TITLE: FOOD AND DRUGS AUTHORITY PUBLIC ASSESSMENT REPORT

PART 1: Administrative Details	
Full Study Title	A Phase IIa observer-blind, randomized, controlled, age-de-escalation, single center interventional study to evaluate the safety, reactogenicity, and immune response of the GVGH iNTS vaccine against S. Typhimurium and S. Enteritidis, in adults, children and infants
Protocol/ Document Number	Protocol Amendment 2 Final dated 30th October 2023
Date of Receipt of the Application	17th May 2023
Phase of Study	Phase IIa
Study Registration Details	PACTR202305722094480 FDA/CT/2313
Name and Address of Applicant(s)	Dr. Anthony Kwame Enimil Senior Lecturer/ Co-Investigator Kwame University of Science and Technology Prvate Mail Bag, University Post Office Tel: +233-3224-99897 E-mail:registrar@knust.edu.gh
Name and Address of Sponsor(s)	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 B-1330 Rixensart Belgium
Name and Address of Principal Investigator(s)	Prof. Ellis Owusu-Dabo School of Public Health, College of Health Sciences, University Post Office, Kwame Nkrumah University of Technology, Kumasi E-mail: eowusu-dabo.chs@knust.edu.gh +233201964425
Study Sites	KNUST-IVI Collaborative Centre Agogo Presbyterian Hospital Asante Akyem North District
Study Duration	39 Months
FAPAR Number	FDA/CT/PAR/CTA/247

PART 2: Investigational Product(s)	
Name of Investigational Product(s) including Comparator(s).	GVGH iNTS-GMMA vaccine Menveo Infanrix Hexa
Justification of Investigational Product(s) including comparators	iNTS disease is a major cause of global morbidity and mortality. Malnourished children, those with recent malaria or anemia, and adults with HIV infection are at particularly high risk of disease. The iNTS-GMMA vaccine will potentially address the urgent need for protection against Salmonella Typhimurium and Enteritidis. Menveo serves as an ethical active control,beneficial by protecting against meningococcal disease in adults,children and infants. Infanrix hexa complements Menveo for infants, aligning with routine vaccination schedules and provides booster vaccination against diphtheria, pertussis and tetanus. Placebo use ensures rigorous safety and immunogenicity assessment in adults. This approach ensures thorough evaluation of the iNTS-GMMA vaccine's potential across diverse age groups.

PART 3: Study Summary

Study Objectives

Primary objectives:

1. To identify the preferred dose of each component of the iNTS-GMMA vaccine (Dose A [low], Dose B [medium], or Dose C [high]) for infant participants 6weeks of age.
2. To evaluate the safety and reactogenicity of the iNTS-GMMA vaccine in all participants

Secondary objectives(s):

1. To evaluate the immunogenicity profile of the iNTS-GMMA vaccine in all participants.
2. To evaluate the Sero responses to the iNTS-GMMA vaccine after each administration in all Participants.
3. To evaluate the immunogenicity of co-administered Hepatitis B and Hib vaccines, and Measles and Rubella Vaccine (MR-VAC) in a subset of infant participants 6 weeks of age.
4. To evaluate the sero-response of the co-administered Hepatitis B and Hib vaccines, and MR-VAC in a subset of infant participants 6 weeks of age.

Study Design

A Phase IIa observer-blind, randomized, controlled, age-de-escalation, single centre interventional study to evaluate the safety, reactogenicity, and immune response of the GVGH iNTS vaccine against S. Typhimurium and S. Enteritidis, in adults, children and infants, including dose-finding in infants, in Africa- Study code 217218 (INTS GMMA GVGH-004) (H04_03TP). Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

In the age de-escalation part (safety lead-in), 4 age populations will be evaluated stepwise: 1 adult safety cohort (18–50 years of age), 2 child safety cohorts (24–59 months of age), 3 infant safety

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cohorts (9 months of age) and 3 infant safety cohorts (6 weeks of age). All age groups will be randomized to receive either iNTS-GMMA or a placebo (adults only) or a control vaccine (Menveo [MenACWY], or Infanrix hexa [DTPa-HBV-IPV+Hib]). Each adult participant will receive either the iNTS-GMMA Dose C (high) (the full dose previously used in a Phase I study, INTS GMMA GVGH-002 study) or the control vaccine administered intramuscularly at Day 1 and Day 57, respectively. For safety purposes and following a dose escalation approach, child participants will receive 1 of the 2 dose levels of the candidate vaccine (Dose B [medium] or Dose C [high]) or the control, while infant participants will get 1 of the 3 dose levels (Dose A [low], Dose B [medium], or Dose C [high]) or the control.

Eligibility Criteria

Inclusion criteria list

- Participants and/or participants' parent(s)/Legally Acceptable Representative(s) (LAR), who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the participant/parent(s)/LAR(s) of the participant prior to performance of any study specific procedure.
- Healthy participants as established by medical history, clinical examination, and laboratory investigations.
- Participants satisfying screening requirements.
- Participants negative for HIV, hepatitis B, and hepatitis C. Adult participants must satisfy ALL the following criteria at study entry:
- A male or female between and including 18 and 50 years of age at the time of the first study intervention administration.
- Female participants of non-childbearing potential may be enrolled in the study. Nonchildbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause. Refer to Section 10.4.1 for definitions of women of childbearing potential, menarche and menopause.
- Female participants of childbearing potential may be enrolled in the study, if the participant: − has practiced adequate contraception for 1 month prior to study intervention administration, and − has a negative pregnancy test on the day of study intervention administration, and − has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the study intervention administration series. Refer to Section 10.4.1 for definitions of woman of childbearing potential and adequate contraception.
- Child participants must satisfy ALL the following criteria at study entry:
- A male or female between and including 24 and 59 months of age at the time of the first study intervention administration.
- Previously completed routine childhood vaccinations to the best knowledge of the participant's parent(s)/LAR's.
- Born after a gestation period of ≥37 weeks. Infant participants must satisfy ALL the following criteria at study entry:
- A male or female 6 weeks or 9 months of age at the time of the first study intervention administration.

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- Born after a gestation period of ≥37 weeks.
- Born to a mother seronegative for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV).

Exclusion criteria list

Medical conditions

- Known exposure to S. Typhimurium or S. Enteritidis during the period starting at birth for infants and children, and at 3 years for adults, as documented by patient records (e.g., history of microbiologically confirmed iNTS infection, no testing is required).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions.
- Hypersensitivity, including allergy, to medicinal products or medical equipment whose use is foreseen in this study.
- Progressive, unstable, or uncontrolled clinical conditions.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Major congenital defects, as assessed by the investigator.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by physical examination or laboratory screening tests. *Participants with a minor illness (such as mild diarrhea or mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator. Acute disease and/or fever at the time of enrollment (fever is defined as temperature ≥ 38.0°C). The participant can still be enrolled into the study at a time when the acute disease and/or fever has resolved.
- Recurrent history or uncontrolled neurological disorders or seizures.
- Any clinically significant* hematological (hemoglobin level, white blood cell, lymphocyte, neutrophil, eosinophil, platelet red blood cell count and erythrocyte mean corpuscular volume) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) laboratory abnormality. *The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.
- Undernutrition defined as WHO Z-score less than -2 standard deviation (SD).
- Malaria infection defined as the presence of asexual parasites in the blood.
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws. Any behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the participant's ability to participate in the study.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

Prior/Concomitant therapy

- History of receiving any investigational iNTS or GMMA vaccines in the participant's life.
- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study interventions during the period beginning 30 days before the first dose of study interventions, or their planned use during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 14 days before each dose and ending 28 days after the last dose of study interventions administration, with the exception of flu vaccines and vaccines administered as part of a public health vaccination campaign. Note: Provisions for receipt of seasonal

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influenza or Coronavirus Disease 2019 (COVID-19) pandemic vaccine may need to be considered depending on the season in which the study is conducted.

- A vaccine not foreseen by the study protocol administered during the period starting at 14 days before the first dose and ending 14 days after the last dose of study interventions administration for live vaccines or 7 days in case of inactivated vaccines*, with the exception of flu vaccines or COVID-19 vaccine which may be considered on a case-by-case basis. *In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by public health authorities outside the routine immunization program, the time period described above can be reduced if, necessary for that vaccine, provided it is licensed and used according to its Product Information. Under such circumstances, a participant may be considered eligible for study enrollment and/or study intervention administration after the appropriate window for delay has passed and inclusion/exclusion criteria have been re-checked, and if the participant is confirmed to be eligible.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).
- Administration of immunoglobulins and/or any blood products or plasma derivatives from birth (for infant 6 weeks of age) or during the period starting 3 months before the administration of the first dose of study intervention(s) or planned administration during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study intervention dose(s). For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants/ ≥0.5 mg/kg/day with maximum of 20 mg/day for pediatric participants (infants and children). Inhaled and topical steroids are allowed.

Prior/Concurrent clinical study experience

• Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational intervention (vaccine and drug). Note: EEC directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body'.

Other exclusions

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- History of/current chronic alcohol consumption and/or drug abuse. This will be decided at the discretion of the investigator. Chronic alcohol consumption is defined as one or more of the following: − a prolonged period of frequent and heavy alcohol use − the inability to control drinking once it has begun − physical dependence manifested by withdrawal symptoms when the individual stops using alcohol tolerance or the need to use increasing amounts of alcohol to achieve the same effects − a variety of social and/or legal problems arising from alcohol use.
- Any study personnel or their immediate dependents, family, or household members.
- Child in care. Please refer to the Glossary of terms for the definition of child in care.

Sex of participants

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Both Male and Female

Age boundaries

18–50 years of age, children 24–59 months of age, infants 9 months of age, and infants 6 weeks of age)

Date of Commencement (Expected or Actual)

15th January 2024

Status of Study

Commenced and actively recruiting

PART 4: Scientific Discussion

Summary of Review Comments

Quality

The quality of the Investigational products; GVGH iNTS-GMMA vaccine, Menveo and Infanrix has been assessed by the FDA. The applicant submitted COAs, GMP certificate and CMC (Chemistry, Manufacturing, and Control Information dated 03/2023) for assessing the quality of the investigational products. Queries and outstanding documents were satisfactorily responded to by applicant.

Safety

Following a first time in humans (FTIH) trial with GVGH iNTS-GMMA vaccine, no serious adverse events was recorded.

The potential risks in this study are anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection.

The following documents were reviewed and found satisfactory to fulfill the safety requirement of the trial:

1. Protocol Amendment 2 Final dated 30th October 2023
2. Investigator Brochure Edition 2.0 dated 21st April 2023
3. Insurance cover for study Participants.

Safety endpoint: Solicited AEs, SAEs, as well as unsolicited AEs and deviations from reference and baseline laboratory values are also evaluated for safety administration. Site and systemic events will be recorded to measure the safety and reactogenicity of the iNTS-GMMA vaccine in all participants. The FDA finds this satisfactory.

Efficacy

The underlisted documents were submitted to support Efficacy;

PART 4: Scientific Discussion

1. Protocol Amendment 2 Final dated 30th October 2023
2. Investigator Brochure Edition 2.0 dated 21st April 2023

Evaluation of the efficacy of the intervention was based on the information provided in the protocol and IB. Potential benefits and risk ratio of the intervention provided in the protocol was found positive and satisfactory.
The study objective is to identify the preferred dose of each component of the iNTS-GMMA vaccine (Dose A [low], Dose B [medium], or Dose C [high]) for infant participants 6weeks of age.
The study outcomes provided in the protocol are measurable and correspond to the objectives.

Overall comments

After initial review of the application, the application was deferred with queries to be addressed by the applicant. Following the satisfactory response to all queries on the submission, the study was approved and issued a clinical trial certificate.

The applicant is committed to ensuring that the study is conducted in compliance with the approved protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

All participants will consent to the protocol prior to participation in any study-related activity.

Based on the assessment of medical and ethical principles, the anticipated benefits to the participant justify the foreseeable risks and inconveniences related to the conduct study.

PART 5: Application Review Process

The application was reviewed under the routine approval pathway within 39 working days.

PART 6: Status after Review

The application was approved on 21st November 2023

REFERENCES

1. Protocol Amendment 2 Final dated 30th October 2023
2. Investigator Brochure Edition 2.0 dated 21st April 2023
3. Informed consent form version 1 dated 14th October 2022 (English & Asanti twi)
4. FDA's Clinical Trial Assessment form version for Clinical Trial Application version 1.0 dated 2nd September 2019
5. Non-Clinical Assessment form for Clinical Trial Application
6. Quality Assessment form for Clinical Trial Application
7. Guidelines for Authorization of Clinical Trials of Medicines, Food Supplements, Vaccines and Medical Devices in Ghana
8. Guidelines for Good Clinical Practice in Ghana