Project Brief: VXA-NVV-108 (VAXART)

Full Title of Study/Programme	A phase I, multicenter, randomized, double-blind, placebo-controlled single dose, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of orally administered bivalent GI.1/GII.4 norovirus vaccine in healthy lactating females ≥ 18 years old and their breast-feeding infants
Technical Focus Area/Key Words	Infectious diseases, Vaccine, Vaccine preventable diseases
Rationale	Noroviruses (NoVs) are a genetically diverse group of small, non-enveloped, single-stranded positive-sense RNA viruses that cause acute gastroenteritis. Although NoVs can affect all age groups, infants aged 6 to 23 months have the highest NoV disease burden. Following adoption of the rotavirus vaccine throughout the world, NoV infection emerged as one of the leading causes of infant diarrheal disease. It is estimated that NoVs contribute to 64,000 cases of diarrhea requiring hospitalization, 900,000 clinic visits among children, and up to 200,000 fatalities in children <5 years in developing countries, annually. This highlights the urgent need for the development of interventions to prevent the spread of this contagious disease. Vaxart's NoV oral vaccine uses a novel non-replicating adenoviral-based oral vaccine platform which has been shown to be well tolerated and safe in over 600 healthy adults. Collaborative efforts between Vaxart and partners showed that immunization of lactating ferrets with the Vaxart vaccine resulted in inducible breastmilk immunogenicity. It is hypothesized that that passive transfer of breastmilk antibodies from breastfeeding mothers could inhibit diarrheal disease in their nursing infants. This study will evaluate the immunogenicity effect of the orally administered NoV vaccine in the breastmilk of lactating females and fecal samples in their infants.
Primary Objectives	**Safety** • To determine the safety and tolerability of oral bivalent dosing regimen of GI.1 and GII.4 norovirus vaccine administration in healthy lactating female participants. **Immunogenicity** • To determine the short-term immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and most critically, the association with vaccine specific antibody responses in breastmilk.
Secondary Objectives	**Safety** • To assess the long-term safety of bivalent GI.1/GII.4 norovirus vaccine through 12 months after the last vaccination. **Immunogenicity** • To assess the immunogenicity of oral bivalent GI.1/GII.4 norovirus vaccine administration in healthy lactating female participants and its association with the immunogenicity response in breastmilk.

Exploratory Objectives	• To determine the additional immunogenicity parameters of bivalent GI.1/GII.4 norovirus vaccine including immunogenicity response in breastfed infants. • To determine the clinical effects in subjects presenting with acute gastroenteritis symptoms during the study period.
Primary Endpoints	**Safety** • Frequency, duration, and severity of solicited symptoms of reactogenicity (local, systemic) for 1 week following each dose of study drug. • Frequency, duration, and severity of unsolicited treatment-emergent adverse events (TEAEs), serious AEs (SAEs), adverse events of special interest (AESIs), and new onset of chronic illness (NOCIs) through the active period (4 weeks post last dose). **Immunogenicity** • Serum VP1 specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level. • Breastmilk VPI specific (GI.1 and GII.4) IgA through the active period measured by Meso Scale Discovery (MSD) assay by dose level.
Secondary Endpoints	**Safety** • Frequency, duration, and severity of all SAEs, AESIs, and NOCIs through 12 months after last study drug dose. **Immunogenicity** • Serum VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level. • Breastmilk VP1 specific (GI.1 and GII.4) IgA through 6 months after study drug dose measured by Meso Scale Discovery (MSD) by dose level. • Serum VP1 specific (GI.1 and GII.4) IgG through 6 months after study drug dose measured by Meso Scale Discovery (MSD) assay by dose level. • Serum Blocking titers 50 (BT50) (GI.1 and GII.4) through 6 months after study drug dose measured by Histo-blood group antigen (HBGA) assay by dose level.
Exploratory Endpoints	**Efficacy** • Occurrence of norovirus acute gastroenteritis. **Immunogenicity** • Saliva VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Enzyme-linked immunosorbent assay (ELISA) by dose level • Nasal VP1 specific (GI.1 and GII.4) IgA from lactating mother measured by Meso Scale Discovery (MSD) by dose level. • Infant stool VP1 specific (GI.1 and GII.4) IgA measured by Enzyme-linked immunosorbent assay (ELISA) by dose level • Breastmilk Blocking titers 50 (BT50) (GI.1 and GII.4) measured by Histo-blood group antigen (HBGA) assay by dose level. • Breastmilk Enterocyte culture neutralizing antibody titers (GI.1 and GII.4) measured by norovirus neutralization in enterocyte culture.

Study Design	This study will investigate the safety, tolerability, and immunogenicity of two distinct monovalent norovirus oral vaccine products given together as a single bivalent dose. Both vaccine drug products (DP) will be supplied in the form of small white enteric-coated tablets containing VXA-G1.1-NN or VXA-G2.4-NS.
Study arms	Participants will be randomized in a 2:2:1 ratio to receive active NoV vaccine at medium dose, active NoV vaccine at high dose or placebo, respectively.
Study population	Healthy adult lactating females aged ≥18 years and their breastfeeding infants aged >30 days to 11 months.
Study sample size	11
Follow up/duration	12 months
Study/Programme sites	Hillbrow, Johannesburg
Study/Programme duration	~14 months
Intervention	Bivalent GI.1 and GII.4 vaccine, administered orally at total doses of 1×10^{11} IU/dose and 2×10^{11} IU/dose, respectively.
Operations	Not applicable
Investigators	Wits RHI Prof. Thesla Palanee-Phillips, Co-Principal Investigator Dr. Nkosiphile Ndlovu, Co-Investigator
Other Partners & Collaborators	Novotech CRO
Progress Update as at 20 February 23	Accrual complete: 11 participants enrolled Participant follow-up is ongoing
Frequency of donor narrative report	N/A
Overall Study/Project Contact	Prof. Thesla Palanee-Phillips
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