not interfere with everyday activities[a]	Adverse event sufficiently discomforting to interfere with everyday activities	Adverse event 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	None	No interference with activity or 1 to 2 episodes	Some interference with activity or >2 episodes	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Vomiting	None	No interference with activity or 24 hours	Some interference with activity or 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 activity include attendance at work, school, and usual habits of the subjects.

Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Contraceptive Guidance

- Contraceptive use by women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. Subjects must be willing to use a highly effective form of contraception for 30 days prior to vaccination and until 60 days after the vaccination. Acceptable forms are oral, implantable, intrauterine, transdermal, intravaginal, injectable, double barrier or abstinence (subjects using diaphragms must also use condom). A reliable form of contraception must be approved by the Investigator.
- While abstinence is allowed, periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- A negative pregnancy test will be required for all female subjects prior to study drug administration, as outlined in the SoA (Table 1).

Collection of Pregnancy Information

Female subjects who become pregnant:

- The investigator will attempt to collect pregnancy information on any female subjects.

After obtaining the necessary signed ICF from the pregnant female subject, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy. The Sponsor will attempt to follow the female subject 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 subject 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.

Appendix 5: ADVERSE EVENTS OF SPECIAL INTEREST

An Adverse event of special interest (AESI) is a serious or non-serious adverse events of scientific and medical concern for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is indicated. The following adverse events (AEs) for potential immune-mediated medical conditions as well as events associated with thrombosis and thrombocytopenia are AEs of special interest (AESIs) and include new onset of chronic illness (NOCIs). These events should be monitored for actively and reported to the Sponsor in an expedited manner as outlined in *Section 9.*

Table 11: Adverse Events of Special Interest

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 angitis), 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

APPENDIX 6: SUMMARY OF CHANGES TO PROTOCOL

PROTOCOL VXA-NVV-108 HISTORY

Name of the Document with Version Number	Date	Summary of Changes and Rationale
VERSION 1.0	17 FEB 2023	INITIAL VERSION
VERSION 2.0	25 JUL 2023	

VXA-NVV-108 Protocol Amendment 1, Version 2.0 <DATE>

Protocol Amendment 1 (Version 2.0) of this phase 1 Norovirus GI.1/G2.4 bivalent protocol (VXA-NVV-108) was finalized on 17 Feb 2023, approved by the regulatory authority, South African Health Products Regulatory Authority, on 19 May 2023 and by the independent ethics committees which also serve as central ethics committees, Pharma Ethics Independent Research Ethics Committee on 14 June 2023 and the University of the Witwatersrand's Human Research Ethics Committee on 27 June 2023. It is being amended to clarify visit procedures, update language on contraception, update language on immunogenicity assessment, administrative updates throughout the protocol and correct other minor typographical errors. A description of the changes along with a brief rationale for each change is presented in the table below.

Section No. & Title	Description of Change	Brief Rationale
footer	Updated all footers-page numbers	Correct typos and pagination errors
Cover Page and headers and Signature Page	Updated Protocol Version and Date	Correct Protocol Version and date
Protocol Version History	**Original Text:** 12 Oct 2022 Page 78 **Updated Text:** 17 Feb 2023 Page 78	Updated typographical error
Table of Contents	Updated Table of Contents	Added Appendix 6 -Summary of Changes to the Protocol
Protocol Synopsis	**Current Text:** TBD CRO **Updated Text:**	Administrative detail updated

	[redacted]	
Protocol Synopsis-Eligibility Criteria and **Section 5.1 inclusion Criteria**	**Updated Exclusion Criteria #8** **Original Text:** The nursing infant is the product of a singleton pregnancy AND does not have any of the following **Updated Text:** The nursing infant is the product of a singleton pregnancy AND does not have any of the following *(therefore, subjects must be willing to provide the infant's medical record at screening and Day 1 and the infant's updated vaccine record at Day 60 or later):*	Clarification to collect infant medical record at screening and Day 1and to provide infant vaccination record at Day 60 or later
Protocol Synopsis-Eligibility Criteria **and** **Section 5.1 Inclusion Criteria**	**Updated Exclusion Criteria #21** **Original Text:** Use of medications known to affect the immune function (including but not limited to systemic corticosteroids, leukotriene modifiers, and JAK inhibitors) within 2 weeks before study drug administration or planned use during the active study period. **Updated text:** Use of medications known to affect the immune function (including but not limited to systemic corticosteroids, leukotriene modifiers, and JAK inhibitors) within 2 weeks before study drug administration or planned use during the active study period. *Ophthalmic, inhaled, and intranasal steroids should follow these restrictions.*	**Clarifications to the use of medications known to affect immune function**
1.1 Schedule of Trial Activities Table 1.0 Schedule of Activities	**Added following text to Notes:** * Also collect the infant's medical record at screening and day 1 and the infant's updated vaccine record at D60 or later	

	Removed the following procedure from the SOA grid: Remove breast milk from D15, Month 4	
Section 3.2.1 Primary Endpoints **Immunogenicity**	Breastmilk VPI specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level Removed Day 15 from GMC and removed Day 1 to Day 15 GMFR	
Section 3.2.2 Secondary Endpoints **Immunogenicity**	Breastmilk VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) by dose level Removed Day 120 from GMC and removed Day 1 to Day 120 GMFR	
Section 7.1.1. Procedure to be followed on Screening Period (Day -45 to Day -1)	**Current Text** The subject can use a manual breast pump if she does not wish to manually express her breastmilk. Timepoints for breastmilk and infant stool sample collection must be thoroughly discussed with the subject. The subject must collect breastmilk sample and infant stool sample at baseline prior to the first dose (Day -2 to Day 1). **Updated Text:** The subject can use a manual **or electric** breast pump if she does not wish to manually express her breastmilk. Timepoints for breastmilk and infant stool sample collection must be thoroughly discussed with the subject. The subject must collect breastmilk sample and infant stool sample **(15ml)** at baseline prior to the first dose (Day -2 to Day 1). **Removed text:** Teach the subject how to properly freeze her milk after expression each time until all samples are collected and shipped.	Allow more flexibility for methods subject can use to provide breastmilk samples Breastmilk will be collected on site instead of home due to difficulty collecting and storing breastmilk properly and difficulty with transport of home collection to site in the required timeframe Provided volume of stool sample required.

7.1.2 Procedure to be followed during Active Study Period (Day 1 to Day 29)	**Current Text:** **…**breastmilk sample (5ml-10ml) …and to remind the subjects to collect and store breastmilk samples **Updated Text:** Ensure the subject collected baseline breastmilk sample (10ml) and infant stool sample between D-2 to D1. **Removed Text:** deleted "5ml" deleted "and to remind the subjects to collect and store breastmilk samples."	Subjects not required to collect breastmilk samples at home due to logistics as mentioned previously
7.1.3 Procedure to be followed during follow-up period (Day 30 to Day 365)	**Updated Text (added number 4)** 4. Collect the most current infant vaccine record on Day 60 or any time after. **Removed Text (bullet 7):** For Day 120, determine if the subjects are still breastfeeding; if yes then remind the subjects to collect and store breastmilk samples	Required for inclusion criterium 8c assessment. Breastmilk will not be collected at home due to difficulty collecting and storing breastmilk properly and difficulty with transport of home collection to site in the required timeframe
8.1.4 Pregnancy Testing	**Current Text:** 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 Section 9.1.7. **Updated Text:** If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours	Correct section specified with link retained for 9.5.4 (page 48). Edited for accuracy.

	of learning of the pregnancy and should follow the procedures outlined in Section ***9.5.4.***	
8.2.1 Primary Immunogenicity Assessments:	**Current Text:** Breastmilk VPI specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level Geometric mean concentration (GMC) at Day 1, Day 8, Day 15 and Day 29 Geometric mean fold rise (GMFR) from Day 1 to Day 8, from Day 1 to Day 15, and from Day 1 to Day 29 **Current Text:** Breastmilk VPI specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level Geometric mean concentration (GMC) at Day 1, Day 8 and Day 29 Geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 29	Align with Schedule of Activities and intended immunogenicity analysis
8.2.2 Immunogenicity Assessments:	**Current Text:** Immunogenicity Endpoints **Updated Text:** Secondary Immunogenicity Endpoints **Current Text:** Breastmilk VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) by dose level	Added "Secondary" to Immunogenicity Assessments to categorize objectives more clearly and appropriately. Align with Schedule of Activities and intended immunogenicity analysis

	Geometric mean concentration (GMC) at Day 60, Day 120 , and Day 180 Geometric mean fold rise (GMFR) from Day 1 to Day 60, from Day 1 to Day 120, and from Day 1 to Day 180 **Updated Text:** Breastmilk VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) by dose level Geometric mean concentration (GMC) at Day 60 and Day 180 Geometric mean fold rise (GMFR) from Day 1 to Day 60, and from Day 1 to Day 180	
11.4.3 Analysis of Primary, Secondary, and Exploratory Immunogenicity and Endpoints	**Current Text:** Immunogenicity samples will be drawn for all subjects **and their infants**. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose. **Updated Text:** Immunogenicity samples will be drawn for all subjects. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.	Deleted "and their infants." Clarified we will not be collecting serum from infants
14.1 Early Safety Data Review AND/OR Committee	**Current Text:** Two or more subjects experience the same treatment-related unsolicited grade ≥3 AE between Day 1 and Day 29 (Active Period). **Updated Text:**	There is no numerical grade for unsolicited AEs.

	Two or more subjects experience the same treatment-related unsolicited grade "severe" AE between Day 1 and Day 29 (Active Period).	
Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	**Updated Text (added):** Contraceptive Guidance Contraceptive use by women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. Subjects must be willing to use a highly effective form of contraception for 30 days prior to vaccination and until 60 days after the vaccination. Acceptable forms are oral, implantable, intrauterine, transdermal, intravaginal, injectable, double barrier or abstinence (subjects using diaphragms must also use condom). A reliable form of contraception must be approved by the Investigator. While abstinence is allowed, periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. A negative pregnancy test will be required for all female subjects prior to study drug administration, as outlined in the SoA (Table 1).	Added to emphasize which contraceptive method is allowed and to clarify that periodic abstinence is not allowed Contraceptive Guidance. Moved to correct section