Protocol Number: VXA-NVV-202

Official Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Single Dose, Dose-ranging Study to Determine the Safety and Immunogenicity of Bivalent GI.1 and GII.4 Vaccine Administered Orally to Healthy Volunteers Aged ≥ 18 Years and ≤ 80 Years Old

NCT Number: NCT05626803

Document Date: 22 February 2023

Clinical Study Protocol

Protocol Title:	A phase 2, multicenter, randomized, double-blind, placebo-controlled, single dose, dose-ranging study to determine the safety and immunogenicity of bivalent GI.1 and GII.4 vaccine administered orally to healthy volunteers aged ≥ 18 years and ≤ 80 years old.
Protocol Number:	VXA-NVV-202
IND Numbers:	BB-IND 16796
Product Names:	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] Ph: [redacted]; Email: [redacted]
Medical Monitor	[redacted] Ph: [redacted] Email: [redacted] [redacted] Ph: [redacted] Email: [redacted]
Protocol Version and Version Date	2.0 09 Feb 2023

Prior Version 1.0 13-Oct-2022

Protocol Title: A phase 2, multicenter, randomized, double-blind, placebo-controlled, single dose, dose-ranging study to determine the safety and immunogenicity of bivalent GI.1 and GII.4 vaccine administered orally to healthy volunteers ≥ 18 years and ≤ 80 years old.

Protocol Number: VXA-NVV-202

Amendment Number: 2.0

Date of Amendment (Optional): .09 Feb 2023

IND Number: BB-IND 16796

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

Phase: II

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

Funding Sponsor: Vaxart, Inc.

SIGNATURE

PROTOCOL TITLE: A phase 2, multicenter, randomized, double-blind, placebo-controlled, single dose, dose-ranging study to determine the safety and immunogenicity of bivalent GI.1 and GII.4 vaccine administered orally to healthy volunteers ≥ 18 years and ≤ 80 years old.

PROTOCOL NUMBER: VXA-NVV-202

PROTOCOL VERSION (Amendment): Not applicable

Signature of Sponsor's authorized representative(s):

[redacted]

2/22/2023

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 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	International units
LAR	Legally Accepted Representative
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	Vaccine Protein 1, major capsid protein of norovirus
WHO	World Health Organization

1. Protocol synopsis

Trial Title: A phase 2, multicenter, randomized, double-blind, placebo-controlled, single dose, dose-ranging study to determine the safety and immunogenicity of bivalent GI.1 and GII.4 vaccine administered orally to healthy volunteers aged ≥ 18 years and ≤ 80 years old.

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

Contract Research Organization: [redacted]

Protocol number	VXA-NVV-202	**IND Number**	BB-IND 16796
Trial Blinding scheme	Double-blind	**Phase of study**	2

Trial Arms:

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=50)

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=50) (sentinel n=10)

Arm 3: Placebo tablets (n= 25)

Description of Investigational Product:

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

- 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)

Dose Regimen: 5×10^{10} IU and 1×10^{11} IU per strain per dose

Route: Oral

Dosage Form: Tablet

This study will investigate the safety and immunogenicity of two monovalent Norovirus (NoV) oral tableted vaccine candidates co-administered (bivalent delivery) against a matching placebo arm. All lots of Drug Product (DP) will be provided as small white enteric-coated tablets.

VXA-G1.1-NN and VXA-GII.4-NS are E1/E3-deleted, replication-incompetent, adenovirus 5 vaccine vectors designed for use as vaccines for prevention of NoV infection. The vaccine vectors encode for a full-length VP1 gene of either Norwalk virus (VXA-G1.1-NN vaccine) or Sydney virus (VXA-GII.4-NS vaccine). In addition to the transgene cassette, a second hCMVie promoter is also present in the vaccine constructs which is used to express a ribonucleic acid (RNA) sequence that acts as an adjuvant. The adjuvant is a short hairpin RNA expressed off a promoter such that only target cells in the intestine that express antigen will also express the adjuvant. This is likely to result in a tight association of antigen with adjuvant in vivo.

Multiple tablets of study intervention will be dispensed to allow delivery of the intended vaccine dose. A matching number of placebo tablets will be dispensed to maintain the study blinding.

Subject Population:

Ten (10) sentinel healthy adult male and female subjects aged ≥ 18 years and ≤ 80 years will be enrolled into an open label portion of the study.

One hundred and twenty -five (125) healthy adult male and female subjects aged ≥ 18 years and ≤ 80 years will be enrolled in a double-blind randomized portion of the study.

Objectives:

Primary Objective:

To determine the safety and immunogenicity of a bivalent dosing regimen of GI.1 and GII.4, to select the dose level with which to safely proceed into Phase 3 development.

Endpoints:

Primary Endpoints:

Safety:

- Frequency, duration, and severity of Solicited Symptoms of Reactogenicity (GI and systemic) for 1 week following study intervention dose
- Frequency, duration, and severity of unsolicited adverse events (AEs) for 28 days following the study intervention dose

Immunogenicity:

- Serum - Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

- Serum - Anti-VP1 GI.1 IgG and Anti-VP1 GII.4 IgG by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

- Serum - Antibody BT50 titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA) Assay
  - geometric mean titer (GMT) Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

Exploratory Endpoints:

Safety:

- Frequency, duration, and severity of serious adverse event (SAEs), adverse event of special interest (AESIs) and New Onset of Chronic Illness (NOCIs) for 1 year following the study drug dose

Immunogenicity:

- Serum - Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 8 and Day 180
  - geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Serum - Anti-VP1 GI.1 IgG and Anti-VP1 GII.4 IgG by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 8 and Day 180
  - geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Serum - Antibody BT50 titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA) Assay
  - geometric mean titer (GMT) Day 8 and Day 180
  - geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Nasal Swab – Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA
  - 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, Day 1 to Day 29 and from Day 1 to Day 180

- Saliva – Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA
  - 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, Day 1 to Day 29 and from Day 1 to Day 180

- Fixed Whole Blood (required for blood draw, optional for testing)
  - B-cell immunophenotyping at Day 1 and Day 8

Trial Rationale

An effective NoV vaccine must prevent the two most common NoV genotypes, GI.1 and GII.4. This vaccine consists of VXA-G1.1-NN and VXA-GII.4-NS; the dose of the vaccine is 5×10^{10} IU and 1×10^{11} IU per strain per dose. GI.1/GII.4 bivalent vaccine is used to prevent illness from NoV.

Noroviruses are a genetically diverse group of small, non-enveloped, single-stranded positive sense Ribonucleic acid (RNA) viruses belonging to the *Caliciviridae* family. Norovirus infections are a leading cause of sporadic and epidemic gastroenteritis across all age groups worldwide. There is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease, including prophylactic measures, such as vaccines.

A unique and advantageous immune response elicited by oral vaccination is the induction of antibodies derived from mucosal cells. Given that the mucosal route of immunization produces superior mucosal immunity compared to injected vaccines, it is hypothesized that GI.1/GII.4 bivalent oral vaccine may enable higher degrees of mucosal protection against infection when compared to a parenteral immunization method The current Phase 2 dose confirmation study is designed to assess the safety and immunogenicity of GI.1/GII.4 bivalent vaccine with a single vaccine dose in healthy volunteers (≥18 years and ≤80 years).

Description of Sites/Facilities

This will be a multi-center trial conducted in the United States of America. The name of Investigators and sites are provided on the site -specific Form FDA 1572 document.

Trial design

This is a multi-center, double-blind, randomized, placebo-controlled, single dose regimen, dose ranging study in healthy volunteers (≥18 years and ≤80 years). The study will enroll 10 sentinel subjects in an open label period and randomize 125 subjects in three double-blind arms.

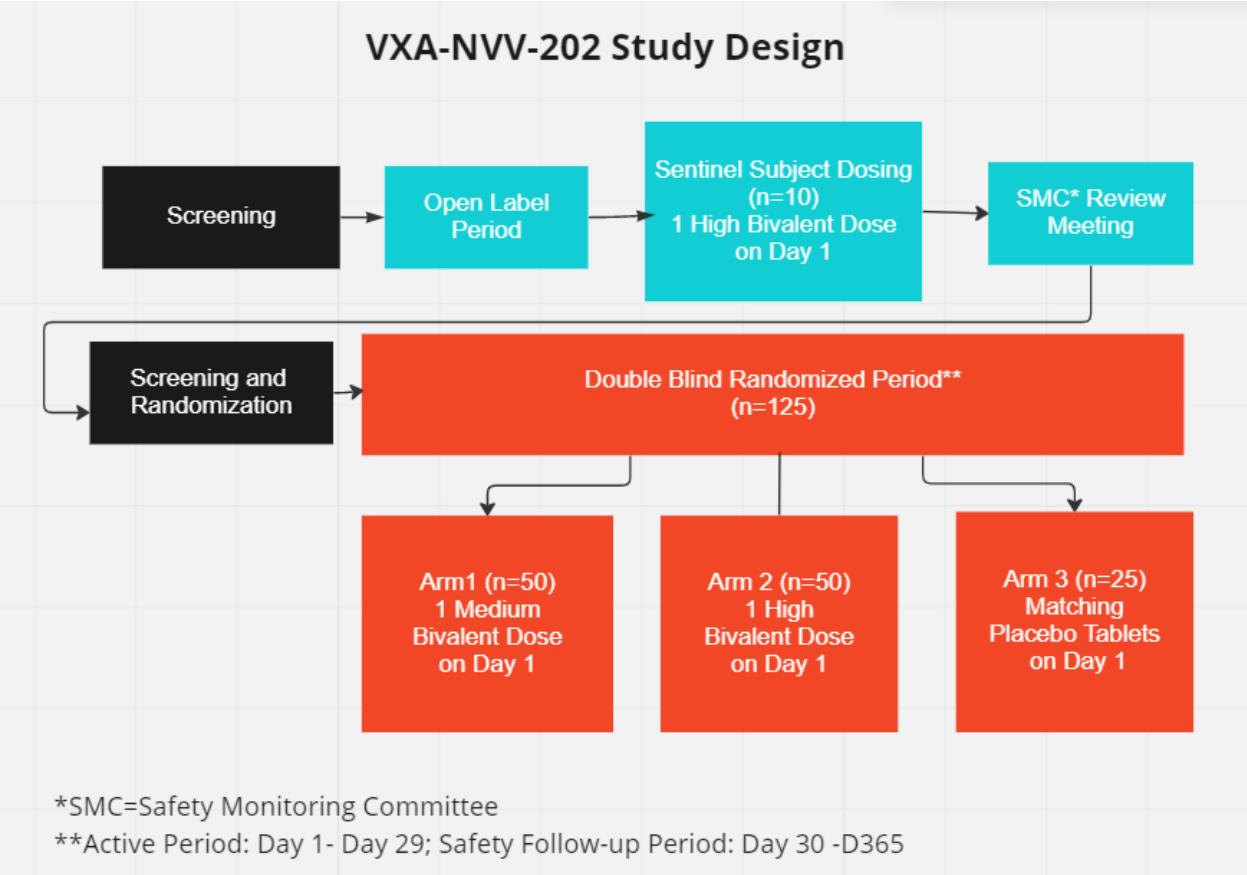
After reviewing and signing an informed consent, the subjects will undergo screening assessments to determine study eligibility up to a 45-day Screening Period.

The first 10 sentinel subjects will receive open label high dose of active vaccine (2×10^{11} IU). If no dose-related toxicities are observed, and upon the recommendation of the Safety Monitoring Committee (SMC) following review of Day 1 through Day 8 safety data, enrollment of the remaining subjects will be initiated. The sentinel subjects will be enrolled in a staggered design, in which no more than two (2) subjects are dosed per 24-hours. All sentinel subjects will be observed on site, for safety at least 2 hours post dose. After the ten (10) sentinel subjects have completed Day 8 post dose, and if no dose-related toxicities are observed, and upon the recommendation of the Safety Monitoring Committee (SMC) following review of safety data up to one week post dose, enrollment of the randomized double-blind study will be initiated. While ten (10) subjects will be dosed in the sentinel group, to allow for dropouts, eight (8) subjects with complete safety data (defined as Day 1 to Day 8) will be enough to convene the SMC.

If pre-established stopping rules are met, enrollment of subsequent subjects will be halted until the SMC has completed the review of all available safety data and provides recommendation for further study conduct.

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 or placebo, as follows (Figure 1):

Figure 1 Study Design



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 or app between site visits to monitor for safety as specified in the SoA (Table 1).

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 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 he/she remains in the study through Day 365 (Month 12). Following completion of the Day 365 a tele-health appointment will be conducted 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 both) for 1 week following the study drug dose (until Day 8 (+2 days)-scheduled site visit (the sentinel subjects do not have a Day 8 (+2) window)). and unsolicited AEs for 28 days post study drug dose (until Day 29-scheduled site visit)) 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 and duration of immune response. Subjects will also have samples collected for evaluation of immunogenicity as specified in the SoA (Table 1).

Planned Number of Subjects:

A total of 10 healthy adult male and female subjects aged ≥18 years and ≤80 years will be enrolled to the high dose investigational vaccine during the open label portion of this study.

A total of 125 healthy adult male and female subjects aged ≥18 years and ≤80 years will be, randomized, in a 2:2:1 fashion, to receive the investigational vaccine or placebo during this study.

Eligibility Criteria

Inclusion Criteria:

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

Age

1. ≥18 to ≤80 years old inclusive at the time of signing the Informed Consent Form (ICF). -

Type of Subjects

2. In stable and good general health, without significant medical illness, based on medical history, physical examination, and vital signs at screening based on investigator judgement.
3. Body mass index (BMI) ≥ 17.0 and ≤ 35.0 kg/m^2 at screening.
4. Available for all planned visits and tele-health appointments, and willing to complete all protocol-defined procedures and assessments (including ability and willingness to swallow multiple small enteric-coated tablets per study dose).

Gender and Reproductive Considerations

5. Male or female subjects
   a. Female subjects must not be breastfeeding and must provide a negative pregnancy test at screening and pre-dose.
   b. Female subjects must fulfill one of the following criteria:
      i. At least 1 year post-menopausal (defined as amenorrhea for ≥ 12 consecutive months prior to screening without alternative medical cause) or surgically sterile.
      ii. Female subjects of childbearing potential must be willing to use a highly effective form of contraception for 30 days prior to initial vaccination and until 60 days after last 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.
      iii. Male subjects must agree to refrain from donating sperm and practice abstinence from all intercourse or to use an effective method of double barrier birth control or condom as noted above from first vaccination to 60 days after last vaccination.

Informed Consent

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

Exclusion Criteria:

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

1. Known clotting/bleeding issues and/or personal and family history with increased risk of bleeding or clotting.
2. Presence of significant uncontrolled medical or psychiatric illness (acute or chronic) including institution of new medical/surgical treatment or significant dose alteration for uncontrolled symptoms or drug toxicity within 3 months prior to screening and reconfirmed at baseline.
3. Cancer, or treatment for cancer or any procedure or preventive medication for cancer or to prevent recurrence within past 3 years (excluding fully treated and resolved basal cell carcinoma or squamous cell carcinoma).
4. Presence of immunosuppression or medical condition possibly associated with impaired immune responsiveness, including diabetes mellitus- type 1 and 2.
5. Left blank intentionally.
6. 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. GI 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 disorder
        iii. peptic ulcer
        iv. cholecystectomy
7. History of any form of angioedema.
8. History of serious reactions to vaccination such as anaphylaxis, respiratory problems, hives or abdominal pain.
9. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic.
10. Any condition that resulted in the absence or removal of the spleen.
11. 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).
12. Presence of a fever ≥38.0 °C measured orally at baseline.
13. Any significant hospitalization within the last year which in the opinion of the investigator or sponsor could interfere with study participation.
14. Any of the following history or conditions that may lead to higher risk of clotting events and/or thrombocytopenia:
    a. Family or personal history of bleeding or thrombosis.
    b. History of heparin-related thrombotic events, and/or receiving heparin treatments.
    c. History of autoimmune or inflammatory disease.
    d. Presence of any of the following conditions known to increase risk of thrombosis within 6 months prior to screening:
        i. Recent surgery other than removal/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 infection.

15. Any other condition that in the clinical judgement of the investigator would jeopardize the safety or rights of a subject taking the study drug, would render the subject unable to comply within the protocol or would interfere with the evaluation of the study endpoints diagnostic assessments.
16. Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) or Hepatitis C virus (HCV) tests at the screening visit.
17. History of GI bleeding including hematochezia (blood in stool) or melena (black stool).
18. Positive urine drug screen for drugs of abuse at screening (positive test for marijuana is not exclusionary; however concurrent use of marijuana during the study Active period through Day 29 is prohibited).
19. Positive breath or urine alcohol test at screening and baseline.

Prior/Concurrent Therapy

20. Receipt of a licensed vaccine (including any COVID-19 vaccines under Emergency Use Authorization) within 14 days prior to baseline vaccination or planned administration during the study active period (Day 29).
21. 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 (Day 29).
22. 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 (Day 29).
23. Daily use of nonsteroidal anti-inflammatory drugs within7 days prior to study drug administration or planned use during the active study period (Day 29). Low dose daily ASA ≤ 100 mg for cardio-protection is not exclusionary.
24. Administration of any investigational vaccine, drug or device within 8 weeks preceding study drug administration, or planned use within the duration of the study.
25. Previous participation in a Vaxart Clinical Trial or other norovirus vaccine trial unless confirmed receipt of placebo

Other Exclusions

26. Donation or use of blood or blood products within 30 days prior to study drug administration or planned donation during the active study period (Day29).
27. History of drug, alcohol, or chemical abuse within 1 year of screening.
28. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin allergy.

Study Duration:

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

Open Label Period (for sentinel subjects)	8 days (staggered dosing and collection of Solicited Symptoms) and then continue through Active and Follow Up Period enrolled in an open label portion.
Screening period:	Up to 45 days
Active study period for reactogenicity, safety, and immunogenicity	29 days

Follow Up Period for safety and duration of immune response, SAEs, AESIs, NOCIs	12 months (from last study dose at Day 365)
Total duration:	12 months

Statistical Method:

The statistical analysis plan (SAP) will be developed and finalized before database lock for any of the planned analyses. It will describe the subject 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 endpoints.

Sample Size Justification

A sample size of 125 randomized subjects (50 each in medium and high dose levels and 25 in placebo) in addition to 10 sentinel subjects are 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.

The numbers of subjects per dose group are predicted to yield meaningful safety and immunogenicity results.

Interim Analysis

No interim analysis will be conducted for this study.

Safety Monitoring Committee:

A safety monitoring committee will be assigned by the Sponsor prior to the beginning of the study and will provide ongoing oversight of the study.

Unblinded data may be provided to the SMC if required during the double-blind period. Further details regarding data safety monitoring guidelines will be included in the SMC Charter.

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 (+2 Days)[g]**	**Day 29/ Early Termination**	**Month 2 Day 60**	**Month 4 Day 120**	**Month 6 Day 180[g]**	**Month 8 Day 240**	**Month 10 Day 300**	**Month 12 Day 365**
Tele-health Appointment	X				📞	📞		📞	📞	📞
Visit Window (days)	X	X		±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									
Breath or urine alcohol	X	X								
Pregnancy Test[b]	X	X								
Physical examination	X	X*	X*	X*[d]						
Vital Signs[c]	X	X	X	X[d]						
COVID-19 Vaccination Status	X									
Study Drug Administration[g]		X								
Access to Solicited Symptom Diary /App		X								

Review Solicited Symptom Diary /App[f]			X[d]	X[d]						
Review prior & concomitant medication	X	X	X	X[d]						
Query for AEs, SAEs, AESIs and NOCIs		X	X	X[d]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Sample Collection for Immunogenicity Assessments – All Subjects										
Study Day	**Day -45 to Day -1**	**Day 1**	**Day 8**	**Day 29/ Early Termination**	**Month 2 Day 60**	**Month 4 Day 120**	**Month 6 Day 180[g]**	**Month 8 Day 240**	**Month 10 Day 300**	**Month 12 Day 365**
Serum blood sample		X	X[g]	X[d]			X			
Nasal Swab		X	X[g]	X[d]			X			
Saliva Sample		X	X[g]	X[d]			X			
Fixed whole blood sample (required for blood draw, optional for testing)		X	X[g]							

Abbreviations: Ab, Antibody; AE, adverse events; AESI, adverse event of special interest; ASC, Antibody secreting cells; BT50, serum blocking antibody titers; EOS, End of Study (Active Period); ET, Early Termination; HBGA, histo-blood group antigen; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; IgA, immunoglobulin A; IgG, immunoglobulin G; MSD, Meso Scale Discovery; NOCI, new onset chronic illness; SAE, serious adverse event; VP1, Vaccine Protein 1

Notes: Tele-health appointment (by app or by phone)
*Targeted
a Serology- Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) or Hepatitis C virus (HCV)
b Serum pregnancy tests will be done at screening on all women. Point-of-Care urine pregnancy test will be performed before dosing on Day 1 on all women, and women found positive with urine pregnancy test will not be enrolled during this study.
c Temperature, blood pressure, heart rate, and respiratory rate will be measured after the subject has been resting for 5 minutes
d Early termination assessments (Solicited Symptoms are to be captured if ET occurs prior to Day 8)
e TEAEs will only be collected during the Active Study period (from time of first dose through 4 weeks post last dose). Only SAEs, AESIs and NOCIs will be collected during the Follow-up Period.

f 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

g Open label subjects will continue through the active period and into the Follow-up Period and have the same procedures as the randomized population with the exception of the Day 8 bio-samples. The Day 8 bio-sampling is not applicable for sentinel subjects. The Day 8 window (Day 8 (+2) is not applicable to the sentinel subjects. The sentinel subjects will not have a Day 180 bio sample collected. As such the sentinel subjects will have a phone call visit to collect safety data.

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 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 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 asimmunoglobulin 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 adult volunteers ages 55-80 (in two age cohorts) were evaluated for immunogenicity, safety, and tolerability at three dosing levels: low, medium or 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 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.

The Phase 2 (VXA-NVV-201) is an ongoing norovirus challenge monovalent GI.1 vaccine trial being conducted in healthy volunteers. Preliminary results obtained to date during this study indicate vaccine safety comparable to previous trials..

2.3 Trial Rationale

An effective NoV vaccine must prevent the two most common NoV genotypes, GI.1 and GII.4. This vaccine consists of VXA-G1.1-NN and VXA-GII.4-NS;the dose of the vaccine is 5×10^{10} IU and 1×10^{11} IU per strain per dose. GI.1/GII.4 bivalent vaccine is used to prevent illness from NoV.

Noroviruses are a genetically diverse group of small, non-enveloped, single-stranded positive sense RNA viruses belonging to the *Caliciviridae* family. Norovirus infections are a leading cause of sporadic and epidemic gastroenteritis across all age groups worldwide. There is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease, including prophylactic measures, such as vaccines.

A unique and advantageous immune response elicited by oral vaccination is the induction of antibodies derived from mucosal cells. Given that the mucosal route of immunization produces superior mucosal immunity compared to injected vaccines, it is hypothesized that GI.1/GII.4 bivalent oral vaccine may enable higher degrees of mucosal protection against infection when compared to a parenteral immunization method.

The current Phase 2 dose confirmation study is designed to assess the safety and immunogenicity of medium and high dose levels of GI.1/GII.4 bivalent vaccine with a single dose vaccination schedule in healthy volunteers (≥18 years and ≤80 years).

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 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 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 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

To determine the safety and immunogenicity of a bivalent dosing regimen of GI.1 and GII.4, to select the dose level and regimen with which to safely proceed into Phase 3 development.

3.2 End Points

3.2.1 Primary End Points

Safety:

- Frequency, duration, and severity of Solicited Symptoms of Reactogenicity (GI and systemic) for 1 week following each study drug dose.
- Frequency, duration, and severity of unsolicited adverse events (AEs) for 28 days following last study drug dose.

Immunogenicity:

- Serum - Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

- Serum - Anti-VP1 GI.1 IgG and Anti-VP1 GII.4 IgG by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

- Serum - Antibody BT50 titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA) Assay
  - geometric mean titer (GMT) Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

3.2.2 Exploratory End Points

Safety:

- Frequency, duration, and severity of SAEs, AESIs and NOCIs for 1 year following last study drug dose.

Immunogenicity:

- Serum - Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 8 and Day 180
  - geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Serum - Anti-VP1 GI.1 IgG and Anti-VP1 GII.4 IgG by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 8 and Day 180
  - geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Serum - Antibody BT50 titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA) Assay

- geometric mean titer (GMT) Day 8 and Day 180
- geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Nasal Swab – Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA
  - 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, Day 1 to Day 29 and from Day 1 to Day 180

- Saliva – Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA
  - 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, Day 1 to Day 29 and from Day 1 to Day 180

- Fixed Whole Blood (required for blood draw, optional for testing)
  - B-cell immunophenotyping at Day 1 and Day 8

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 volunteers (≥18 years and ≤80 years). The study will enroll 10 sentinel subjects in an open label period and randomize 125 subjects in 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.

The first 10 sentinel subjects, in a staggered manner of up to 2 subjects per 24-hour period, will receive the open label high dose of bi-valent active vaccine (2×10^{11}) shown in Table 2. If no dose-related toxicities are observed, and upon the recommendation of the SMC following review of safety data, enrollment of the randomized double-blind study will be initiated.

Table 2: Sentinel Subjects

Treatment Group	Study drug	Per Strain Dose (IU)	Total Dose (IU/dose)	Dosing Schedule	No of Subjects
Open label	Bivalent GII.4/GI.1 vaccine	1×10^{11}	2×10^{11}	Day 1	2
Open label	Bivalent GII.4/GI.1 vaccine	1×10^{11}	2×10^{11}	*	3-10

*Two (2) subjects can be dosed in a staggered manner, at least 24 hours from the dosing date of the last 2 subjects

If pre-established stopping rules are met, enrollment of subsequent subjects will be halted until the SMC has completed the review of all available safety data and provides recommendation for further study conduct.

On Day 1 of the double-blind portion, subjects will be randomized in a 2:2:1 ratio to one of the 3 study arms to receive active vaccine or placebo, as follows (Table 3):

Table 3: Study Design

Treatment Group	**Study drug**	**Per Strain Dose (IU)**	**Total Dose (IU/dose)**	**Dosing Schedule**	**No of Subjects**
Sentinel Open Label	Bivalent GII.4/GI.1 vaccine	1×10^{11}	2×10^{11}	Day 1	10
Arm 1	Bivalent GII.4/GI.1 vaccine	5×10^{10}	1×10^{11}	Day 1	50
Arm 2	Bivalent GII.4/GI.1 vaccine	1×10^{11}	2×10^{11}	Day 1	50
Arm 3	Placebo	N/A	N/A	Day 1	25
Total					135

Abbreviations: IU=infectious units; N/A=not applicable

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 or app between site visits to monitor for safety as specified in the SoA (Table 1).

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 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 he/she remains in the study through Day 365 (Month 12). Following completion of the Day 365 a tele-health appointment phone contact will be conducted 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 both) 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 serious adverse events (SAEs), AEs of special interest (AESIs), and new onset of chronic illness (NOCIs) through Day 365 (Month 12) for safety. Subjects will also have samples collected for evaluation of immunogenicity and duration of immune response as specified in the SoA (Table 1).

Planned Number of Subjects:

A total of 10 healthy adult male and female subjects aged ≥18 years and ≤80 years will be enrolled to the high dose investigational vaccine during the open label sentinel, first portion of this study.

A total of 125 healthy adult male and female subjects aged ≥18 years and ≤80 years are planned to be randomized in one of three study arms, post SMC assessment of safety is complete, and the decision post SMC is favorable towards starting the randomized, second portion of this study to investigational vaccine or placebo during this study.

Study Duration:

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

Table 4: Study Duration

Screening period:	Up to 45 days
Open Label Period (for 10 sentinel subjects)	8 days (staggered dosing and collection of Solicited Symptoms and continue through Active and Follow Up Period)
Randomized Period (for 125 randomized subjects	8 days (dosing and collection of Solicited Symptoms) and continue through Active (Day 29) and Follow Up Period (Day 30-Day 365)
Active study period for primary immunogenicity and safety	29 days
Follow Up Period for safety and duration of immune response	12 months (from study dose at Day 1)
Total duration:	12 months

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 in subjects up to age 80

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
- Demonstration of efficacy that would warrant stopping
- 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 New Zealand Medicines and Medical Devices Safety 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 archived 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 to ≤80 years old inclusive at the time of signing the Informed Consent Form (ICF).

Type of Subjects

2. In stable and good general health, without significant medical illness, based on medical history, physical examination, and vital signs at screening based on investigator judgement.
3. Body mass index (BMI) $\geq$ 17.0 and $\leq$ 35.0 kg/m2 at screening .
4. Available for all planned visits and tele-health appointment, and willing to complete all protocol-defined procedures and assessments (including ability and willingness to swallow multiple small enteric-coated tablets per study dose).

Gender and Reproductive Considerations

6. Male or female subjects
   a. Female subjects must not be breastfeeding and must provide a negative pregnancy test at screening and pre-dose.
   b. Female subjects must fulfill one of the following criteria:
      i. At least 1 year post-menopausal (defined as amenorrhea for $\geq$ 12 consecutive months prior to screening without alternative medical cause) or surgically sterile.
      ii. Female subjects of childbearing potential must be willing to use a highly effective form of contraception for 30 days prior to initial vaccination and until 60 days after last 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.
      iii. Male subjects must agree to practice abstinence from heterosexual intercourse or to use an effective method of birth control as noted above from first vaccination to 60 days after last vaccination. Male subjects must agree to refrain from donating sperm and practice abstinence from all intercourse or to use an effective method of double barrier birth control or condom as noted above from first vaccination to 60 days after last vaccination.

Informed Consent

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

Exclusion Criteria

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

1. Known clotting/bleeding issues and/or personal and family history with increased risk of bleeding or clotting. -
2. Presence of significant uncontrolled medical or psychiatric illness (acute or chronic) including institution of new medical/surgical treatment or significant dose alteration for uncontrolled symptoms or drug toxicity within 3 months prior to screening and reconfirmed at baseline.
3. Cancer, or treatment for cancer or any procedure or preventive medication for cancer or to prevent recurrence, within past 3 years (excluding fully treated and resolved basal cell carcinoma or squamous cell carcinoma)
4. Presence of immunosuppression or medical condition possibly associated with impaired immune responsiveness, including diabetes mellitus- type 1 and 2
5. Left blank intentionally.
6. 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. GI 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. gastro esophageal reflux disorder
        iii. peptic ulcer
        iv. cholecystectomy
7. History of any form of angioedema
8. History of serious reactions to vaccination such as anaphylaxis, respiratory problems, hives or abdominal pain
9. Diagnosed bleeding disorder or significant bruising or bleeding difficulties that could make blood draws problematic
10. Any condition that resulted in the absence or removal of the spleen

11. 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)
12. Presence of a fever ≥38.0°C measured orally at baseline.
13. Any significant hospitalization within the last year which in the opinion of the investigator or sponsor could interfere with study participation.
14. Any of the following history or conditions that may lead to higher risk of clotting events and/or thrombocytopenia:
    a. Family or personal history of bleeding or thrombosis.
    b. History of heparin-related thrombotic events, and/or receiving heparin treatments.
    c. History of autoimmune or inflammatory disease.
    d. Presence of any of the following conditions known to increase risk of thrombosis within 6 months prior to screening:
        i. Recent surgery other than removal/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 infection.
15. Any other condition that in the clinical judgement of the investigator would jeopardize the safety or rights of a subject taking the study drug, would render the subject unable to comply within the protocol or would interfere with the evaluation of the study endpoints diagnostic assessments.
16. Positive human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) or Hepatitis C virus (HCV) tests at the screening visit.
17. History of GI bleeding including hematochezia (blood in stool) or melena (black stool)
18. Positive urine drug screen for drugs of abuse at screening (positive test for marijuana is not exclusionary; however concurrent use of marijuana during the study Active period through Day 29 is prohibited).
19. Positive breath or urine alcohol test at screening and baseline.

Prior/Concurrent Therapy

20. Receipt of a licensed vaccine (including any COVID-19 vaccines under emergency use authorization) within 14 days prior to baseline vaccination or planned administration during the study active period (Day 29).
21. 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 (Day 29).
22. Use of medications known to affect the immune function (e.g., 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 (Day 29).

23. Daily use of nonsteroidal anti-inflammatory drugs within7 days prior to study drug administration or planned use during the active study period (Day 29). Low dose daily ASA ≤ 100 mg for cardio-protection is not exclusionary.
24. Administration of any investigational vaccine, drug or device within 8 weeks preceding study drug administration, or planned use within the duration of the study
25. Previous participation in a Vaxart Clinical Trial or other NoV vaccine trial unless confirmed receipt of placebo.

Other Exclusions

26. Donation or use of blood or blood products within 30 days prior to study drug administration or planned donation during the active study period (Day 29).
27. History of drug, alcohol, or chemical abuse within 1 year of screening.
28. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin allergy.

5.2 Early Termination/ Withdrawal criteria

In case of Early Termination (ET) prior to Day 8, all procedures marked as 'early termination assessments' should be completed 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 medical 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. Screen failure data will be captured in EDC.

Re-screening/re-assessment 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 such subjects will be determined to be permanent screen failures after the second screening determines a subject is ineligible.

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 5: 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 9.1.1
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 5.3.
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-GII.4-NS are E1/E3-deleted, replication-incompetent, adenovirus 5 vaccine vectors designed for use as vaccines for prevention of NoV infection. The vaccine vectors encode for a full-length VP1 gene of either Norwalk virus (VXA-G1.1-NN vaccine) or Sydney virus (VXA-GII.4-NS vaccine). In addition to the transgene cassette, a second hCMVie promoter is also present in the vaccine constructs which is used to express a ribonucleic acid (RNA) sequence that acts as an adjuvant. The adjuvant is a short hairpin RNA expressed off a promoter such that only target cells in the intestine that express antigen will also express the adjuvant. This is likely to result in a tight association of antigen with adjuvant in vivo.

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 API, tromethamine, sucrose, arginine, hydrolyzed fish gelatin (type A), and polyvinyl pyrrolidone (PVP-grade K90). The formulated and dried drug substance is blended with tableting excipients consisting of: microcrystalline cellulose, pre-gelatinized starch, magnesium stearate, and hydrophobic colloidal silica. 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.

Multiple tablets of study drug will be dispensed to allow delivery of the intended vaccine dose. A matching number of placebo tablets will be dispensed to maintain the study blinding.

Table 6: 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 7: Study Arm(s)

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

Each subject who signs informed consent will be assigned a subject number. Only the first 10 sentinel subjects will receive open label high dose of active vaccine (2×10^{11} IU). Following SMC recommendation on review of sentinel safety data up to and including Day 8, 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 signs the informed

consent form (ICF), the Investigator (or designee) will enter the subject into the sites Screening Log. All screen failed and randomized subjects will have data entered in the study specific EDC.

After signing an informed consent, the subjects in the randomized double blind portion of the study will undergo screening assessments to determine study eligibility up to 45-day for 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, as follows (Table 7).

6.7.2 Blinding Procedures

The first 10 sentinel subjects will be enrolled and receive the high dose of active vaccine in an open label manner for a safety evaluation.

If pre-established stopping rules are met, enrollment of subsequent subjects will be halted until the study SMC has completed the review of all available safety data and provides guidance regarding continuation of study.

For remaining subjects, Investigators, site personnel and the Sponsor (except as described below) will be blinded to individual subject 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 periodically convene to review unblinded overall safety as 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 5.1 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 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/subject's legally Accepted Representative (LAR). 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 / subject's LAR, the subject will be undergone for screening procedure 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 sitting blood pressure, pulse rate and respiratory rate after at least 5 minutes of rest to the subject.
- 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; pulmonary; gastrointestinal (GI); musculoskeletal; extremities; neurological; and lymph nodes.
- Perform a serum pregnancy test for all female 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).
- Ensure that all inclusion criteria are met and that none of exclusion criteria are met.
- 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.
- Obtain COVID-19 vaccination status.
- Complete the source documents.
- The Investigator or an authorized designee completes the eCRFs.

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 for both the open label and randomized groups of the study.

- The Principal Investigator will ensure that all inclusion criteria and none of the exclusion criteria are met on Day1, prior to vaccination.
- A urine pregnancy test will be done for all female subjects prior to dosing.
- 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.
- Vital signs will be obtained, including temperature, sitting blood pressure, pulse rate and respiratory rate after at least 5 minutes of rest to the subject during the active study period.
- The subject's number (open label) or randomization number will be noted.
- 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.
- For the subjects enrolled into the open label sentinel study arm, the site staff must observe the subjects at the site, in the ≥18 to ≤80 years old age group, for at least 2 hours 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, and on a serious adverse event (SAE) form, as applicable.
- For the subjects enrolled into the randomized double blind portion study arm, the site staff must observe the subjects at the site, in the ≥18 to ≤80 years old age group 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, and on a serious adverse event (SAE) form, 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 (as specified in SOA) and a blood, nasal and saliva samples will be collected for immunogenicity assessment.
- 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, while permitted, is not recommended on the day of study drug administration (before or after vaccination). If prophylactic antipyretic/pain medication is used, 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 data online 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 11) and 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.

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

- Ensure that the subject meets none of the withdrawal criteria as described in Section 5.2.

- Verify understanding of and compliance with protocol requirements for contraception (see Appendix 4).
- Collect a blood sample for Immunogenicity assessment as noted in the SoA (Table 1).
- Review the subject's Diary data with the subject and collect the Diary. Collect stop dates of any Diary events ongoing on the last day that the Diary was completed and record stop dates in the eCRF if required.
- 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 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 5.3.

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.

7.1.4 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 systemic events (specify the events of interest) that are present, in accordance with the reactogenicity grading scale.
- Ask the subject if he/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 Samples

7.2.1 Blood / Saliva/Nasal Sample Collection

Blood / saliva/nasal 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 study specific Laboratory Manuals.

7.2.2 Blood/ Saliva/Nasal 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 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 and nasal 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

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the 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.

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; pulmonary; 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 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 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 9.1.8.

8.2 Immunogenicity Assessments

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

Primary Immunogenicity Assessments:

- Serum –Anti IgA for both GI.1 and GII.4 by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

- Serum-Antibody titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA)-Blocking Assay (BT50) –
  - geometric mean titer (GMT) Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

- Serum Anti- IgG for both GI.1 and GII.4 by MSD assay
  - geometric mean concentration (GMC) at Day 1 and Day 29
  - geometric mean fold rise (GMFR) from Day 1 to Day 29

Exploratory Immunogenicity Assessments:

- Serum - Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 8 and Day 180
  - geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Serum - Anti-VP1 GI.1 IgG and Anti-VP1 GII.4 IgG by Meso Scale Discovery (MSD) assay by dose level
  - geometric mean concentration (GMC) at Day 8 and Day 180
  - geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Serum - Antibody BT50 titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA) Assay
  - geometric mean titer (GMT) Day 8 and Day 180
  - geometric mean fold rise (GMFR) from Day 1 to Day 8 and from Day 1 to Day 180

- Nasal Swab – Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA
  - 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, Day 1 to Day 29 and from Day 1 to Day 180

- Saliva – Anti-VP1 GI.1 IgA and Anti-VP1 GII.4 IgA
  - 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, Day 1 to Day 29 and from Day 1 to Day 180

- Fixed Whole Blood (required for blood draw, optional for testing)
  - B-cell immunophenotyping at Day 1 and Day 8

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.

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

9. ADVERSE EVENTS

9.1.1 Definition of an Adverse Event, Serious Adverse Event, Adverse Event of Special Interest, New Onset of Chronic Illness, and Unanticipated problems

Adverse Event

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

Serious Adverse Event

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: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Note: Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE/SAE.

Adverse Event of Special Interest

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 Table 12.

New Onset of Chronic Illness

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 events of special interest and NOCIs will be collected and reported for all participants from the moment of first study drug administration until the end of the Safety -Follow-up Period through Day 365.

Unanticipated problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions (AR).

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.)

The following additional definitions are being used by the Sponsor.

Solicited Adverse Events:

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
- diarrhoea
- malaise/fatigue

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.

Unsolicited AE:

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. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AE.

Sentinel subjects will be kept at the site under observation for 2 hours after vaccination to ensure their safety. If there are no safety concerns during this period then randomized subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation period should be documented (including the actual time of observation) in the source document.

9.1.2 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".

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

There are five principles that underpin the causality assessment for vaccine adverse events:

1. Biological plausibility
2. Temporal relation
3. Consistency
4. Specificity
5. Strength of association

For more details, refer to the 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 (clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment). The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- 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.

9.1.4 Monitoring of Adverse Events during Trial

9.1.4.1 Monitoring of AE/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)

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

All AEs AESIs and NOCIs will be collected from the first dose of study product until the follow-up visit at the timepoints specified in the SoA (Table 1).

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 it does not have a causal relationship with study participation. There are two situations to note as below.

1. 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."
2. 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.

9.1.6 Follow-up of AEs, 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 5.3).

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

9.1.7 Reporting of Adverse Event, Adverse Event of Special Interest, New Onset of Chronic Illness, Serious Adverse Events and Unanticipated problems

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 cause 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 8 below summarizes the different reporting timelines for TEAEs (unsolicited and solicited), AESIs, NOCIs, SAEs, and SUSAR.

Table 8 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

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).

Serious Adverse Events Reporting

The Investigator or designee will immediately 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 immediately 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.

The study Sponsor will be responsible for notifying 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.

All SAEs will be recorded and reported to the Sponsor or designee immediately 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.

9.1.8 Pregnancy

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 or female partner of male subject (after obtaining the necessary signed informed consent from the female partner) 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 (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The subject/pregnant female partner will be followed to determine the outcome of the pregnancy. If the subject/pregnant female partner (after consent is obtained to follow the pregnancy) delivers an infant, the subject/pregnant female partner and the infant will be followed up to one month post-delivery. The Investigator will collect follow-up information on the subject/pregnant female partner and the neonate 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/pregnant female partner) beyond the resolution of the pregnancy, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study may request continuation of study drug.

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.

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

The first 10 sentinel subjects will receive open label high dose of active vaccine (2×10^{11}) in a staggered manner, no more than two (2) subjects dosed in a 24-hour period. All subjects dosed will be observed for a minimum of 2 hours post dose. While ten (10) subjects will be dosed in the sentinel group, to allow for dropouts, eight (8) subjects with complete safety data (defined as Day 1 to Day 8) will be enough to convene the SMC. If no dose-related toxicities are observed, and upon consideration of the SMC recommendations following review of safety data, enrollment of the randomized double-blind study will be initiated.

Alternatively, if pre-established stopping rules are met, enrollment of subsequent subjects will be halted until the study SMC has completed a review of all available safety data and offers a recommendation to proceed.

If any of the events described below are met during the overall conduct of the study (open label and randomized phase), the study will be halted, and no new randomization/vaccinations will be allowed pending an SMC safety review

- 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).

The SMC will provide study oversight throughout the duration of the trial active and safety follow-up periods (Day 1 through Day 365 post-vaccination).

The IRB, US FDA-CBER will be notified if the study is halted for safety concerns.

A SMC will be created to provide oversight of the conduct of the trial to ensure the safety of subjects and the validity and integrity of study data. 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. Please refer to the study specific SMC for details.

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 of the composition, pre-specified meetings and objectives of the SMC will be outlined in the SMC Charter.

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 Hypothesis

No hypothesis testing is planned for this study.

11.2 Sample Size Determination

A sample size of 125 randomized subjects (50 each in medium and high dose levels and 25 in placebo) in addition to 10 sentinel subjects 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.

11.3 Multiplicity Adjustment

No multiplicity adjustment will be implemented for this study.

11.4 Population for Analysis

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

Table 9: 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.

Analysis Population	Description
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.

11.5 Statistical Analysis Plan

11.5.1 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.

11.5.2 Analysis of the Primary 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).

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 last 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.
Exploratory (measured from Day 30 through Day 365)	Frequency, duration, and severity of SAEs, AESIs and NOCIs for 1 year following the study drug dose.

11.5.3 Analysis of Primary and Exploratory Immunogenicity End Points

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).

Endpoint	Statistical Analysis Methods
Primary (Key Immunogenicity 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. .For specific primary immunogenicity endpoints please refer to Section 8.2-Immunogenicity Assessments- Primary Immunogenicity Assessments:
Exploratory	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. The analysis of these bio samples is optional. For specific exploratory immunogenicity endpoints please refer to Section 8.2-Immunogenicity Assessments- Exploratory Immunogenicity Assessments

11.5.4 Baseline descriptive Statistics

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

11.5.5 Sub-group Analysis

The primary endpoint will be summarized and analyzed by the following subgroups using the ITT set:

The primary endpoint will be summarized and analyzed by the following subgroups using the ITT set:

- Age
  - Up to and including age 65 years
  - Age 66 years and older
- Sex
- Race

11.5.6 Tabulation of Individual Subject Data

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

12. ETHICAL CONSIDERATION

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 Inform 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 document 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 form 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.

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 adverse events (AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into an 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.

An initial safety review for this study is planned for the first 10 sentinel subjects who will receive the high dose and provide safety data after administration of 2×10^{11} dose level in a staggered manner, no more than two (2) subjects dosed in a 24-hour period. All subjects dosed will be observed for a minimum of 2 hours post dose. All safety data collected will be summarized and reviewed by the (Sponsor's internal/external safety monitoring committee) for agreement of next steps.

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 tele-health appointment, 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.

16. REFERENCES

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Vega, E., Barclay, L., Gregoricus, N., Shirley, S.H., Lee, D., Vinjé, J., 2014. Genotypic and Epidemiologic Trends of Norovirus Outbreaks in the United States, 2009 to 2013. J Clin Microbiol 52, 147–155.

Appendix 1: Clinical Laboratory Tests

- The tests detailed in Table 10 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 10 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

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 11.

Table 11 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).

Contraception Guidance

Male Subjects:

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

- Refrain from donating sperm.

  PLUS**:**

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

  OR

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

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 12: 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 6.0 Protocol Version History

Name of the Document with Version Number	Date	Summary of Changes and Rationale
VERSION 1.0	12 OCT 2022	INITIAL VERSION
VERSION 2.0 `	**09 FEB 2023**	AMENDMENT 1.0

VXA-NVV-202 Protocol Amendment 1 (Version. 2.0), 09 Feb 2023

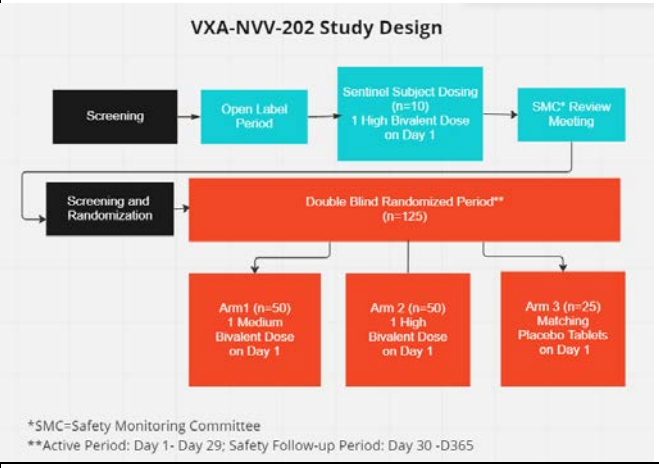
Overall Rationale for the Amendment:

The original version of this phase 2 Norovirus protocol (VXA-NVV-2022) was finalized in October 2022 and submitted for CBER (US FDA), MedSafe (New Zealand Regulatory Authority) and IRB review. Although approvals were obtained, the study design was modified to a US only study to include 10 open label sentinel subjects receiving the high dose. After SMC review of the sentinel safety data 1 week after dosing, a 125 subject double blind randomization portion of the study will follow.

The table below summarizes the changes incorporated into Amendment 1 as well as a brief rationale for each modification.

Section No. & Title	Description of Change	Brief Rationale
All headers	Updated to date of amendment	All headers have been updated to match the date of the Amendment 1
Cover page	Update information for protocol version and date and prior version	To provide accurate information
Protocol Title Page	Amendment No: 2 and Date of Amendment-09 Feb 2023	To provide accurate information
Entire protocol	Removed any referenced to subjects Legally Authorized Representative	This study is enrolling health volunteers
Protocol Synopsis	Contract Research Organization: [redacted] Updated to: [redacted]	To provide accurate information

Protocol Synopsis trial Arms	Changed sample for the randomized double-blind portion of the study: Trial Arms: Arm 1: Bivalent GII.4/GI.1 medium dose vaccine (VXA-GII.4-NS plus VXA-G1.1-NN) 5×1010 tablets; total dose is 1×1011 IU/dose (n=50) Arm 2: Bivalent GII.4/GI.1 high dose vaccine (VXA-GII.4-NS plus VXA-G1.1-NN) 1×1011 tablets; total dose is 2×1011 IU/dose (n50) and (sentinel n=10) Arm 3: Placebo tablets (n=25)	To provide accurate information and reflect changes to the design of the study
Protocol Synopsis Subject Population	Removed 613 sample size and replaced with 125 sample size	Changed study design and sample size of the study
Endpoints: Immunogenicity	Added Day 8 to Serum anti IgA for both GI.1 and GII.4, Serum BT50	Updated bio sample assays at Day 8
Endpoints: Immunogenicity	Removed: PBMC: Anti- IgA Antibody Secreting Cells (ASC) for both GI.1 and GII.4 by ELISpot at Day 8	PBMC samples will not be collected in this study
Protocol Synopsis : Description of Sites/Facilities	Removed the country of New Zealand. This study will be a single country study.	Single country study-USA only.
Protocol Synopsis-trial design	Changed sample size from 613 to 125 and added the following text for the sentinel subjects: The sentinel subjects will be enrolled in a staggered design, in which no more than two (2) subjects are dosed per 24-hours. All sentinel subjects will be observed for safety at least 2 hours post dose. After the ten (10) sentinel subjects have been enrolled, and if no dose-related toxicities are observed, and upon the recommendation of the Safety Monitoring Committee (SMC) following review of safety data up to one week post dose, enrollment of the randomized double-blind study will be initiated.	a. Sample size modification to accurately reflect current study. b. The original version of the protocol allowed for enrollment of the 10 sentinel subjects without limitations. This amendment limits sentinel dosing to 2 subjects per 24-hour period and extends the sentinel observation period to 2 hours post dose. These parameters were added in response to MedSafe (New Zealand Regulatory Authority) request, and not due to any new safety findings or concerns. Although the study will no longer include sites in New Zealand after modification of the study design and size, Vaxart has decided to keep the increased sentinel safety oversight .

Protocol Synopsis-Figure 1-Study Design	Arm 2 is the High Dose arm. Both the High and Medium dose arms are labelled as Arm 1 in the study design schematic in error. 	a. Schematic updated and replaced.
Protocol Synopsis-Planned Number of Subjects	Updated sample size to 125: A total of 125 healthy adult male and female subjects aged ≥18 years and ≤80 years will be , randomized and assigned to investigational vaccine during this study.	To accurately reflect the study design sample size
Protocol Synopsis-Exclusion Criteria	Exclusion #5: Removed History of Gilberts Syndrome. Left blank intentionally to ensure exclusion criteria numbers reconcile with the EDC. Exclusion #14, d: Presence of any of the following conditions known to increase risk of thrombosis within 6 months prior to screening: letter “v”: Recent clinically significant infection.	Gilbert’s syndrome is a common inherited condition where the liver doesn’t properly process bilirubin, leading to harmless elevated bilirubin lab results. Gilbert’s has not been an exclusion in any previous protocols for our vaccines and was added in error in the earlier version of NVV 202 before the decision was made not to require chemistry labs during this trial. The intent was to avoid potential confounding of safety labs in subjects with known Gilbert’s. There have been no safety signals or concerns with Vaxart’s oral vaccine platform with regard to liver enzymes or bilirubin. Severe covid infection is known to be associated with risk of thrombosis. Since we are not screening specifically for covid

	added the following: v. Including hospitalization for COVID-19 infection	infection, this is a way to exclude severe covid infections.
Protocol Synopsis-Other Exclusions	Exclusion #28: History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish **gelatin** allergy.	Added the word "gelatin" as this was omitted in error in last protocol version.
Protocol Synopsis- Study Duration	Open Label Period (for sentinel subjects): 8 days (dosing and collection of Solicited Symptoms and continue through Active and Follow Up Period) Added "staggered to the previous text: 8 days (staggered dosing and collection of Solicited Symptoms and continue through Active and Follow Up Period)	Accurate reflection of the dosing schedule for the sentinels
Protocol Synopsis : Sample Size Justification	Sample Size Justification: A sample size of 613 randomized subjects (245 each in medium and high dose levels and 123 in placebo) are required to achieve 80% power, at the 7% significance level (one-sided) using a 2-group fisher exact test with equal allocation to each dose level. Calculation assumes a difference of 10.2% in MSD IgA fold rise between the two dose groups (72.7 % Vs. 62.5%). Placebo was added for safety comparison. Updated to: A sample size of 125 randomized subjects (50 each in medium and high dose levels and 25 in placebo) in addition to 10 sentinel subjects are 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.	Accurately reflect sample size change and impact on statistics

Protocol Synopsis : Table 1 : Schedule of Activities	Updated SOA to align with modifications to protocol dated 13 Oct 2022. 1. Updated immunogenicity testing. 2. Remove PBMC visits. 3. Added a Day 8 serum and whole blood sample collection. 4. Added a Day 180 serum, nasal and saliva sample collection. 5. Made Day 180 an in person visit at the clinic. 6. Added a SOA grid for Sample Collection for immunogenicity Assessments-all subjects. 7. Added clarification of procedures for Early Termination subjects 8. Updated legend and superscripts in the SOA grid 9. Added temperature to Vital Signs-legend “c” Now reads: temperature, blood pressure, heart rate, and respiratory rate will be measured after the subject has been resting for 5 minutes	Provide accurate information specific to the SOA
Protocol Synopsis : Trial Rationale	Last paragraph: Original text: The current Phase 2 dose confirmation study is designed to assess the safety and immunogenicity of GI.1/GII.4 bivalent vaccine with a 1-dose vaccination schedule in healthy volunteers (≥18 years and ≤80 years). Updated text: The current Phase 2 dose confirmation study is designed to assess the safety and immunogenicity of GI.1/GII.4 bivalent vaccine with a single vaccine dose in healthy volunteers (≥18 years and ≤80 years).	Provide accurate information specific to the study design
2.2.3 Clinical experience with	Updated non clinical experience	Provide accurate information specific to the study design and updates

Bivalent GI.1 and GII.4 vaccine	Removed VXA-NVV-106 text since it was specific to the low titer/high tablet lot and was not included in the IB	
2.3 Trial Rationale	Original text: The current Phase 2 dose confirmation study is designed to assess the safety and immunogenicity of GI.1/GII.4 bivalent vaccine with a 2-dose vaccination schedule in healthy volunteers (≥18 years and ≤80 years). Updated to: The current Phase 2 dose confirmation study is designed to assess the safety and immunogenicity of **medium and high dose levels** of GI.1/GII.4 bivalent vaccine with a **single** 2-dose vaccination schedule in healthy volunteers (≥18 years and ≤80 years).	Provide accurate information specific to the study design
3.2.1 Primary End Points	Added Day 8 to the following calculation. • Geometric mean concentration (GMC) at Day 8 and Day 29 • Geometric mean fold rise (GMFR) from Day 1 to Day 8 to Day 29	Provide accurate information specific to the modified study design and bio-sample analysis for serum samples
	The current Phase 2 dose confirmation study is designed to assess the safety and immunogenicity of medium and high dose levels of GI.1/GII.4 bivalent vaccine with a single dose2-dose vaccination schedule in healthy volunteers (≥18 years and ≤80 years).	
3.2.2 Exploratory-End Points-Immunogenicity	Added Day 8 to the following: • Serum: • Antibody titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA)-Blocking Assay (BT50) - geometric mean titer (GMT) and GMFR at Day 8, Day 29 and Day 180 • Anti- IgG for both GI.1 and GII.4 by MSD assay -GMC and GMFR at Day 8, Day 29 and Day 180 • Anti- IgA for both GI.1 and GII.4 by MSD assay - GMC and GMFR at Day 8 Day 180 Removed PBMC sampling and analysis	Provide accurate information specific to the modified study design and bio-sample analysis for serum, nasal, saliva and whole blood sampling

	• Nasal Swab: • Anti- IgA for both GI.1 and GII.4 - GMC and GMFI at Day 8, Day 29 and Day 180 • Saliva: • Anti- IgA for both GI.1 and GII.4 - GMC and GMFI at Day 8, Day 29 and Day 180 Added Day 1 and Day 8 collection to the following: • Fixed Whole Blood (required for blood draw, optional for testing) • B-cell immunophenotyping - Day 1, Day 8 and Day 29	
4.1 Overall Description of Trial Design	Original text: This is a multi-center, double-blind, randomized, placebo-controlled, single dose, dose ranging study in healthy volunteers (≥18 years and ≤80 years). The study will enroll 10 sentinel subjects in an open label period and randomize 613 subjects in three arms. Updated text: This is a multi-center, double-blind, randomized, placebo-controlled, single dose, dose ranging study in healthy volunteers (≥18 years and ≤80 years). The study will enroll 10 sentinel subjects in an open label period and randomize 125 subjects in three arms. Original Text: The first 10 sentinel subjects will receive the open label high dose of active vaccine (2×1011) shown in Table 2. 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. Updated Text: The first 10 sentinel subjects, in a staggered manner of up to 2 subjects per 24-hour period, will receive the open label high dose of bi-valent active vaccine (2×1011) shown in Table 2. If no dose-related toxicities are observed, and upon the recommendation of the	Accurately reflect sample size change from 613 to 125 for the double-blind randomized portion of the study The original version of the protocol allowed for enrollment of the 10 sentinel subjects without limitations. This amendment limits sentinel dosing to 2 subjects per 24-hour period and extends the sentinel observation period to 2 hours post dose.

<table>
<tr>
<td></td>
<td>SMC following review of safety data, enrollment of the randomized double-blind study will be initiated.

Table 2 Sentinel Subjects deleted.

Updated Table 2: Sentinel Subjects

Table 2: Sentinel Subjects
<table>
<tr><th>~~Treatment Group~~</th><th>~~Study drug~~</th><th>~~Per Strain Dose (IU)~~</th><th>~~Total Dose (IU/dose)~~</th><th>~~Dosing Schedule~~</th><th>~~No of Subjects~~</th></tr>
<tr><td>~~Open label~~</td><td>~~Bivalent GII.4/GI.1 vaccine~~</td><td>~~1×10^{11}~~</td><td>~~2×10^{11}~~</td><td>~~Day 1~~</td><td>~~10~~</td></tr>
<tr><td>Treatment Group</td><td>Study drug</td><td>Per Strain Dose (IU)</td><td>Total Dose (IU/dose)</td><td>Dosing Schedule</td><td>No of Subjects</td></tr>
<tr><td>Open label</td><td>Bivalent GII.4/GI.1 vaccine</td><td>1×10^{11}</td><td>2×10^{11}</td><td>Day 1</td><td>2</td></tr>
<tr><td>Open label</td><td>Bivalent GII.4/GI.1 vaccine</td><td>1×10^{11}</td><td>2×10^{11}</td><td>*</td><td>3-10</td></tr>
</table>
*Two (2) subjects can be dosed in a staggered manner, at least 24 hours from the dosing date of the last 2 subjects</td>
<td>Updated Table 2 accurately reflects the study design modifications for the sentinel subjects</td>
</tr>
<tr>
<td>4.1 4.1 Overall Description of Trial Design</td>
<td>Table 3: Study Design

1. Updated the table to reflect the new sample size and sample size per arm.
2. Added a row for the sentinels to Table 3

Table 3: Study Design
<table>
<tr><th>Treatment Group</th><th>Study drug</th><th>Per Strain Dose (IU)</th><th>Total Dose (IU/dose)</th><th>Dosing Schedule</th><th>No of Subjects</th></tr>
<tr><td>Arm 1</td><td>Bivalent GII.4/GI.1 vaccine</td><td>5×10^{10}</td><td>1×10^{11}</td><td>Day 1</td><td>~~245~~50</td></tr>
<tr><td>Arm 2</td><td>Bivalent GII.4/GI.1 vaccine</td><td>1×10^{11}</td><td>2×10^{11}</td><td>Day 1</td><td>~~245~~50</td></tr>
<tr><td>Sentinel Open Label</td><td>Bivalent GII.4/GI.1 vaccine</td><td>1×1011</td><td>2×1011</td><td>Day 1</td><td>25</td></tr>
<tr><td>Arm 3</td><td>Placebo</td><td>N/A</td><td>N/A</td><td>Day 1</td><td>~~123~~25</td></tr>
<tr><td colspan="5">Total</td><td>~~613~~135</td></tr>
</table>
Abbreviations: IU=~~international~~ infectious units; N/A=not applicable

Abbreviations: IU: International Units,

Corrected to: Infectious Units (IU)</td>
<td>Provide accurate information specific to the modified study design</td>
</tr>
<tr>
<td>Table 4 :</td>
<td>Original text:

Open Label Period (for 10 sentinel subjects)-8 days (dosing and collection of Solicited Symptoms and continue through Active and Follow Up Period)

Updated to:</td>
<td>Provide accurate information specific to the modified study design</td>
</tr>
</table>

	Added “staggered” Open Label Period (for 10 sentinel subjects) 8 days (staggered dosing and collection of Solicited Symptoms and continue through Active and Follow Up Period)	
5.1 Inclusion Criteria	Inclusion #3: Original text: 3. Body mass index (BMI) between 17.0 and 35.0 kg/m2 at screening SNG. Updated text: Removed SNG-erroneous text and clarify range: 3. Body mass index (BMI) $\geq$ 17.0 and $\leq$ 35.0 kg/m2 at screening	Correct a text error
Section 5.1 Inclusion Criteria-Exclusion Criteria	Exclusion #14: Original Text 14. Any of the following history or conditions that may lead to higher risk of clotting events and/or thrombocytopenia: e. Family or personal history of bleeding or thrombosis. f. History of heparin-related thrombotic events, and/or receiving heparin treatments. g. History of autoimmune or inflammatory disease. h. Presence of any of the following conditions known to increase risk of thrombosis within 6 months prior to screening: i. Recent surgery other than removal/biopsy of cutaneous lesions ii. Immobility (confined to bed or wheelchair for 3 or more successive days)	No change to actual text for Exclusion 14,h. Changed classification (i to a, ii to b, etc.)

	iii. Head trauma with loss of consciousness or documented brain injury iv. Receipt of anticoagulants for prophylaxis of thrombosis v. .Recent clinically significant infection Updated text: 14. Any of the following history or conditions that may lead to higher risk of clotting events and/or thrombocytopenia: a) Family or personal history of bleeding or thrombosis. b) History of heparin-related thrombotic events, and/or receiving heparin treatments. c) History of autoimmune or inflammatory disease. d) Presence of any of the following conditions known to increase risk of thrombosis within 6 months prior to screening: i. Recent surgery other than removal/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	
Section 5.1 Inclusion Criteria- Exclusion Criteria	Exclusion #28 Original text: 29. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish allergy. Updated text: Added “gelatin”	Corrected exclusion criteria

	28. History of hypersensitivity or allergic reaction to any component of the investigational vaccine, including but not limited to fish gelatin allergy.	
6.1Investigational Product Description	Original Text: VXA-G1.1-NN and VXA-GII.4-NS are E1/E3-deleted, replication-incompetent, adenovirus 5 vaccine vectors designed for use as vaccines for prevention of NoV infection. The vaccine vectors encode for a full-length VP1 gene of either Norwalk virus (VXA-G1.1-NN vaccine) or Sydney virus (VXA-GII.4-NS vaccine). In addition to the transgene cassette, a second hCMVie promoter is also present in the vaccine construct which is used to express an RNA sequence that acts as an adjuvant. The adjuvant is a short hairpin RNA expressed off a promoter such that only target cells in the intestine that express antigen will also express the adjuvant. This is likely to result in a tight association of antigen with adjuvant in vivo. Updated text: VXA-G1.1-NN and VXA-GII.4-NS are E1/E3-deleted, replication-incompetent, adenovirus 5 vaccine vectors designed for use as vaccines for prevention of NoV infection. The vaccine vectors encode for a full-length VP1 gene of either Norwalk virus (VXA-G1.1-NN vaccine) or Sydney virus (VXA-GII.4-NS vaccine). In addition to the transgene cassette, a second hCMVie promoter is also present in the vaccine constructs which is used to express a ribonucleic acid (RNA) sequence that acts as an adjuvant. The adjuvant is a short hairpin RNA expressed off a promoter such that only target cells in the intestine that express antigen will also express the adjuvant. This is likely to result in a tight association of antigen with adjuvant in vivo.	Provide accurate information specific to the Investigational Product
6.7.1 Randomization procedures	Original text: After signing an informed consent, the subjects will undergo screening assessments to determine study eligibility over a 45-day Screening Period. On Day 1, subjects will be randomized in a 2:2:1 ratio to one of	Provide accurate information specific to how screen failed subjects will be captured in the EDC (reason for screen failure)

	the three treatment arms to receive active vaccine or placebo, as follows (Table 6). Updated Text: After signing an informed consent, the subjects will undergo screening assessments to determine study eligibility over a 45-day Screening Period. <u>All subjects who sign a study specific informed consent form will have data entered into the EDC</u>. 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, as follows (Table 6).	
7.1.Procedure to be followed on screening (Day -45 to Day -1)	Original text-bullet 5: •Measure subject's temperature (oral). Updated text: •Measure subject's temperature (oral). <u>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</u>. Original text-bullet 7 •Perform a urine pregnancy test for all female subjects at screening. Updated text: •Perform a urine pregnancy test for all female subjects at screening. <u>At screening all women will have a negative serum HCG. Prior to dosing all women will have a negative urine HCG.</u>	Allow alternatives to oral temperatures and clarify the preferred use of the sponsor provided thermometers for reporting daily diary specific temperatures. Clarify that all subjects must have a negative pregnancy test (serum) at screening and a negative pregnancy test (urine) prior to dosing.
7.1.2 Procedure to be followed	Procedures to be followed during the Active Study Period (Day 1 to Day 29): Subjects will return the site	Provide accurate information specific to the original intent of the study procedures

during Active Study Period (Day 1 to Day 29)	(as specified in SOA) and a blood sample will be collected for immunogenicity assessment. Update to: Subjects will return to the site (as specified in SOA) and blood, nasal and saliva samples will be collected for immunogenicity assessment. Added: For the subjects enrolled into the open label sentinel study arm, the site staff must observe the subjects at the site, in the ≥18 to ≤80 years old age group, for at least 2 hours 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, and on a serious adverse event (SAE) form, as applicable. Original text: The Investigator or appropriately qualified designee will review the Diary data online 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). Updated test: The Investigator or appropriately qualified designee will review the Diary data online 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 evaluate for potential alternative etiology.**	Provide clarification on the post dose observation period for the sentinel subjects To clarify if ≥ Grade 3 Solicited Adverse Events are related to study drug or other etiology

7.2 Management of Blood / Saliva / Nasal Samples	Added text to be consistent about bio samples collection, preparation, storage, and shipment	Provide clarification
7.2.4 Future use of stored specimens and data	Removed the following text: In addition to the research, you are consenting to under this research study, Vaxart, would like to store your samples for future development of a NoV vaccine. At this time, the exact tests are not known but this will help to further understand the how the oral NoV vaccine works in the body and in the prevention of NoV illness. If you agree to permit your samples to be analyzed, the results on your particular sample will not be provided to you, because it will not be known which samples belong to you.	Removed subject facing language from the protocol.
8.2 Immunogenicity Assessments	Updated to match the SOA-Immunogenicity Assessments and testing. Original text: Primary Immunogenicity Assessments: •Serum: oAnti IgA for both GI.1 and GII.4 by Meso Scale Discovery (MSD) assay by dose level-geometric mean concentration (GMC) at Day 29 and geometric mean fold rise (GMFR) from Day 1 to Day 29. Exploratory Immunogenicity Assessments: •Serum: oAntibody titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA)-Blocking Assay (BT50) - geometric mean titer (GMT) and GMFR at Day 29 and Day 180 oAnti- IgG for both GI.1 and GII.4 by MSD assay - GMC and GMFR at Day 29 and Day 180 oAnti- IgA for both GI.1 and GII.4 by MSD assay - GMC and GMFR at Day 180	Updated to accurately reflect the SOA

	•PBMC: Anti- IgA Antibody Secreting Cells (ASC) for both GI.1 and GII.4 by ELISpot at Day 8 •Nasal Swab: oAnti- IgA for both GI.1 and GII.4 - GMC and GMFI at Day 29 and Day 180 •Saliva: oAnti- IgA for both GI.1 and GII.4 - GMC and GMFI at Day 29 and Day 180 •Fixed Whole Blood (required for blood draw, optional for testing) oB-cell immunophenotyping - Day 8 Updated text: Primary Immunogenicity Assessments: •Serum: oAnti IgA for both GI.1 and GII.4 by Meso Scale Discovery (MSD) assay by dose level-geometric mean concentration (GMC) at Day 8 and Day 29 and geometric mean fold rise (GMFR) from Day 1 to Day 8 to Day 29. Exploratory Immunogenicity Assessments: •Serum: oAntibody titers for both GI.1 and GII.4 by Histo-blood group antigen (HBGA)-Blocking Assay (BT50) - geometric mean titer (GMT) and GMFR at Day 8 and Day 29, and Day 180 oAnti- IgG for both GI.1 and GII.4 by MSD assay - GMC and GMFR at Day 8, Day 29 and Day 180 oAnti- IgA for both GI.1 and GII.4 by MSD assay - GMC and GMFR at Day 8, Day 29 and Day 180	

	•Nasal Swab: oAnti- IgA for both GI.1 and GII.4 - GMC and GMFI at Day 1, Day 8, Day 29 and Day 180 •Saliva: oAnti- IgA for both GI.1 and GII.4 - GMC and GMFI at Day 1, Day 8, Day 29 and Day 180 •Fixed Whole Blood (required for blood draw, optional for testing) oB-cell immunophenotyping -– Day 1, Day 8, Day 29 and Day 180	
9.1.1 Definition of an Adverse Event, Serious Adverse Event, Adverse Event of Special Interest, New Onset of Chronic Illness, and Unanticipated problems	Adverse Event of Special Interest Original text: 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. Updated text: Updated text (addition): 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, an AESI is a 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 Table 12.** **Unsolicited Adverse Events:** Original text: If there are no safety concerns during this period then randomized Subjects will be kept under	Clarify Adverse Event of Special Interest (AESI) Clarify sentinel post dose observation period

	observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation period should be documented (including the actual time of observation) in the source document. Updated text: **Sentinel subjects will be kept at the site under observation for 2 hours after vaccination to ensure their safety.** If there are no safety concerns during this period then randomized Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation period should be documented (including the actual time of observation) in the source document.	
9.1.3 Relationship of Adverse Event Following Immunization to Experimental Vaccine /Vaccine Adverse Event Causality Assessment	Original text: For more details refer to https://www.who.int/publications/i/item/causality-assessment-aefi-user-manual-2019. Updated text: For more details, refer to the 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	Provide updated information
9.1.5 Time Period and Frequency for Collecting AE, AESI, NOCIs, and SAE Information	Original text: All AEs AESIs and NOCIs will be collected from the first dose of study product until the follow-up visit at the timepoints specified in the SoA (Table 1). 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. Updated text: 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 it does not have a causal relationship with study participation. There are two situations to note as below.** **1. 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."** **2. 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.	
9.1.7 Reporting of Adverse Event, Adverse Event of Special Interest, New Onset of Chronic Illness, Serious Adverse Events and Unanticipated problems	Original text: 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 cause the subject to be excluded from the study or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure. Updated text: 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 cause 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.	Provide clarification on reporting of AEs

10.2 Safety Monitoring Committee	Original text: The first 10 randomized subjects will receive open label high dose of active vaccine (2×10^{11}). After Day 8 is completed for the 10 sentinel subjects, enrollment will be paused for a safety review of Solicited Symptoms and unsolicited adverse events. If no dose-related toxicities are observed, and upon consideration of the SMC recommendations following review of safety data, enrollment of the remaining subjects will be initiated. Updated text: The first 10 sentinel subjects will receive open label high dose of active vaccine (2×10^{11}) **in a staggered manner, no more than two (2) subjects dosed in a 24-hour period. All subjects dosed will be observed for a minimum of 2 hours post dose. While ten (10) subjects will be dosed in the sentinel group, to allow for dropouts, eight (8) subjects with complete safety data (defined as Day 1 to Day 8) will be enough to convene the SMC.** If no dose-related toxicities are observed, and upon consideration of the SMC recommendations following review of safety data, enrollment of the **randomized double-blind** study will be initiated.	Provide clarification on the open label-sentinel dosing portion of the study
11.1 Hypothesis	Original text: The following hypotheses will be tested using MSD IgA fold rise as the endpoint of interest. Null Hypothesis: H0: P1 - P2 ≤ 0. Alternative Hypothesis: Ha: P1 – P2 > 0. Where p1 is the percentage of MSD IgA fold rise for the low dose level and P2 for the high dose level. All statistical tests will be performed at the 7% level of significance and confidence intervals will also be presented. Updated text: No hypothesis testing is planned for this study.	There will be no hypothesis testing for this study

11.2 Sample Size Determination	Original text: A sample size of 613 randomized subjects (245 each in medium and high dose levels and 123 in placebo) are required to achieve 80% power, at the 7% significance level (one-sided) using a 2-group fisher exact test with equal allocation to each dose level. Calculation assumes a difference of 10.2% in MSD IgA fold rise between the two dose groups (72.7 % Vs. 62.5%). Placebo was added for safety comparison. The numbers of subjects per dose group are predicted to yield meaningful safety and immunogenicity results. Updated text: A sample size of 125 randomized subjects (50 each in medium and high dose levels and 25 in placebo) in addition to 10 sentinel subjects are 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.	Modification based on clinical judgement
11.5.2 Analysis of the Primary Safety End Points	Original text: Primary-(measured from Day 1 through Day 365) requency, 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 last dose). **Frequency, duration, and severity of SAEs, AESIs and NOCIs for 1 year following the study drug 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	

	Removed: **Frequency, duration, and severity of SAEs, AESIs and NOCIs for 1 year following the study drug dose.** **Added a new endpoint:** Exploratory (measured from Day 30 through Day 365) Frequency, duration, and severity of SAEs, AESIs and NOCIs for 1 year following the study drug dose.	
11.5.3 Analysis of Primary Immunogenicity End Points	Original text: 11.5.3 Analysis of Primary End Points Updated text: 11.5.3 Analysis of Primary and Exploratory Immunogenicity End Points Original Text-Primary: 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. Anti- IgA for both GI.1 and GII.4 by Meso Scale Discovery will be summarized descriptively. Updated text: 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. **For specific primary immunogenicity endpoints please refer to Section 8.2-Immunogenicity Assessments- Primary Immunogenicity Assessments:** Original text Exploratory: none	Clarified Primary Immunogenicity and added Exploratory Immunogenicity

<table>
<tr><td></td><td>Updated text:

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. The analysis of these bio samples is optional.

For specific exploratory immunogenicity endpoints please refer to Section 8.2-Immunogenicity Assessments- Exploratory Immunogenicity Assessments</td><td></td></tr>
<tr><td>14.1 Early Safety Data Review AND/OR Committee</td><td>Original text:

An initial safety review for this study is planned for the first 10 sentinel subjects who will receive the high dose and provide safety data after administration of 2×1011 dose level. All safety data collected will be summarized and reviewed by the (Sponsor’s internal/external safety monitoring committee) for agreement of next steps.

Updated text:

An initial safety review for this study is planned for the first 10 sentinel subjects who will receive the high dose and provide safety data after administration of 2×1011 <u>dose level in a staggered manner, no more than two (2) subjects dosed in a 24-hour period. All subjects dosed will be observed for a minimum of 2 hours post dose</u>. All safety data collected will be summarized and reviewed by the (Sponsor’s internal/external safety monitoring committee) for agreement of next steps.</td><td>The original version of the protocol allowed for enrollment of the 10 sentinel subjects without limitations. This amendment limits sentinel dosing to 2 subjects per 24-hour period and extends the sentinel observation period to 2 hours post dose. This modification was originally captured in a protocol clarification letter (PCL#3) and the ICF modified prior to this amendment.</td></tr>
<tr><td>Appendix 6.0</td><td>Original text:

PROTOCOL VERSION HISTORY
<table><tr><th>Name of the Document with Version Number</th><th>Date</th><th>Summary of Changes and Rationale</th></tr><tr><td>VERSION 1.0</td><td>12 OCT 2022</td><td>INITIAL VERSION</td></tr></table>
Updated text:</td><td>Capture protocol version history and provide a table of protocol changes and rationale</td></tr>
</table>

APPENDIX 6.0 PROTOCOL VERSION HISTORY

Name of the Document with Version Number	Date	Summary of Changes and Rationale
VERSION 1.0	12 OCT 2022	INITIAL VERSION
VERSION 2.0 `	**PENDING**	AMENDMENT 1.0

VXA-NVV-202 Protocol Amendment 1 (Version. 2.0), DATE OF FINAL AMENDMENT

Overall Rationale for the Amendment:

The original version of this phase 2 Norovirus protocol (VXA-NVV-2022) was finalized in October 2022 and submitted for CBER (US FDA), MedSafe (New Zealand Regulatory Authority) and IRB review. Although approvals were obtained, the study design was modified to a US only study to include 10 open label sentinel subjects receiving the high dose. After SMC review of the sentinel safety data 1 week after dosing, a 125 subject double blind randomization portion of the study will follow.

The table below summarizes the changes incorporated into Amendment 1 as well as a brief rationale for each modification.

Section No. & Title	Description of Change	Brief Rationale