Protocol Title

A Phase 3 Randomized, Active-Comparator Controlled, Open-Label Trial to Evaluate the Immunogenicity and Safety of Alternate Two-Dose Regimens of a Bivalent Human Papillomavirus (HPV) Vaccine (Cecolin®) Compared to a Licensed Quadrivalent HPV Vaccine (Gardasil®) in Healthy 9-14 Year-Old Girls in Low and Low-Middle Income Countries

Protocol Number

CVIA 087

Trial Registration

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Sponsor

PATH

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III. ABBREVIATIONS AND ACRONYMS

AE	Adverse Events
ALT	Alanine Aminotransferase
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CIN	Cervical Intraepithelial Neoplasia
cm	Centimeter
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CVIA	Center for Vaccine Innovation and Access
DAIDS	Division of Acquired Immunodeficiency Syndrome
DMC	Data Monitoring Center
DNA	Deoxyribonucleic acid
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
E. coli	Escherichia coli
eCRF	electronic Case Report Form
ED50	Effective Dose producing 50% response
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
ERC	Ethical Review Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HIC	High Income Countries
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
IARC	International Agency for Research on Cancer
ICC	Invasive Cervical Cancer
icddr,b	International Centre for Diarrhoeal Disease Research, Bangladesh
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Unit

Kg	Kilogram
L	Liter
LAR	Legally Acceptable Representative
LD50	Median Lethal Dose
LLOQ	Lower Limit of Quantitation
LMIC	Low- and Middle-Income Countries
Mcg or µg	microgram
md	million doses
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mm	millimeter
MMR	Measles, Mumps, and Rubella
MRC	Malaria Research Center
NMPA	National Medical Products Administration
NRA	National Regulatory Agency
PBNA	Pseudovirion-based Neutralization Assay
PI	Principal Investigator
PPS	Per-Protocol Subset
PSRT	Protocol Safety Review Team
PT	Preferred Term
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Sprague Dawley
SMP	Safety Management Plan
SOC	System Organ Class
SOP	Standard Operating Procedure (s)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBD	To be determined
U	Unit
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantitation
VLP	Virus Like Particles
WHO	World Health Organization
WCG IRB	WIRB-Copernicus Group Institutional Review Board

INVESTIGATOR'S AGREEMENT

Protocol Title

A Phase 3 Randomized, Active-Comparator Controlled, Open-Label Trial to Evaluate the Immunogenicity and Safety of Alternate Two-Dose Regimens of a Bivalent HPV Vaccine (Cecolin®) Compared to a Licensed Quadrivalent HPV Vaccine (Gardasil®) in Healthy 9-14 Year-Old Girls in Low and Low-Middle Income Countries

"The signature below constitutes approval of this protocol and the attachments and provides the required assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements, applicable US federal regulations, and ICH E6 guidelines."

_____ _____

Name and Signature of Principal Investigator **Date**

STATEMENT OF COMPLIANCE AND SPONSOR'S APPROVAL

This trial will be conducted in accordance with Good Clinical Practices (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);
- And the local laws and regulations of Bangladesh and Ghana.

Compliance with these standards provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

_____ _____

Name of the Sponsor's Signatory **Date**
PATH

IV. KEY ROLES AND CONTACT INFORMATION

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V. PROTOCOL SUMMARY

Title	A Phase 3 Randomized, Active-Comparator Controlled, Open-Label Trial to Evaluate the Immunogenicity and Safety of Alternate Two-Dose Regimens of a Bivalent HPV Vaccine (Cecolin®) Compared to a Licensed Quadrivalent HPV Vaccine (Gardasil®) in Healthy 9-14 Year-Old Girls in Low and Low-Middle Income Countries (LMIC)
Short Title	Two Dose Cecolin® (Innovax Bivalent HPV Vaccine) Trial
Protocol Number	CVIA 087
Trial Phase	Phase 3

Investigational Products	• Cecolin® (Innovax), Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine, administered as a 0.5 mL intramuscular dose (IM) • Gardasil® (Merck Sharp Dohme), Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, administered as a 0.5 mL IM
Study Hypotheses **Primary** **Secondary**	• The immunogenicity of Bivalent HPV vaccine (Cecolin®) is non-inferior to Gardasil® in females 9-14 years of age in a two-dose regimen for HPV types 16 and 18 • Bivalent HPV vaccine (Cecolin®) is safe and immunogenic in 9-14 year old females in LMIC
Study Objectives	*Co-Primary Objectives* • Demonstrate the non-inferiority of Cecolin® administered on 0, 6-month; 0, 12-month; and 0, 24-month two-dose regimens, to Gardasil® using a 0, 6-month two-dose regimen, based on HPV Immunoglobulin G (IgG) antibody levels measured one month after the last dose for HPV types 16 and 18 *Secondary Objectives* • Evaluate immunogenicity of Cecolin® and Gardasil®, in all study arms, based on a functional assay pseudovirion-based neutralization assay (PBNA) to measure antibody levels at all time points • Describe seroconversion rates one month after the last dose of Cecolin® (All schedules: 0, 6-month; 0, 12-month; 0, 24-month; and mixed 0, 24-month) and after the last dose of Gardasil® (0, 6-month schedule)) • Evaluate the non-inferiority of a mixed 2-dose regimen consisting of a single dose of Gardasil® followed by a single dose of Cecolin® given 24 months later (0, 24-month schedule), to Gardasil® using a 0, 6-month two dose regimen for HPV types 16 and 18 • Evaluate the non-inferiority of Cecolin® administered on 0-6 months to Gardasil® given on a 0-6 month schedule at 24 months post-first dose • Evaluate the safety of Cecolin® in 9-14-year-old females across multiple geographies administered in two-dose regimens *Exploratory Objectives* • Conduct anti-HPV antibody kinetic modeling based on measurements at baseline, at the time of second dose, and one month after the second dose to determine dose response curves and optimized windows for length of the dose interval • Conduct immunologic bridging to external data (as they become available) from ongoing reduced-dose efficacy studies by enzyme-linked immunosorbent assay (ELISA) or pseudovirion-based neutralization assay (PBNA) at the time of the second dose and one month after the second dose • Evaluate the persistence of antibody responses following a single dose of either Gardasil® or Cecolin® at 6, 12, and 24 months

Study Endpoints	*Primary Endpoint:* • Anti-HPV 16 and 18 IgG antibody geometric mean concentration (GMC), measured by ELISA one month after the second dose on Month 7 (for the 0, 6-month arms), Month 13 (for the 0, 12-month arm) or Month 25 (for the 0, 24-month arm) following vaccination *Secondary Immunologic Endpoints:* • Anti-HPV 16 and 18 serum neutralizing antibody geometric mean titer measured by PBNA compared to ELISA at all time points (in a representative subset) • Seroconversion rate, defined as a 4-fold rise in anti-HPV 16 and 18 IgG antibody as measured by ELISA, at baseline and one month following the last dose • Anti-HPV16 and 18 IgG antibody GMC measured by ELISA one month following the last dose of the Gardasil® 0-6 month two dose regimen and the Gardasil®-Cecolin® 0-24 month two dose regimen • Anti-HPV16 and 18 IgG antibody GMC measured by ELISA 24 months following the first dose of the Gardasil® 0-6 month two dose regimen and the Cecolin® 0-6 month two dose regimen *Secondary Safety Endpoints:* • Number of subjects in each study arm reporting solicited adverse events within 7 days after each dose • Number of subjects in each study arm reporting unsolicited adverse events within one month after each dose • Number of subjects in each study arm reporting serious adverse events (SAEs) occurring at any time throughout study participation *Exploratory Endpoints:* • HPV IgG GMC by ELISA and Geometric Mean Titer (GMT) by PBNA at baseline, at the time of second dose, and one month after the second dose (for immunologic bridging and kinetic modeling) • HPV IgG GMC by ELISA following a single dose of Gardasil® or Cecolin® at 6, 12, and 24 months
Study Rationale	Human papillomaviruses belong to the family Papillomaviridae. The virions are non-enveloped and contain a double-stranded DNA genome. The genetic material is enclosed by an icosahedral capsid composed of major and minor structural proteins, L1 and L2 respectively. These viruses are highly tissue-specific and infect both cutaneous and mucosal epithelium. Based on the genomic sequence of L1, the gene encoding the principal capsid protein, over 200 HPV types have been identified and characterized. Persistent infection with high-risk HPV types is strongly associated with the development of cervical cancer. As of 2018, the International Agency for Research on Cancer (IARC) estimates that there are nearly 570,000 new cases of cervical cancer and over 311,000 cervical cancer-related deaths per annum globally, with over 85% of invasive cervical cancer (ICC) cases occurring in low- and middle-income countries (LMICs). HPV-16 and

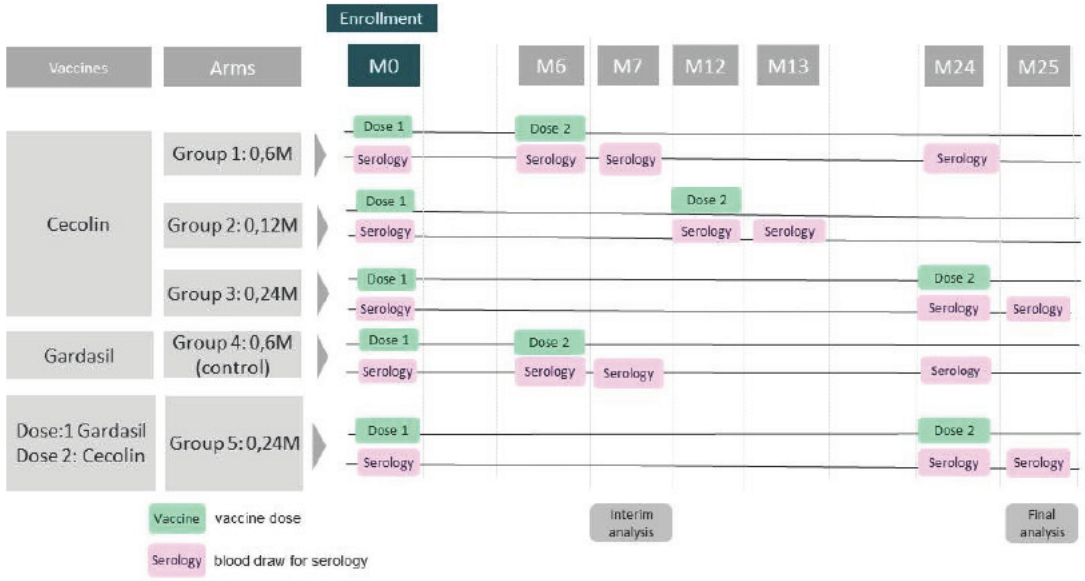
HPV-18 together are responsible globally for 71% of cases of cervical cancer. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers.

Although most infections with HPV cause no symptoms, persistent genital HPV infection can cause cervical cancer in women. Virtually all cervical cancer cases (99%) are linked to genital infection with HPV and it is the most common viral infection of the reproductive tract. HPV can also cause other types of anogenital cancer, head and neck cancers, and genital warts in both men and women. HPV infections are primarily transmitted through sexual contact and can also be transmitted through direct skin-to-skin contacts at other sites of infection.
As recommended by the WHO, the primary target group for HPV vaccinations is young adolescent girls, age 9-14 years.

Three prophylactic HPV vaccines, Gardasil®, Gardasil® 9, and Cervarix® directed against high risk HPV types, are currently available and marketed in many countries worldwide for the prevention of HPV related disease: the quadrivalent vaccine was first licensed in the United States in 2006, the bivalent vaccine in 2007 in the European Union and the nonavalent vaccine in 2014 in the United States. Current evidence suggests that the 3 licensed HPV vaccines have relatively similar efficacy in preventing vaccine type-specific HPV infections and precancerous lesions (grade 2+), the necessary precursors for development of cervical cancer. Following licensure of HPV vaccines, in 2009 WHO initially recommended the vaccine should be included in all national immunization programs, with a primary target population of girls aged 9-13 years, prior to sexual activity. The 2017 WHO guidelines recommended vaccinating all girls ages 9 to 14 years in the initial year of introduction to have a greater impact on future cases of disease.

Although three licensed highly efficacious HPV vaccines produced by multinational manufacturers are available, uptake in LMICs has been slower than expected, due to delayed availability of vaccine from Gavi, the Vaccine Alliance, cost, global supply constraints, and other issues. Unfortunately, despite many calls for the inclusion of the HPV vaccine in national immunization programs, the high cost and other issues related to the vaccines has hindered their wider use in low-resource countries. Any new HPV vaccine coming into the global marketplace must be shown to be comparable to the established vaccines in terms of immunogenicity using the 2-dose schedule, and preferably receive WHO prequalification on that basis. Additionally, for Chinese and Indian HPV Vaccine manufacturers, a broader geographic representation, particularly outside of their countries and in the low-resource populations of interest, will be needed to provide the confidence necessary for country adoption.

Therefore, this planned randomized controlled trial will be evaluating a bivalent HPV vaccine, Cecolin®, in alternate 2-dose regimens, compared to an established HPV vaccine. Gardasil® will be used as the comparator vaccine, as this vaccine is the most widely used in low- and low-middle income countries.

Study Design	This randomized, active-comparator controlled, open-label study will enroll total of approximately 1025 girls aged 9 to 14 years, in one country in Africa (Ghana) and one country in South/Southeast Asia (Bangladesh). Subjects will be randomized 1:1:1:1:1 to receive Cecolin® at 0 and 6 months, 0 and 12 months, or 0 and 24 months, Gardasil® at 0 and 6 months, or Gardasil® at 0 months and Cecolin® at 24 months (see Figure 1). For each arm, blood will be collected for immunologic testing at baseline and one month following second dose. Additional blood collections will occur immediately prior to the administration of the second dose, as well as at additional later time points, for immunobridging to other published and ongoing trials. The study also aims to evaluate the performance of a mixed arm (group 5) of Gardasil followed by Cecolin and collect data on effects of interchangeability. *Figure 1. Study schematic*  Girls of target age will be identified, and their parents contacted to attend an informational session for individual discussion, informed consent, and randomization. The study will be conducted by the research groups in icddr,b in Bangladesh and Malaria Research Center (MRC) in Ghana.
Inclusion Criteria	1. A healthy female between the ages of 9 - 14 years (all inclusive) at time of enrolment 2. Ability and willingness to provide parental consent and, if applicable based on local in-country regulations, participant assent. 3. Parent/Legally acceptable representative (LAR) provides informed consent 4. Anticipated ability and willingness to complete all study visits and evaluations

	5. Living within the catchment area of the study without plans to move during the conduct of the study
Exclusion Criteria	1. Presence of fever or acute disease on the day of vaccination (oral or axillary temperature ≥38˚ C) 2. If participants have childbearing potential, must not be breastfeeding or confirmed pregnant. Women of childbearing potential is defined as any woman or adolescent who has begun menstruation. 3. Receipt of an investigational product within 30 days prior to randomization or planning to participate in another research study involving investigational product during the conduct of this study 4. Receipt of blood and/or blood products (including immunoglobulin) in 3 months prior to any dose of vaccination or blood sampling 5. Receipt of a live virus vaccine (varicella virus containing vaccine, any measles, mumps, or rubella virus containing vaccine such as MMR, or yellow fever vaccine but not including live attenuated influenza virus vaccine) 4 weeks prior and after each dose of HPV vaccine 6. History of any physical, mental, or developmental disorder that may hinder a participant's ability to comply with the study requirements 7. Any malignancy or confirmed or suspected immunodeficient condition such as HIV infection, based on medical history and physical examination 8. Receipt of or history of receipt of any medications or treatments that affect the immune system, such as immune globulin, interferon, immunomodulators, cytotoxic drugs or other drugs known to be frequently associated with significant major organ toxicity since six months prior to the first HPV vaccine dose. Receipt of long-term (greater than or equal to 2 weeks) potentially immunosuppressive corticosteroid use within six months prior to HPV vaccine dose 1 and enrollment or anticipated receipt during the study period. Specifically, potentially immunosuppressive corticosteroids are any parenteral corticosteroid, high dose (>800 mcg/day) beclomethasone dipropionate or equivalent medication. Nasal and topical steroids are allowed. 9. Allergies to any components of the vaccines 10. Current or former participation in HPV vaccine related research. 11. Prior receipt of an investigational or licensed HPV vaccine 12. Any other condition(s) that in the opinion of the investigator would jeopardize the safety or rights of a participant participating in the trial or would render the participant unable to comply with the protocol
Study population	1025 girls (205 per arm) 9-14 years of age

Number of participating sites	Two sites recruited from icddr,b in Bangladesh in South/Southeast Asia and MRC in Ghana in Africa
Study Duration	Overall study duration will be approximately 30 months, assuming a 5- to 6-month period of enrollment.
Participant Duration	Study participation for each individual will be dependent on treatment assignment; either 13, 24, or 25 months.
Safety Monitoring	Throughout the study, the site investigators will provide continuous monitoring to identify, evaluate, and manage adverse events. PATH Medical Officer and CRO medical monitors on an on-going basis will review all severe AE's and Serious Adverse Events (SAE's). The CRO Data Monitoring Center (DMC) will provide periodic safety reports of accruing safety data for review. All SAEs will be reported to local ethics committees, WCG IRB and regulatory authorities, as required. A PATH Data and Safety Monitoring Board (DSMB) formed by independent vaccine, pediatric and infectious disease experts, as well as a biostatistician, will be established to periodically review cumulative data. The responsibilities and procedures of the DSMB will be defined in a DSMB Charter. The PATH DSMB will be responsible for safeguarding the interests of trial participants, assessing safety during the trial, and for monitoring the overall conduct of the clinical trial.
Statistical Considerations	**Sample Size** To control the type I error for the three co-primary non-inferiority hypotheses, a Bonferroni correction resulting in a one-sided alpha of 0.008 and corresponding 98.3% confidence intervals is used. Additional assumptions include 15% dropout, 10% baseline seropositivity, a 0.5 lower bound for non-inferiority of the GMC ratios, and an IgG standard deviation of 0.65 on the log base 10 scale. With these assumptions, 205 subjects per arm or 1025 subjects overall for the primary comparisons are required to achieve 95% for each serotype (16 and 18) or 90% power overall. The mixed 0,24 Gardasil® and Cecolin® will similarly have 205 subjects to provide the same precision for immunogenicity and safety estimates as the four primary arms.

1 BACKGROUND AND RATIONALE

1.1 Burden of Disease

Invasive cervical cancer (ICC), caused by persistent infection with human papillomavirus (HPV), is a major public health problem, especially in developing countries. As of 2018, the International Agency for Research on Cancer (IARC) estimates that there are nearly 570,000 new cases of cervical cancer and over 311,000 cervical cancer-related deaths per annum globally, with over 85% of ICC cases occurring in low- and middle-income countries (LMICs). [1] Approximately 70% of these cases are associated with infection with HPV viral types 16 and 18. In addition to cervical cancer, HPV can lead to genital warts, anogenital cancers and oropharyngeal cancers which further contribute to the burden of disease. Fortunately, primary prevention of cervical cancer is possible through vaccination. Vaccination holds tremendous potential to save lives, particularly in countries where secondary prevention through screening for pre-cancerous lesions and treatment of cervical cancer may not be available or accessible. [2] HPV vaccination has generally been shown to be cost-effective, particularly in resource-constrained settings. HPV vaccination in Gavi-supported countries is expected to avert 20 deaths per 1000 people immunized, which would make HPV the most impactful vaccine in Gavi's portfolio. [3] In the absence of further intervention, 44.4 million cervical cancer cases would be diagnosed globally over the period from 2020 to 2069, with almost two-thirds of cases occurring in LMICs. [4] 311,000 women died in 2018 from cervical cancer, more than 85% of these deaths occurring in low- and middle-income countries. To reach cervical cancer elimination, efforts must be aligned and accelerated. Every country must reach the following global targets by 2030: 90% coverage of HPV Vaccination of girls by 15 years of age; 70% coverage of screening (70% of women are screened with high-performance tests by the ages of 35 and 45 years) and 90% treatment of precancerous lesions; management of 90% of invasive cancer cases.[5]

Four licensed vaccines are currently available against HPV, including Cecolin®. Merck manufactures two vaccines, a quadrivalent vaccine covering four HPV viral types (6, 11, 16, and 18), first licensed in the US in 2006, and a nonavalent vaccine covering 9 viral types (6, 11, 16, 18, 31, 33, 45, 52, and 58), first licensed in the US in 2014. GlaxoSmithKline (GSK) manufactures a bivalent HPV vaccine that protects against two viral types (16 and 18), first licensed in Europe in 2007. Cecolin® which is a bivalent HPV (Types 16, 18) vaccine was licensed in China in December 2019. All four vaccines are composed of the L1 capsid structural protein, which self-assembles into type-specific virus-like particles (VLPs). The Merck vaccines are produced by expression of the L1 protein in *Saccharomyces cerevisiae* (yeast) and formulated with amorphous aluminum hydroxyphosphate sulfate as adjuvant. For the GSK vaccine, the L1 protein is expressed and purified from insect cells infected with recombinant baculovirus, and the vaccine is formulated with AS04, a proprietary adjuvant containing aluminum hydroxide and monophosphoryl lipid A. All three vaccines have been shown to be highly protective against persistent HPV infection as well as premalignant anogenital lesions and cervical and anal cancers related to the HPV types included in the vaccine. GSK's bivalent vaccine seems more efficacious against non-vaccine HPV types 31, 33, and 45 than the quadrivalent vaccine, but the differences were not all significant and might be attributable to differences in trial design. Efficacy against persistent infections with types 31 and 45 seemed to decrease in bivalent trials with increased follow-up, suggesting a waning of cross-protection; more data are needed to establish duration of cross-protection.[14]

In 2009, the World Health Organization (WHO) initially recommended that HPV vaccination should be included in all national immunization programs, with a primary target population of a single-age cohort of girls between the ages of 9 to 13 years, prior to sexual activity. At that time, two HPV vaccines (GSK's bivalent and Merck's quadrivalent) were licensed with a three-dose vaccination schedule (0, 1, and 6 months for the bivalent vaccine or 0, 2, and 6 months for the quadrivalent vaccine). [6] A subsequent reduced dose schedule of two doses for girls aged 9 to 14 years was approved by regulatory agencies for the two HPV vaccines in 2013 (bivalent) and 2014 (quadrivalent), based on immunogenicity data demonstrating responses that were non-inferior to the responses seen in young adult women in whom efficacy was established. In response, WHO updated its policy recommendation to countries in 2014, recommending a two-dose schedule for girls with a spacing of 6 months (5 to 15 months permitted). A three-dose schedule would still be used in those who are immunocompromised or aged greater than 15 years. Licensure of the nonavalent HPV vaccine by Merck in 2014 also included the reduced two-dose schedule for young adolescent girls aged 9 to 14 years. More recently, data from multi-dose clinical trials and observational studies in both girls and women have suggested that even a single dose of HPV vaccine may be substantially protective against 6- or 12-month persistent infection. As a result, several ongoing trials and observational studies of the licensed vaccines are specifically examining single dose efficacy in greater depth.

Since introduction in 2006, HPV vaccine uptake has been highly variable and broadly correlated with country income levels. While introductions were initially weighted toward high-income countries (HIC) in Europe, the Americas, and Australia, tiered pricing later facilitated introduction into middle-income countries. However, introduction in LMICs during those years was largely dependent on external support for limited-scale demonstration projects. Ultimately, Gavi initiated support for HPV vaccination in 2012 to encourage introductions in LMICs. While this has improved uptake substantially, the pace of national introductions has still been slower than anticipated. Factors contributing to the slower introduction of HPV vaccines in LMICs include vaccine cost and the initial delay in financing support, inexperience with rapid vaccine introduction in these age groups, initial Gavi requirements for demonstration projects, low prioritization of cervical cancer prevention, and perceptions of difficult and expensive delivery. According to 2017 data, during the period from 2010 to 2016, the total market volume was approximately 230 million doses (md), of which 5.5 md were for Gavi-supported countries. In addition, constraints in global supply of HPV vaccines have become apparent in the past 1 to 2 years, as annual global demand is expected to increase from 30 to 35 md in 2016 to 70 to 90 md in 2020. From 2021, annual peaks may reach 90 to 100 md per year. The market is expected to stabilize at 80 to 90 md per year when multi-age cohort campaigns are completed in most territories, after 2026. Currently available supply for Gavi-supported countries from 2017 to 2019 cannot accommodate the approved and expected introductions under the new Gavi HPV program. Due to this supply shortfall, the Gavi demand estimates have led to a spreading of country introductions over time and delayed implementation of campaigns for all 9 to 14-old girls. Following this adjustment in demand and introduction approach, supply in 2018 to 2019 is expected to narrowly meet demand for both vaccines with very limited or no buffer capacity.

The two-dose schedule has resulted in lower costs and simplified delivery, which has facilitated adoption in additional LMICs. Adoption of a single-dose regimen would likely accelerate introductions further. Regardless of improved delivery schedules, however, supply and cost

considerations drive the need for new vaccines. Entry of additional low-cost HPV vaccines in the market may represent the most effective solution to provide stability in the global supply and improve access to the vaccine in LMICs.

1.2 Pathogen

HPV is a virus with double-stranded circular DNA from the papillomavirus family. All HPVs have icosahedral capsids. They include genes that express nonstructural proteins needed for DNA replication, transcription, or viral assembly and release. Genes transcribed late (L-genes) include L1 and L2, which encode viral capsid proteins referred to as L1 and L2, respectively. The papillomavirus capsid is made of two structural proteins: the major basic protein (L1) and the minor basic protein (L2). Each capsid contains 72 pentameric capsomeres, each made of 5 L1 and L2 proteins. Viral assembly occurs in the nucleus of the cell; L1 protein self-assembles into virus-like particles, while L2 has a lesser-known role, but may be involved with virion production. [7-9] Expression of proteins E6 and E7 is associated with integration of viral DNA into the host genome, malignant transformation, and ultimately progression to cancer. [10]

More than 200 different HPV types have been identified and classified into five genera, α, β, γ, μ, and ν. The HPV types with a proven oncogenic potential, a well-established role in cervical carcinoma and a significant percentage of other anogenital tract and oral carcinomas belong to the α genus. When integrated into the host squamous epithelial cell genome, the high-risk HPV types (16 and 18) will express gene E6, which will degrade tumor suppressor protein p53. E7, also expressed early, is an oncoprotein that binds the tumor suppressor retinoblastoma protein and allows HPV DNA synthesis.

High risk HPVs, particularly HPV 16 and 18, are associated with high-grade cervical and anal dysplasia and invasive carcinoma. HPV is transmitted by skin-to-skin or mucosa-to-mucosa contact and enter the body via cutaneous or mucosal trauma. HPV infects skin and mucous membrane keratinocytes. HPV is believed to infect keratinocytes and remain dormant, suppressed by the immune system. The dormant virus will also be non-transmissible until a patient is immunosuppressed, at which time it may cause differentiation of the basal epithelial cells of the infected host. HPV generally avoids blood and humoral immune detection but is cleared via a cell-mediated immune response. Estimates of duration of HPV infection are 8 months. Median duration of infection for oncogenic types is estimated to be 13 months and less for nononcogenic HPV types (8 months), with time for clearance similarly affected (8 months for oncogenic and 5 months for nononcogenic types).

Oncogenic HPV types have an affinity for infecting the immature squamous cells in both the anus and cervix. This area, referred to as the transformation zone, occurs where the outer cervix squamous epithelium transitions to columnar cells of the endocervix, and in the anus where the epithelium changes from the nonkeratinizing squamous epithelium of the anus to the columnar epithelium of the rectum. Persistent infection with high-risk types of HPV is necessary for progression to high-grade lesions or cancer.

HPV infection has a critical role in common dermatologic and sexually transmitted diseases, as well as in some of the most frequent and most burdensome cancers worldwide. More than 600,000 cancers are attributed to HPV infection worldwide. Mortality from HPV is caused by oncogenic

HPV types whose infections lead to dysplasia and cancer. The role of vaccines in prevention of the consequences of this common infection is paramount. As worldwide HPV vaccination strategies are struggling against poor compliance, ignorance, and misconceptions, proper knowledge spreading among professionals and common people is the main future endeavor. Further studies showing evidence of HPV etiology with other types of cancer, other than cervical and other diseases will also add more volume to the value, function, and potential of HPV vaccination.[9]

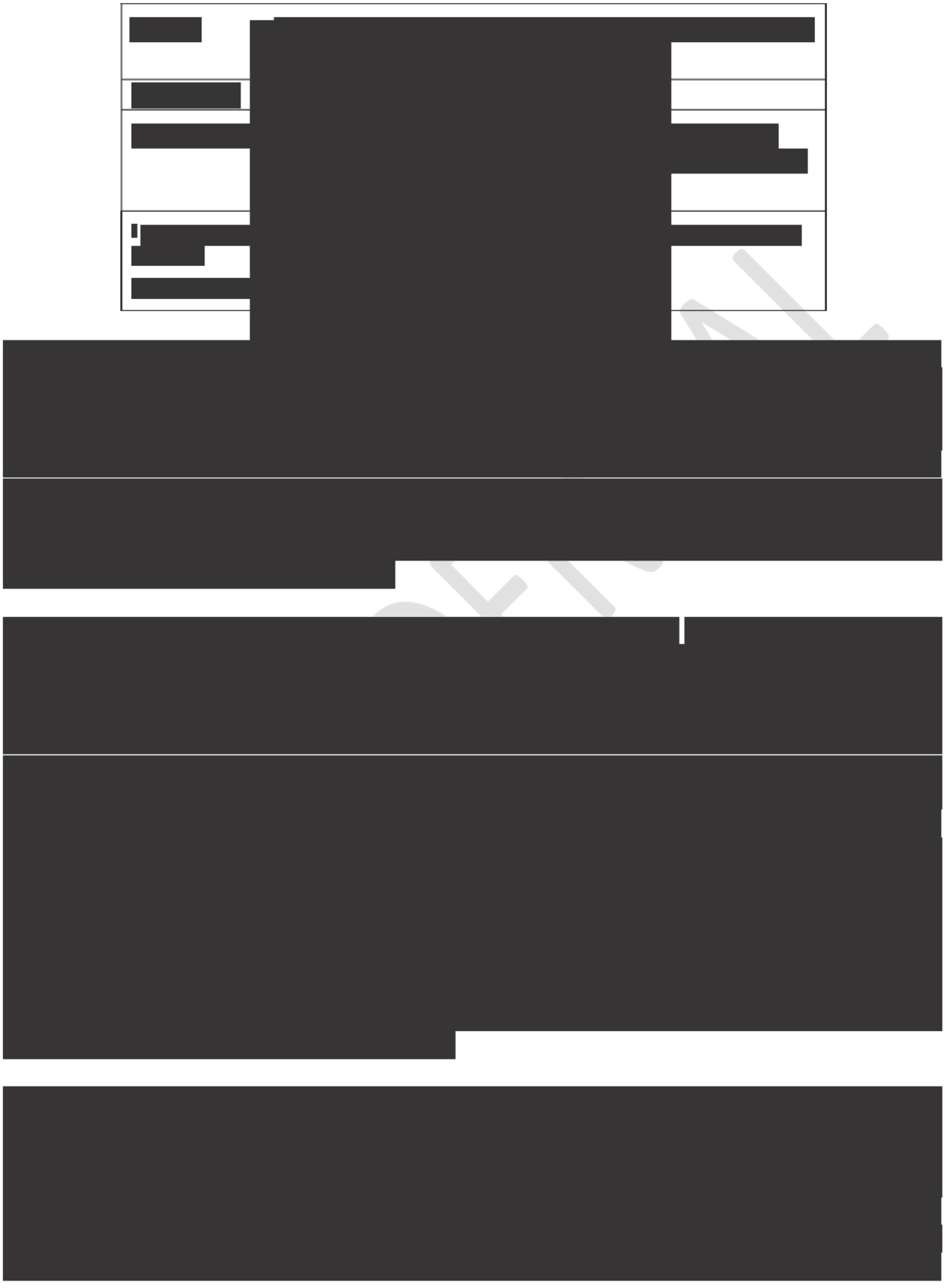
1.3 Description of Study Vaccine

Cecolin® (Innovax), developed by Innovax, based in Xiamen, China is a bivalent vaccine directed against HPV types 16 and 18. This VLP-based vaccine is composed of L1 proteins produced in a recombinant E. coli expression system and adjuvanted with aluminum hydroxide.
Each dose of the vaccine contains 40µg HPV16 VLPs & 20µg HPV18 VLPs. In late December 2019, Cecolin® was approved for licensure by the Chinese National Medical Products Administration (NMPA), in a three-dose regimen in women aged 18 to 45 years and a two-dose regimen in girls aged 9 to 14 years. It is presented as 0.5 ml of suspension per dose in 2ml vial. Shelf life is 2 - 8°C 36 months in application.

1.4 Summary of Nonclinical Studies of Study Vaccine

1.4.1 Toxicology

[redacted]. These studies demonstrated that the vaccine was well-tolerated and had no signs of systemic toxicity. Please see the Investigators' Brochure for further details.



[redacted]

1.4.2 Preclinical Immunogenicity studies

The pharmacology program included primary pharmacodynamics studies conducted in vivo. Secondary pharmacodynamics, safety pharmacology, drug interaction and pharmacokinetic studies were considered not to be relevant to the safety or activity of this prophylactic vaccine and were therefore not conducted. [redacted]

[redacted]

1.5 Summary of Clinical Studies of Study Vaccine

1.5.1 Phase 1 Data

The safety of this vaccine was analyzed in an open-label Phase 1 clinical trial in Jiangsu province, China. Thirty-eight healthy women from 18 to 55 years of age were enrolled and vaccinated at 0, 1, and 6 months. Adverse events that occurred within 30 days after each vaccination and serious adverse events that occurred throughout the study were recorded. In addition, blood parameters were tested before and after each vaccination. All but one woman received all three doses. Changes in blood parameters after each injection were random, most of those mild, and not clinically significant. [11] Some post-vaccination sample values were worse than the pre-vaccination sample, including 68 pairs that changed from normal to grade 1, 2 pairs that changed from normal to grade 2, 1 that changed from grade 1 to grade 2 and 1 that changed from grade 2 to grade 3. Most of the abnormal indexes were mild or moderate, with the exception of one 21 year-old woman who suffered from a grade 3 abnormality after the first vaccination. Her Alanine Aminotransferase (ALT) level was 97 U/L (3.1 times over the upper limit of normal range [ULN], grade 2) at enrollment and increased to 167 U/L (5.4 ULN, grade 3) after the first vaccination. Without any medical intervention, her ALT level spontaneously recovered to within normal levels after one month (10 days later: 66 U/L, 20 days later: 44 U/L, 30 days later: 20 U/L).

Adverse Events: Thirty-two (84.2%) of the participants reported adverse events, most adverse events were mild, of short duration and resolved spontaneously. No serious adverse events occurred during the study. The rate of local AEs after each vaccination was similar (P = 0.1143). Systemic AEs were less frequent after the last vaccination than they were after the first vaccination (P = 0.0405). The rate of unsolicited AEs was lower after the last vaccination than it was after the first and the second vaccinations (P = 0.0006 and 0.023[9], respectively). Most AEs were mild or

moderate, 80.8% were grade 1 and 19.2% were grade 2. No unsolicited AEs of grade 3 or higher were reported. The most common local, systemic, and unsolicited AEs were pain in injection site (17/38, 44.7%), raised body temperature (11/38, 28.9%), headache (7/38, 18.4%), fatigue (6/38, 15.8%), nausea (5/38, 13.2%), and upper respiratory tract infection (10/38, 26.3%). There was no significant difference between women less than 40-year-old and women over 40-year-old with regard to the rates of solicited AEs (P = 0.4384) and unsolicited AEs (P = 0.1786).

Reactogenicity: The results of the study showed that a new Escherichia coli expressed recombinant HPV 16/18 bivalent vaccine is well tolerated in healthy women and supported further immunogenicity and efficacy studies for this HPV vaccine candidate.

1.5.2 Phase 2 Data:

Cecolin® was subsequently evaluated for safety and immunogenicity in a large Phase 2 randomized, double-blinded, controlled trial that enrolled women ages 18–25 years in China. Total 1600 eligible participants were randomized to receive 90 mcg, 60 mcg, or 30 mcg of the recombinant HPV 16/18 bivalent vaccine or the control hepatitis B vaccine on a 0, 1- and 6-month schedule. [12] The vaccine was given by intramuscular injection at day 0, month 1 (±10 day), and month 6 (±30 day). After vaccination, all the participants remained at the vaccination site and were observed for 30 min for immediate adverse reactions. They were then visited or called by the investigators at 6-hour, 24-hour, 48-hour, 72-hour, 7-day, 14-day and 28-day after each dose. Any observed or reported adverse events (AEs) that occurred within one month after each vaccination were recorded by the participants on safety memory aids, using a four-grade scale of symptom intensity under the guidance of investigators. Serious adverse events (SAEs) were recorded throughout the study. Serum samples were collected at Day 0 before the first vaccination and at month 7 for all the participants.

Assessment of the immunogenicity of the bivalent HPV vaccine was based primarily on the neutralizing antibody response to the corresponding types in the baseline seronegative participants. Compared with the 0.8% seroconversion rate of neutralizing antibodies in the control group, 100% of the participants who received three doses of the HPV vaccine produced neutralizing antibodies against HPV 16, with GMTs of approximately 10,000 (range 160 to 163,840). Except for one participant in the 30-mcg group, all the participants who received three doses of the HPV vaccine were seroconverted for neutralizing antibodies against HPV 18, with similar GMTs of approximately 7,500 (range160 to 81,920) for the three dosage groups. Although the GMTs of antibodies against type 18 in the three vaccine groups were similar, the GMTs of antibodies against type 16 in the 30-mcg group were marginally lower than those in the 60 mcg and 90 mcg groups.

With respect to the antibody response to type 16, the titers of the participants in the 30-mcg group seemed lower than those in the 60 mcg and 90 mcg groups. However, the antibody response titers to type 18 were similar for the three dosage groups. The IgG antibody responses were also assessed by a VLP-based ELISA. The findings were quite similar to those for the neutralizing antibodies. All the participants who received three doses of the HPV vaccine were seroconverted for IgG antibodies against both HPV types, and the GMTs of antibodies against both types induced by the 30-mcg dose were lower than those with the higher doses. The preexisting type-specific antibodies had no or minimal effect on the vaccine-induced antibody levels.

The tested vaccine was well tolerated. The safety outcomes between the dose groups and the control group were generally similar. The adverse events were generally mild and self-limiting and did not affect overall compliance with the vaccination schedule. No serious adverse events were related to the vaccination. The frequency of local, systemic, and unsolicited adverse events was similar in the participants receiving the 30, 60, or 90 mcg dose or the control vaccine. Almost all the adverse events were mild or moderate (<grade 3). Pain at the injection site was the most common local adverse event in any of the vaccine groups as well as in the control group, with a similar rate of approximately 20%. The second most common local reaction was induration at a much lower rate of 3–5%. The most common systemic adverse event was pyrexia, with a similar rate of 37–39% in all the groups. The rates of headache and fatigue were both approximately 7–9%. The frequencies of other systemic events were all less than 5%. Three participants, all in 90 mcg vaccine group, reported solicited adverse events of grade 3. Two of them reported an induration with a diameter of approximately 40 mm; they recovered within 5 days without treatment. The third participant reported the highest sub-axillary body temperature of 39.1˚C on day 5 after the second dose and completely recovered 6 days later following treatment. There was no notable difference in the reported solicited adverse events in the vaccine recipients who were IgG seropositive at baseline compared with the IgG seronegative vaccine recipients in the same group. None of the fourteen reported serious adverse events (SAEs) was related to the vaccination.

Based on the safety and immunogenicity data, a 60-mcg dose formulation, containing 40 mcg of HPV 16 L1 VLPs and 20 mcg of HPV 18 L1 VLPs, was planned for further efficacy trials.

A separate Phase 2 trial of the Cecolin® was a single-center, age-stratified immune-bridging study (ClinicalTrials.gov, NCT02562508) conducted in China. A total of 979 participants were enrolled to evaluate whether the immunogenicity of girls aged 9–17 years receiving 3 doses (day 0, month 1 (day 28–60) (n=453) and month 6 (day 150–240)) or girls aged 9–14 years receiving 2 doses (at months 0 and 6)) (n=301) was non-inferior to that in women aged 18–26 years receiving 3 doses (at months 0, 1 and 6) (n=225).[17] Most of the reported adverse events in the participating girls and women were mild, and none of the SAEs reported were vaccine related. Two antibody indexes, IgG antibody and neutralizing antibody, were measured. For both antibody indexes and for both HPV-16 and HPV-18, the antibody levels in girls aged 9–17 years receiving 3 doses and girls aged 9–14 years receiving 2 doses were higher than and noninferior to those in women receiving 3 doses. The GMT ratios were similar to the three licensed HPV vaccines. Additionally, in the 3-dose groups, noninferiority at month 6 was established in girls compared with women, further verifying the data at month 7.

In this study a total of 57.6% (564/979) of the study participants reported adverse reactions, and only 1.2% (12/979) were judged as grade 3 or more severe. The most frequently reported symptoms, with occurrence rates of more than 10% in at least one study group, were pain, fever and cough, among which all but 2 were mild, at grade 1 or 2. Three participants reported serious adverse events (SAEs) during the study (from day 0 to month 7), and none of them were considered vaccine-related. In the ages 9-14 year old, there were 163 solicited AEs reported (54.2%) in two dose group and 190 solicited AEs (61.4%) in the three dose group, most of them were mild in nature.

In conclusion, the immunogenicity of the E. coli-expressed candidate HPV bivalent vaccine in girls aged 9–17 years receiving 3 doses or girls aged 9–14 years receiving 2 doses is non-inferior to that in women aged 18–26 years receiving 3 doses.

1.5.3 Phase 3 Data:

In the next stage, Cecolin® was evaluated in a three-dose regimen (0, 1, and 6 months) in a Phase 3 randomized active-controlled trial in China in 7,372 women aged 18 to 45 years (divided equally among the 18 to 26 year and 27 to 45 year age groups).[13] Co-primary endpoints included high-grade genital lesions and persistent infection (over 6 months) associated with HPV-16/18. The primary analysis was performed on a per-protocol susceptible population of individuals who were negative for relevant HPV type-specific neutralizing antibodies (at day 0) and DNA (at day 0 through month 7) and who received three doses of the vaccine.

The participants were followed for an average of 3.3 years. In the per-protocol subset (PPS) for the pathological endpoint, which included 6602 of 7372 women who underwent randomization (89.6%), 10 women in total, all in the control group, developed high-grade genital lesions associated with HPV-16/18 (seven CIN2 cases and three CIN3 cases). The HPV vaccine prevented 100.0% (95% CI 55.6% to 100.0%, 0 of 3306 in the vaccine group versus 10 of 3296 in the control group) of HPV-16/18–related high-grade genital lesions in this population. Furthermore, the vaccine provided an efficacy of 97.8% (95% CI 87.1% to 99.9%, 1 of 3240 versus 45 of 3246) against persistent infection (over 6 months) associated with HPV-16/18 in the per protocol cohorts. Additionally, the vaccine statistically significantly lowered the risk of incident infection and cytological abnormalities of the cervix related to HPV-16/18.

One month after the third dose of the HPV vaccine, all 2302 baseline seronegative women seroconverted for anti-HPV-16 (100.0%); the mean IgG antibody level (GMC) was 790.4 IU/mL (95% CI 767.5 to 813.9 IU/mL), which was over 100 times higher than the mean antibody level acquired from natural infection (7.1 IU/mL, calculated from the antibody level at day 0 of 367 seropositive participants at entry). For HPV-18, the seroconversion rate was 99.9% (2799 of 2802), with a GMC of 267.9 IU/mL (95% CI 260.4 to 275.6 IU/mL), which was over 50 times higher than the mean antibody level acquired from natural infection (4.7 IU/mL, the GMC of day 0 from 149 seropositive participants at entry). The vaccine-induced IgG antibodies decreased approximately 8 times (anti-HPV-16) or approximately 10 times (anti-HPV-18) during the first year after the third vaccination and then remained relatively stable to month 42 at levels of approximately 100 IU/mL (anti-HPV-16) and approximately 25 IU/mL (anti-HPV-18).

Total AEs, local or systemic reactions, and unsolicited events occurred at similar rates between groups. Pain at the injection site (34.0%) and fever (>37.0˚C, 35.1%) were the most common reactions that occurred in the vaccine group. Grade 1 fever was defined as a temperature of more than 37.0ºC, and grade 3 fever was defined as a temperature of more than 39.0ºC. Only 0.2% of the subjects developed grade 3 fever. Most AEs were mild. The participants reporting SAEs were distributed similarly between groups, and none of the SAEs were considered to be related to vaccination.

Ultimately, Cecolin® demonstrated consistent high prevention efficacy against HPV-16/18–associated CIN2+ lesions, CIN1+ lesions, and persistent infection in susceptible women.

Additionally, the vaccine statistically significantly lowered the risk of incident infection as well as cytological abnormalities of the cervix related to HPV-16/18. Similar to the three licensed HPV vaccines, the test vaccine showed no effect on reducing genital lesions or clearing the prevalent infections for women with detectable HPV DNA of the vaccine types at baseline.

1.6 Potential Risks and/or Benefits of Study Vaccine

Participants may potentially benefit from receiving a recommended vaccine that is not routinely available if they are in a Gardasil® arm of the study. Potential benefits to enrolled participants in the current trial could be protection from HPV related infections, the identification of undetected medical conditions during medical examination, education about HPV and cervical cancer and its prevention and treatment, education on safe practices and access to medical care for the participant for any illnesses occurring during the trial period.

Hypersensitivity reactions may occur following the administration of any vaccine, including licensed vaccines, which in rare circumstances may be life-threatening. Investigators are informed in the protocol and product insert of this possibility following study vaccine administration. The main risks of this study are risks of HPV vaccines to cause some side effects including development of fever, headache, fatigue, cough, muscle pain, nausea, diarrhea, dizziness, vomiting, allergic dermatitis, rash, syncope, abscess, anorexia, pruritus, pain, induration, swelling, erythema, or discomfort at injection site. Most of the above adverse reactions are mild to moderate. These events are similar to those reported in other HPV vaccine clinical trials. These will be explained to parents in the consent form.

1.7 Overall Development Strategy

[redacted]

Cecolin® was licensed in China in December 2019, and obtained WHO prequalification October 2021. [redacted]

[redacted]

1.8 Study Rationale

Cervical cancer and other diseases related to HPV infection continue to cause a significant burden of disease worldwide, particularly in LMICs. Although three licensed highly efficacious HPV vaccines produced by multinational manufacturers are available, uptake in LMICs has been slower than expected, due to delayed availability of vaccine from Gavi, cost, recent global supply constraints, and other issues. Demand forecasts from several organizations have estimated that the annual global HPV vaccine supply will need to be 100 md by 2025 with LMIC supply needs leveling at about 65 md from 2026 onwards, assuming Gavi-funded large-scale catch-up vaccinations of all 9 to 14 year old girls are completed by that time. Hence, additional safe and efficacious HPV vaccine sources are desirable to lower the acquisition cost, particularly for developing countries.

Cecolin® has been recently approved in China, but additional data will be needed to support global use, including: 1) safety and immunogenicity data from outside China and in countries of highest potential impact; 2) direct comparative data versus a WHO-prequalified HPV vaccine; and 3) flexible schedules to permit extended-interval (i.e. ≥12 months) vaccination. Data generated to address the latter gap would support alternative delivery strategies and would additionally provide critical information on immune responses following a single dose of vaccine.

Gardasil controls the largest share of the HPV vaccine market in low- and low-middle income countries worldwide, and therefore represents the most appropriate reference standard to generate evidence for WHO prequalification, global policy, and country -level decision-making.

Therefore, we propose to conduct this phase 3 trial to evaluate Cecolin®, in which we compare three different two-dose regimens, with Gardasil®. We propose to use Gardasil® as the comparator vaccine, as this vaccine is the most widely used in LMICs. This study design will also permit an exploratory evaluation of a single dose of the vaccine for as long as 24 months, and the performance of a mixed regimen of Gardasil® and Cecolin® which will be administered 24 months apart.

2 HYPOTHESIS, OBJECTIVES AND ENDPOINTS

2.1 Study Hypothesis / Hypotheses

- The immunogenicity of Bivalent HPV vaccine (Cecolin®) is non-inferior to Gardasil® in females 9-14 years of age in two dose regimens for HPV types 16 and 18
- Bivalent HPV vaccine (Cecolin®) is safe and immunogenic in 9-14 year old females in LMIC

2.2 Study Objectives

2.2.1 Co-Primary Objectives

- Demonstrate the non-inferiority of Cecolin® administered on 0, 6-month; 0, 12-month; and 0, 24-month two-dose regimens, to Gardasil® using a 0, 6-month two-dose regimen, based on HPV Immunoglobulin G (IgG) antibody levels measured one month after the last dose for HPV types 16 and 18

2.2.2 Secondary Objectives

- Evaluate immunogenicity of Cecolin® and Gardasil®, in all study arms, based on a functional assay pseudovirion-based neutralization assay (PBNA) to measure antibody levels at all time points
- Describe seroconversion rates one month after the last dose of Cecolin® (All schedules: (0, 6-month; 0, 12-month; and 0, 24-month) and after the last dose of Gardasil® (0, 6-month schedule))
- Evaluate the non-inferiority of a mixed 2-dose regimen consisting of a single dose of Gardasil® followed by a single dose of Cecolin® given 24 months later (0, 24-month schedule), to Gardasil® using a 0, 6-month two dose regimen for HPV types 16 and 18
- Evaluate the non-inferiority of Cecolin® administered on 0-6 months to Gardasil® given on a 0-6 month schedule at 24 months post-first dose
- Evaluate the safety of Cecolin® in 9-14-year-old females across multiple geographies administered in two-dose regimens

2.2.3 Exploratory Objective

- Conduct anti-HPV antibody kinetic modeling based on measurements at baseline, at the time of second dose, and one month after the second dose to determine dose response curves and optimized windows for length of the dose interval
- Conduct immunologic bridging to external data (as they become available) from ongoing reduced-dose efficacy studies by ELISA or PBNA at the time of the second dose and one month after the second dose
- Evaluate the persistence of antibody responses following a single dose of either Gardasil® or Cecolin® at 6, 12, and 24 months

2.3 Study Endpoints

2.3.1 Primary Endpoints

- Anti-HPV 16 and 18 IgG antibody geometric mean concentration (GMC), measured by enzyme-linked immunosorbent assay (ELISA) one month after the second dose on Month 7 (for the 0, 6-month arms), Month 13 (for the 0, 12-month arm) or Month 25 (for the 0, 24-month arm) following vaccination

2.3.2 Secondary Endpoint

2.3.2.1 Secondary Immunologic Endpoints:

- Anti-HPV 16 and 18 serum neutralizing antibody geometric mean titer measured by PBNA compared to ELISA at all time points (in a representative subset)
- Seroconversion rate, defined as a 4-fold rise in anti-HPV 16 and 18 IgG antibody as measured by ELISA, at baseline and one month following the last dose
- Anti-HPV16 and 18 IgG antibody GMC measured by ELISA one month following the last dose of the Gardasil® 0-6 month two dose regimen and the Gardasil®-Cecolin® 0-24 month two dose regimen

- Anti-HPV16 and 18 IgG antibody GMC measured by ELISA 24 months following the first dose of the Gardasil® 0-6 month two dose regimen and the Cecolin® 0-6 month two dose regimen

2.3.2.2 Secondary Safety Endpoints:

- Number of subjects in each study arm reporting solicited adverse events within 7 days after each dose
- Number of subjects in each study arm reporting unsolicited adverse events within one month after each dose
- Number of subjects in each study arm reporting serious adverse events (SAEs) occurring at any time throughout study participation

2.3.3 **Exploratory Endpoints**

- HPV IgG GMC by ELISA and GMT by PBNA at baseline, at the time of second dose, and one month after the second dose (for immunologic bridging and kinetic modeling)
- HPV IgG GMC by ELISA following a single dose of Gardasil® or Cecolin® at 6, 12, and 24 months

3 STUDY DESIGN

This randomized, active-comparator controlled, open-label Phase 3 study will enroll approximately 1025 girls aged 9 to 14 years in one country in Africa (Ghana) and one country in South/Southeast Asia (Bangladesh).

Subjects will be randomized 1:1:1:1:1 to receive Cecolin® at 0 and 6 months, 0 and 12 months, or 0 and 24 months, Gardasil® at 0 and 6 months, or Gardasil® at 0 months and Cecolin® at 24 months (see Figure 1). For each arm, blood will be collected for immunologic testing at baseline and one month following second dose. Additional blood collections will occur immediately prior to the administration of the 6-month, 12-month or 24-month dose for immunobridging to other published and ongoing trials and 24 months after the first dose in groups 1 and 4 for noninferiority comparison.

Girls of target age will be identified, and their parents contacted to attend an informational session for individual discussion, informed consent, and randomization.

The study will be conducted by two research groups in two selected countries Bangladesh and Ghana.

The vaccination arms will be divided into 5 groups as below:
Group 1: Cecolin® 0 and 6 months
Group 2: Cecolin® 0 and 12 months
Group 3: Cecolin® 0 and 24 months
Group 4: Gardasil® 0 and 6 months (control)
Group 5: Gardasil® 0 months and Cecolin® 24 months

4 STUDY POPULATION

4.1 Description of Study Population

The study population will include approximately 1025 girls (205 per arm) 9-14 years of age. The study will have two sites recruited from one country in Africa (Ghana) and one country in South/Southeast Asia (Bangladesh).

Final eligibility determination will depend on the results of the medical history, clinical examination, fulfillment of all the inclusion and absence of any of the exclusion criteria, and appropriate understanding of the study and completion of the consent process by parents of all participants and assent of adolescent participants.

Investigators should always use good clinical judgment in considering a participant's overall fitness for inclusion in the trial. Some participants may not be appropriate for the study, even if they meet all the eligibility criteria. In addition, the participants should reside in reasonable proximity to the study site, without plans to leave the area prior to the end of the study. A sufficient number of healthy young adolescents will be screened, with consent, to randomize the required sample size for the study.

4.2 Inclusion Criteria

1. A healthy (determined by investigator's assessment following medical history and physical examination) female between the ages of 9 - 14 years (all inclusive) at time of enrollment
2. Ability and willingness to provide parental consent and, if applicable based on local in-country regulations, participant assent.
3. Parent/LAR provides informed consent
4. Anticipated ability and willingness to complete all study visits and evaluations
5. Living within the catchment area of the study without plans to move during the conduct of the study

4.3 Exclusion Criteria

1. Presence of fever or acute disease on the day of vaccination (oral or axillary temperature ≥38˚ C)
2. If participants have childbearing potential, must not be breastfeeding or confirmed pregnant. Women of childbearing potential is defined as any woman or adolescent who has begun menstruation.
3. Receipt of an investigational product within 30 days prior to randomization or planning to participate in another research study involving investigational product during the conduct of this study
4. Receipt of blood and/or blood products (including immunoglobulin) in 3 months prior to any dose of vaccination or blood sampling
5. Receipt of a live virus vaccine (varicella virus containing vaccine, any measles, mumps, or rubella virus containing vaccine such as MMR, or yellow fever vaccine but not including live attenuated influenza virus vaccine) 4 weeks prior and after each dose of HPV vaccine

6. History of any physical, mental, or developmental disorder that may hinder a participant's ability to comply with the study requirements
7. Any malignancy or confirmed or suspected immunodeficient condition such as HIV infection, based on medical history and physical examination
8. Receipt of or history of receipt of any medications or treatments that affect the immune system, such as immune globulin, interferon, immunomodulators, cytotoxic drugs or other drugs known to be frequently associated with significant major organ toxicity since six months prior to the first HPV vaccine dose. Receipt of long-term (greater than or equal to 2 weeks) potentially immunosuppressive corticosteroid use within six months prior to HPV vaccine dose 1 and enrollment or anticipated receipt during the study period. Specifically, potentially immunosuppressive corticosteroids are any parenteral corticosteroid, high dose (>800 mcg/day) beclomethasone dipropionate or equivalent medication. Nasal and topical steroids are allowed.
9. Allergies to any components of the vaccine
10. Current or former participation in HPV vaccine related research.
11. Prior receipt of an investigational or licensed HPV vaccine
12. Any other condition(s) that in the opinion of the investigator would jeopardize the safety or rights of a participant participating in the trial or would render the participant unable to comply with the protocol.

4.4 Continued Eligibility Confirmation for Subsequent Vaccination

The following events constitute absolute contraindications to HPV vaccination. If any of these events occur during the study, the participant must not receive additional doses of the vaccine but should be appropriately followed up for safety by the investigators.

- Hypersensitivity reaction following the administration of the study vaccine.
- Detection of one or more of the exclusion criteria during dosing period. (except fever)
- Significant intercurrent illness.
- Protocol deviation rendering data unusable or increasing risk for subsequent vaccinations.
- Receipt of HPV vaccine outside of study.
- Any condition which, in the opinion of the investigator, might jeopardize the safety of the participant or interfere with the evaluation of the study objectives.

The following events constitute contraindications to administration of the study vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the participant may be vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the Investigator.

- Acute disease and / or fever at the time of vaccination. (temporary deferment)
    - Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection without fever.

- Fever is defined as temperature ≥38°C on oral or axillary setting.
- Gastroenteritis within 72 hours preceding the study vaccine administration (temporary deferment).

For participants with temporary exclusion criteria (acute illness or gastroenteritis) prior to receiving the subsequent dose of study vaccine, vaccination may be deferred within the defined vaccination windows. The study vaccine can be administered outside the study window based on investigators discretion and a protocol deviation will be filed for the same. If subsequent study vaccinations are discontinued, every effort will be made to encourage the participants to remain in the study for safety follow up.

4.5 Screen Failures

Screen failures are participants who consent to participate in the trial but are not subsequently enrolled in the study as they do not meet the inclusion/exclusion criteria. Individuals who are screen failures due to an acute illness at the time of screening maybe rescreened once the acute illness has resolved and if study participation does not increase any risk to the subject in the opinion of the clinical investigator. Rescreened participants should be assigned the same participant number as for the initial screening. Screen failures will be referred to a proper place for treatment outside of the study, as warranted.

5 STUDY PRODUCT/S

5.1 Study Vaccine

5.1.1 Product Description

Cecolin® is a mixture of two aluminum hydroxide adjuvant absorbed recombinant L1 capsid proteins of human papillomavirus (HPV) type-16 and type-18 each self-assembled into virus-like particles (VLPs). The HPV-16 and HPV-18 L1 antigens are expressed in Escherichia coli by recombinant DNA technology.

5.1.2 Manufacturer

Cecolin® is manufactured by Xiamen Innovax Biotech Co. Ltd., in Xiamen, China.

5.1.3 Presentation and Formulation

Recombinant plasmids containing the HPV 16 or 18 L1 genes were transferred into E.coli. [redacted] The vaccine lot for the clinical trial was produced

under the good manufacturing practice conditions according to the requirements of the China Food and Drug Administration.

Cecolin® is presented as 0.5 mL suspension for injection in a single-dose vial. Upon storage, a fine white deposit with a clear colorless supernatant can be observed. Cecolin® is a suspension after thorough agitation.

5.1.4 Stability and Storage

Cecolin® must be stored refrigerated at 2°C to 8°C (36ºF and 46ºF) and protected from light. Do not freeze. Discard if vaccine has been frozen. Cecolin® will be stored in monitored, temperature-controlled fridge with back-up power supply.

5.2 Control Vaccine

5.2.1 Product Description

Gardasil®, Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant, is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. Gardasil® is locally licensed in Bangladesh and Ghana.

5.2.2 Manufacturer

Gardasil® is manufactured by Merck Sharp Dohme, Inc.

5.2.3 Presentation and Formulation

The L1 proteins are produced by separate fermentations in recombinant Saccharomyces cerevisiae and self-assembled into VLPs. The fermentation process involves growth of ***Saccharomyces cerevisiae*** on chemically defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate). The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

Gardasil® is a suspension for intramuscular administration available in 0.5-mL single dose vials and prefilled syringes. Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.

Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein/dose, and water for injection. The product does not contain a preservative or antibiotics.

After thorough agitation, Gardasil® is a white, cloudy liquid.

5.2.4 Stability and Storage

Gardasil® must be stored refrigerated at 2 to 8°C (36 to 46°F) and protected from light. Do not freeze.

Gardasil® should be administered as soon as possible after being removed from refrigeration. Gardasil® can be out of refrigeration (at temperatures at or below 25°C/77°F), for a total time of not more than 72 hours. Gardasil® will be stored in monitored, temperature-controlled fridge with back-up power supply.

5.3 Dose Preparation and Administration

In this open-label study, the vials of Cecolin® and Gardasil® vaccine will be labeled with the licensed product labels. It will be labeled with the following minimum information: name of the medicinal product, route of administration, expiry date, lot number, dose volume, and a cautionary statement ("For Clinical Trial Use Only"). Dose preparation and administration for each vaccine will be completed according to manufacturer recommendations and carried out by qualified study staff members with preparation witnessed by another study staff member. Vaccine vials will be labeled with the participant's study number for monitoring purposes. 0.5 mL of Gardasil® will be withdrawn from the single-dose vial using a sterile needle and syringe and use promptly.

Cecolin® and Gardasil® are injected intramuscularly and the preferred site for vaccination is deltoid muscle of upper arm.

Cecolin® should be shaken well before use, and it should be a white homogeneous suspension after shaking. A separate sterile auto-disabled syringe and needle must be used for each vaccination. Cecolin® should be administered as soon as possible after removal from the refrigeration container. Any vial with crack, label unclear or invalid and vaccine with abnormal appearance should not be used.

5.4 Accountability and disposal

The Site Principal Investigator (PI) is responsible for ensuring study product distribution and disposition and has ultimate responsibility for study product accountability. The Site PI will delegate to a Site Research Pharmacist responsibility for study product accountability. Study product accountability records should include date received, date administered, product administered, treatment assignment, and the subject identification number to whom the study product was administered. The designated Site Research Pharmacist(s) will be responsible for maintaining accurate records of the shipments and dispensing the investigational vaccine product. The pharmacy records must be available for inspection by the CRO clinical monitor and is subject to inspection by the local regulatory agency at any time. Used and unused vaccine vials will be retained until monitored and released for disposition per PATH and local regulatory agencies, but syringes and other dry materials used will be destroyed per site SOPs immediately following study vaccinations.

It is the responsibility of pharmacist to ensure that vaccine has not been exposed to temperatures outside the allowed range during transport or storage at the facility prior to being dispensed for vaccination. Should there be a deviation outside the allowed temperature range, the affected

vaccine(s) will be quarantined. The temperature deviation will be reported to the CRO who will advise on the action to be taken based on the magnitude and duration of the temperature deviation.

6 STUDY PROCEDURES

6.1 Recruitment and Consent

Recruitment will take approximately 6 months, allowing for approximately 1/2 to 2/3 of participants to be enrolled in one country and 1/3 to 1/2 of participants to be enrolled in the second country. Following community sensitization activities, participants for this study will be recruited from homes and may also be recruited from field sites and schools. In Ghana, as schools will be a central focus point for gathering eligible and participating girls for study visits, sensitization activities will also be conducted with the Ministry of Education and participating schools. Detailed recruitment procedures and community sensitization plans will be outlined in a site-specific document.

In Ghana, trained field workers will visit households in the study catchment area of the participating study clinic to discuss the study with parents/LARs and their 9-14 year old age-eligible girls, for signing of consent and assent according to local requirements. Girls who complete the consent/assent process and are thought to be eligible for the study will be transported either from the community or in groups from their school to the study clinic on the scheduled day of the first study visit where they will be screened by trained study clinicians for verification of eligibility and study enrollment. Girls at this site who are enrolled in the study will be transported from either their homes or from school to the study clinic or be provided with transportation reimbursement to travel to the study clinic for subsequent study visits.

In the Bangladesh site, field workers may visit households in the study catchment area of participating study clinics to preliminarily discuss the study with parents/LARs and their 9-14 year old age-eligible girls. Girls identified as interested in participating in the study and who have parental/LAR support for participation will be invited to Matlab Hospital for parental consent and participant assent, as required per local requirements, conducted by trained study team members and subsequently will be screened and enrolled into the study. Girls at this site who are enrolled into the study will be seen at the Matlab Hospital for all subsequent study visits.

At the time of consent for both sites, a trained study staff member will provide parents and their prospective participants a detailed description of the study objectives and study participation requirements, as well as potential health risks and benefits associated with study participation. The parent will be required to read the full consent and receive a full oral explanation in an appropriate language. Copies of study information and signed assent and consent forms will be provided to the participants. A parent who can only write his/her name and cannot read or write in the local language will be considered illiterate for the purpose of this study and an impartial literate witness will be utilized in this case.

6.2 Study visits

6.2.1 Visit 0: Screening Visit (All Groups: Day -28 to -1)

After the site PI or designee has verified that informed consent has been obtained from parents and the assent from age-eligible participants, the following procedures will be completed to determine study eligibility. Additional screening visits may be scheduled for any follow-up, as needed, as long as they are conducted within 14 days of the initial screening visit. Participants who have an acute illness identified during screening may be asked to return once the acute illness resolves or 7 days later, whichever occurs later, and will be re-screened upon their return to verify eligibility.

Baseline data are obtained during screening between 28 days prior to and on Day 1, the day of first vaccination; however, it is anticipated that it will generally take no more than a visit to determine eligibility, and participants are to be randomized and vaccinated as soon as possible after determination of eligibility, which can be the same day.

All inclusion/exclusion criteria must be assessed from data obtained within that period, unless otherwise specified in the eligibility criteria. During this visit:

- Collect demographic, phone, and address information
- Assess behavioral eligibility
- Collect medical, medication and vaccination history*
- Height and weight
- Perform full physical exam, including vital signs (oral or axillary temperature, pulse, respiratory rate and blood pressure).
- Perform urine pregnancy test for women of childbearing potential

*A comprehensive medical history will be collected including details of any previous vaccinations and reaction to vaccinations, and history of any chronic or recurrent medical and psychiatric conditions.

6.2.2 Visit 1: Day 1: Enrollment / First Vaccination Visit: (All Groups)

Prior to vaccine administration:

- Confirm continued eligibility (if participant returning in 28-day period since initial evaluation)
    - Verify written informed consent and assent completed per local requirements
    - Update interval medical history, including medications
    - Perform full or targeted physical exam
    - Record vital signs (oral or axillary temperature, pulse, respiratory rate and blood pressure)
    - Review inclusion/exclusion criteria if day of screening and day of enrollment is different.
    - Perform urine pregnancy test for women of childbearing potential
- Collect 10 mL blood samples for baseline immunological testing.
- Follow procedures for randomization assignment

Vaccine administration:

- Administer study vaccine according to randomization assignment
    - Second study staff member to verify treatment assignment and vaccine prepared prior to administration.

- Subjects will be in a seated or lying position for vaccination, to reduce the risk of fall and injury if any syncope, and will be keep in that position for part of the observation period.
- The prospective injection site will be cleaned with an alcohol swab and allowed to dry completely.
- The HPV vaccine will be administered by study staff (0.5 ml intramuscularly) in the deltoid region, with clear documentation regarding the arm in which the vaccine is administered.

After vaccine administration:

- Observe subject for 30 minutes for immediate reactogenicity, post vaccination check for solicited adverse event / reactogenicity per section 8.1.1
- Before discharge from the study clinic, the participant will be provided with supplies (including a thermometer for daily temperature recording and a memory aid to record solicited AE information for the next 7 days) and instructed in their use, and follow-up visit information and contact telephone numbers for study staff will be provided. Participants are to be instructed to contact study staff for any solicited AE greater than mild and for any events they perceive as serious.
- Participants will be called or visited in their homes daily through 7 days post-vaccination to verify daily completion of the memory aid.

Randomization is defined as the process of assigning a participant to a study arm; assignments are made by a DMC computer-generated by the Protocol Statistician. The first study vaccination (Day 1) must occur within 24 hours of randomization otherwise the participant is ineligible for continued study participation. Participants will be replaced if randomized but not vaccinated. The evaluations obtained prior to the first vaccination are the baseline for subsequent safety assessments.

6.2.3 Visit 2: Day 8+3 Visit*: (All Groups)

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Study staff will review and record the participant's interval health history, medication use and the participant's assessment of the post-vaccination experience through personal interview, assisted by the memory aid.
- Findings of site PI or study staff that suggest inaccuracy of reported self-assessments will be clearly documented.
- Participants with any ongoing AEs or SAEs will be transported to the study clinic for assessment by study clinician. Study staff will instruct the participant regarding continued health assessment (without memory aid) and need to contact study staff in follow-up (a) of ongoing solicited AEs, (b) of unsolicited AEs through Day 30 post-vaccination, (c) if symptoms worsen or do not resolve, (d) if SAEs occur at any time during the study.
- Participants will be reminded of the next study visit, scheduled for Day 30 (4 weeks after the first vaccination), including the importance of bringing the memory aid to the clinic at the time of this visit.

*Note: This visit must be conducted in-person, but may be conducted in the participant's home, school, or at a study or field clinic, depending on the site.

6.2.4 Visit 3: Day 30+7 Visit: (All groups) *

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Study staff will collect, review, and record the participant's interval health history, medication use and the participant's assessment of the post-vaccination experience through personal interview, assisted by the memory aid.
- Collect memory aid for filing in the participant file.
- Participants with any ongoing AEs or SAEs will be transported to the study clinic for assessment by study clinician.
- Record vital signs (oral or axillary temperature, pulse, respiratory rate and blood pressure)
- Targeted physical examination, if indicated based on review of medical history
- Upon return of the memory aid to the study clinic, solicited and unsolicited AE review will be performed by the site PI (or designee) and any events identified as needing physician follow-up will be identified and participants contacted and transported to the clinic, as needed.
- Findings of site PI or study staff that suggest inaccuracy of reported self-assessments will be clearly documented.
- Study staff will instruct the participant regarding continued health assessment and need to contact study staff in follow-up (a) of ongoing solicited AEs, (b) of ongoing unsolicited AEs, (c) if symptoms worsen or do not resolve, (d) if SAEs occur at any time through the end of the study.
- Participants will be reminded of the next study visit according to their treatment assignment.

*Note: This visit must be conducted in-person, but may be conducted in the participant's home, school, or at a study or field clinic, depending on the site.

6.2.5 Visit 4: Day 180±28 Visit: (Groups 1 and 4)

Six months after the first vaccination for Groups 1 and 4:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures. Any topics or new information considered by site PI to be important to continued informed consent will be shared with the participant.
- Review any SAEs that have occurred since the last visit and confirm resolution of any ongoing solicited and unsolicited AEs following the last visit as well as update the medical history and concomitant medications as necessary
- Record oral or axillary temperature, pulse, respiratory rate and blood pressure
- Targeted or full physical examination, if indicated based on review of medical history
- Perform urine pregnancy test for women of childbearing potential
- Collect 10 mL of whole blood for immunological testing prior to vaccination
- Verify study treatment assignment and administer study vaccination according to the procedures outlined in the study Day 1 visit.
- Observe subject for 30 minutes for immediate reactogenicity, post vaccination check for solicited adverse event / reactogenicity per section 8.1.1
- Before discharge from the study clinic, the participant will be provided with a memory aid to record solicited AE information for the next 7 days, and follow-up visit information and contact telephone numbers for study staff will be provided. Participants are to be instructed to contact study staff for any solicited AE greater than mild.

- Participants will be called or visited in their homes daily through 7 days post-vaccination to verify daily completion of the memory aid.

6.2.6 Visit 5: Day 187+3 Visit*: (Groups 1 and 4)

7 days after the second vaccination for Groups 1 and 4:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Study staff will review and record the participant's interval health history, medication use and the participant's assessment of the post-vaccination experience through personal interview, assisted by the memory aid.
- Participants with any ongoing AEs or SAEs will be transported to the study clinic for assessment by a study clinician.
- Findings of site PI or study staff that suggest inaccuracy of reported self-assessments will be clearly documented.
- Study staff will instruct the participant regarding continued health assessment and need to contact study staff in follow-up (a) of ongoing solicited AEs, (b) of unsolicited AEs through Day 30 post-vaccination, (c) if symptoms worsen or do not resolve, (d) if SAEs occur at any time during the study.
- Participants will be reminded of the next study visit, scheduled for Day 210 (7 months after the first vaccination), including the importance of bringing their memory aid to the visit.

*Note: This visit must be conducted in-person, but may be conducted in the participant's home, school, or at a study or field clinic, depending on the site.

6.2.7 Visit 6: Day 210+7 Visit: (Groups 1 and 4)

One month after the second vaccination for Groups 1 and 4:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Any topics or new information considered by site PI to be important to continued informed consent will be shared with the participant.
- Study clinician will review and record the participant's interval health history, medication use and the participant's assessment of the post-vaccination experience, including a review of ongoing solicited AEs and unsolicited AEs one month following dose 2, through personal interview and assisted by the memory aid.
- Findings of study clinician suggesting inaccuracy of reported self-assessments will be clearly documented.
- Provide care to participants or refer them for further treatment with any ongoing AEs or SAEs, as required.
- Collect memory aid for filing in the participant file.
- Record oral or axillary temperature, pulse, respiratory rate and blood pressure
- Targeted physical examination, if indicated based on review of medical history
- Collect 10 mL of whole blood for immunological testing

6.2.8 Visit 7: Day 730±28 Visit: (Groups 1 and 4)

18 months after the second vaccination for Groups 1 and 4:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Any topics or new information considered by site PI to be important to continued informed consent will be shared with the participant.
- Review to confirm that any ongoing unsolicited AEs at the time of the last visit have resolved and for any SAEs that have occurred since the last visit
- Update the medical history and concomitant medications as necessary
- Record oral or axillary temperature, pulse, respiratory rate and blood pressure
- Conduct a full physical examination
- Collect 10 mL of whole blood for immunological testing
- Exit participants in Groups 1 and 4 from the study.

6.2.9 Visit 4: Day 365±28 Visit: (Group 2)

One year after the first vaccination for Group 2:

- Confirm ongoing consent/ assent and continued eligibility prior to performing any study procedures.
- Any topics or new information considered by site PI to be important to continued informed consent will be shared with the participant.
- Review to confirm that any ongoing unsolicited AEs at the time of the last visit have resolved and for any SAEs that have occurred since the last visit
- Update the medical history and concomitant medications as necessary
- Record oral or axillary temperature, pulse, respiratory rate and blood pressure
- Conduct a full physical examination
  - Perform urine pregnancy test for women of childbearing potential
- Collect 10 mL of whole blood for immunological testing prior to vaccination
- Verify study treatment assignment and administer study vaccination according to the procedures outlined in the study Day 1 visit.
- Observe subject for 30 minutes for immediate reactogenicity, post vaccination check for solicited adverse event / reactogenicity per section 8.1.1
- Before discharge from the study clinic, the participant will be provided with a memory aid to record solicited AE information for the next 7 days, and follow-up visit information and contact telephone numbers for study staff will be provided. Participants are to be instructed to contact study staff for any solicited AE greater than mild.
- Participants will be called or visited in their homes daily through 7 days post-vaccination to verify daily completion of the memory aid.

6.2.10 Visit 5: Day 372+3 Visit: (Group 2)

One week after the second vaccination for Group 2:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Study staff will review and record the participant's interval health history, medication use and the participant's assessment of the post-vaccination experience through personal interview, assisted by the memory aid.
- Participants with any ongoing AEs or SAEs will be transported to the study clinic for assessment by a study clinician.

- Findings of site PI or study staff that suggest inaccuracy of reported self-assessments will be clearly documented.
- Study staff will instruct the participant regarding continued health assessment and need to contact study staff in follow-up (a) of ongoing solicited AEs, (b) of unsolicited AEs through Day 30 post-vaccination, (c) if symptoms worsen or do not resolve, (d) if SAEs occur at any time during the study.
- Participants will be reminded of the next study visit, scheduled for Day 395 (30 days after the second vaccination), including the importance of bringing their memory aid to the visit.

*Note: This visit must be conducted in-person, but may be conducted in the participant's home, school, or at a study or field clinic, depending on the site.

6.2.11 Visit 6: Day 395+7 Visit: (Group 2)

One month after the second vaccination for Group 2:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Any topics or new information considered by site PI to be important to continued informed consent will be shared with the participant.
- Study clinician will review and record the participant's interval health history, medication use and the participant's assessment of the post-vaccination experience, including a review of ongoing solicited AEs and unsolicited AEs one month following dose 2, through personal interview and assisted by the memory aid.
- Findings of study clinician suggesting inaccuracy of reported self-assessments will be clearly documented.
- Provide care to participants or refer them for further treatment with any ongoing AEs or SAEs, as required.
- Collect memory aid for filing in the participant file.
- Record oral or axillary temperature, pulse, respiratory rate and blood pressure
- Targeted physical examination, if indicated based on review of medical history
- Collect 10 mL of whole blood for immunological testing
- Exit participants in Group 2 from the study.

6.2.12 Visit 4: Day 730±28 Visit: (Groups 3 and 5)

Two years after the first vaccination for Groups 3 and 5:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Any topics or new information considered by site PI to be important to continued informed consent will be shared with the participant.
- Review to confirm that any ongoing unsolicited AEs at the time of the last visit have resolved and for any SAEs that have occurred since the last visit
- Update the medical history and concomitant medications as necessary
- Record oral or axillary temperature, pulse, respiratory rate and blood pressure
- Conduct a full physical examination
- Perform urine pregnancy test for women of childbearing potential
- Collect 10 mL of whole blood for immunological testing prior to vaccination

- Verify study treatment assignment and administer study vaccination according to the procedures outlined in the study Day 1 visit.
- Observe subject for 30 minutes for immediate reactogenicity, post vaccination check for solicited adverse event / reactogenicity per section 8.1.1
- Before discharge from the study clinic, the participant will be provided with a memory aid to record solicited AE information for the next 7 days, and follow-up visit information and contact telephone numbers for study staff will be provided. Participants are to be instructed to contact study staff for any solicited AE greater than mild.
- Participants will be called or visited in their homes daily through 7 days post-vaccination to verify daily completion of the memory aid.

6.2.13 Visit 5: Day 737+3 Visit: (Groups 3 and 5)

One week after the second vaccination for Groups 3 and 5:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Study staff will review and record the participant's interval health history, medication use and the participant's assessment of the post-vaccination experience through personal interview, assisted by the memory aid.
- Participants with any ongoing AEs or SAEs will be transported to the study clinic for assessment by a study clinician.
- Findings of site PI or study staff that suggest inaccuracy of reported self-assessments will be clearly documented.
- Study staff will instruct the participant regarding continued health assessment and need to contact study staff in follow-up (a) of ongoing solicited AEs, (b) of unsolicited AEs through Day 30 post-vaccination, (c) if symptoms worsen or do not resolve, (d) if SAEs occur at any time during the study.
- Participants will be reminded of the next study visit, scheduled for Day 760 (one month after the second vaccination), including the importance of bringing their memory aid to the visit.

*Note: This visit must be conducted in-person, but may be conducted in the participant's home, school, or at a study or field clinic, depending on the site.

6.2.14 Visit 6: Day 760+7 Visit: (Groups 3 and 5)

One month after the second vaccination for Groups 3 and 5:

- Confirm ongoing consent/assent and continued eligibility prior to performing any study procedures.
- Any topics or new information considered by site PI to be important to continued informed consent will be shared with the participant.
- Study clinician will review and record the participant's interval health history, medication use and the participant's assessment of the post-vaccination experience, including a review of ongoing solicited AEs and unsolicited AEs one month following dose 2, through personal interview and assisted by the memory aid.
- Findings of study clinician suggesting inaccuracy of reported self-assessments will be clearly documented.

- Provide care to participants or refer them for further treatment with any ongoing AEs or SAEs, as required.
- Collect memory aid for filing in the participant file.
- Record oral or axillary temperature, pulse, respiratory rate and blood pressure
- Targeted physical examination, if indicated based on review of medical history
- Collect 10 mL of whole blood for immunological testing
- Exit participants in Groups 3 and 5 from the study.

6.2.15 Interim Contacts and Visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study. All interim contacts and visits will be documented in participants' study records and if applicable on electronic case report forms.

Any of the following activities may be performed during this visit:

- Review of solicited adverse events (if within 7 days of last vaccination), unsolicited non-serious AE information (if within 1 month of last vaccination), or any SAE information (anytime during study), as well as any ongoing/unresolved solicited and unsolicited AEs that continue beyond the 7 and 28 day post vaccination period, respectively.
- Review of concomitant medications (if within 30 days of last vaccination)
- Obtain interim medical history and vital signs
- Targeted physical examination, if indicated

6.3 Discontinuation of vaccination or study procedures

The Sponsor may terminate the trial for safety, administrative, or other reasons. Documentation explaining premature termination of the study will be forwarded to the study site, regulatory authorities, and IECs/IRBs. A complete final examination will be carried out on the participants if the study is terminated.

The Sponsor reserves the right to terminate or curtail this clinical study for any reason, including but not limited to the following:

- Risk to participant safety
- The scientific question is no longer relevant, or the objectives will not be met (e.g., slow accrual)
- Failure to comply with GCP or terms of Clinical Trial Agreement
- Risks that cannot be adequately quantified
- Ethical concerns raised by the local community or local medical care/health care authorities
- Failure to remedy deficiencies identified through site monitoring (e.g., data recording is inaccurate and/or incomplete on a chronic basis or failure to meet other identified Sponsor performance standards)
- It becomes apparent that participant enrolment is unsatisfactory with respect to quality and/or quantity

In addition, the PATH DSMB may recommend the Sponsor terminate the study based on review of safety data or interim analysis. If the study is prematurely discontinued by the Sponsor for any reason, a summary report will be submitted to regulatory authorities. The summary report will

provide a brief description of the study, the number of participants exposed to the vaccine, dose and duration of exposure, details of adverse drug reactions, if any, and the reason for discontinuation of the study.

6.4 Participant Discontinuation/Withdrawal from the Study

Participation in the study is strictly voluntary. Participants have the right to decline study treatment or procedures for any reason and at any time during the study. If a participant declines further vaccination or study procedures this will be recorded as a study deviation and the reason will be clearly documented in the source document. The participant will be encouraged to complete the remaining applicable safety related follow-ups and immunogenicity blood draw. If the participant does not wish to remain in the study by declining any follow-ups or procedures, the participant can choose to withdraw consent and be withdrawn from the study as per section 6.5

Discontinuation from further vaccination may be at the discretion of the Principal Investigator if it is in the interest of the subject or based on the DSMB safety review as per section 9.2. In addition, participants will be discontinued from further vaccination for the following reasons:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event that requires discontinuation of study treatment or results in inability to continue to comply with trial procedures
- Intercurrent illness or diseases or medical treatment that occur during the trial and might influence the study results or ability to continue to comply with trial procedures

The reason for withdrawal will be documented in source document and relevant CRF.

In the event of withdrawal from study, reasonable efforts should be made to conduct the following procedures:

- Review memory aid if still in use prior to withdrawal
- Updating any ongoing AE/SAEs that remain ongoing at time of subject's last visit prior to withdrawal
- Query about AEs, SAEs and concomitant medications if the interval between the subject's last visit and the time of withdrawal is within the protocol defined reporting period
- Physical examination
- Blood for immunologic testing, if applicable
- Update contact information of the study participants

6.5 Lost to follow-up

To avoid participants being lost to follow-up, participants will be reminded of their clinic visit by phone call, text message, or home visit 3 days or within a period deemed appropriate by site staff before scheduled visits. In the event of a missed visit, participants will be contacted by phone, or text message the next business day following the missed visit. In case the participant cannot be reached by phone, a home visit will be done to remind the participant of study visit. A participant

who cannot be located after 3 contacts and has missed 2 consecutive visits may be considered lost to follow-up. Efforts to contact the participant will be documented in source documents. Any participant who fails to attend the final study visit will also be classified as lost to follow-up. There will be no replacement of participants who are lost to follow-up.

6.6 Use of concomitant vaccine(s) during the study

HPV vaccine mass immunization campaign in the targeted countries are currently not planned and GAVI-supported demonstration projects have been discontinued in both the countries on HPV vaccines.

Routine vaccinations, which are listed in the exclusion criteria (section 4.3) should not be given 4 weeks prior and after each dose of study vaccination. However, administration of rabies, tetanus, COVID-19 or other types of vaccine for prevention or post-exposure indications will take priority over the study considerations. Such vaccines used during the study will be reported in the Concomitant Medication CRF.

6.7 Management of pregnancy during study

If a female participant becomes pregnant following vaccination, she will be encouraged to complete remaining visits and safety follow up but will not receive any further vaccination. The investigator is required to notify the CRO within 24 hours of confirmation of a pregnancy.
All efforts will be made to continue to follow any participant who becomes pregnant during the period between vaccination and the last study visit, for pregnancy outcome, even if birth occurs after the scheduled end of the study for the subject. The pregnancy and its outcome will be reported on the Pregnancy CRF. Participants who become pregnant after vaccination will be followed to term. Following birth, investigators will arrange to refer the mother and the child to a local pediatrician and/or obstetrician for consultation and this consultation report will be submitted to the IRBs. The following information will be gathered for outcome: date of delivery; health status of the mother and child, including the child's gender, height, and weight. Complications and/or abnormalities should be reported, including any premature terminations. A pregnancy is reported as an AE or SAE only when there is suspicion that the vaccine may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy, including a spontaneous abortion or an elective termination for medical rationale.

6.8 Clinical procedures

Vital Signs

- Temperature in degrees Celsius (recorded to the nearest 0.1 degree) will be measured by oral or axillary thermometer.
- Respiratory rate in breaths per minute.
- Heart rate in beats per minute will be measured by automated device or manually.
- Systolic and diastolic blood pressure will be obtained and measured in millimeters of mercury by automated device or manually.

Height and Weight

- Height is measured and recorded to the nearest cm.
- Weight is measured in kg and recorded to the nearest 0.1 kg.

Physical Examination
Full physical examination (at screening and before each vaccination) will include assessment of vital signs, head, eyes, ears, nose, oropharynx, neck, chest (auscultation), lymph nodes (neck, supraclavicular, axillary, inguinal), abdomen (auscultation and palpation), musculoskeletal, skin (especially injection sites), and neurological.

Targeted physical examination
A focused physical examination based on symptoms reported by the participant and the presence or absence of solicited adverse events collected to assess local and systemic vaccine reactogenicity or intercurrent events.

Medical History
A comprehensive medical history will be collected including details of any previous vaccinations and reaction to vaccinations, participation in clinical trials, surgery, previous hospitalization, allergy to food/drugs, current medication, and history of any chronic or recurrent medical conditions.

An interval medical history will consist of inquiring regarding changes since the last medical history discussion (healthcare events, signs, symptoms, and changes in use of prescription or nonprescription drugs or herbal preparations).

Injection Site Examination
Injection site assessment will be done by trained study personnel. Timing and severity grading of local reactions will be according to section 8 (safety assessment) and toxicity grading scale in Appendix II respectively.

The following parameters for reactogenicity will be assessed during the 7 days after each study vaccine injection.

- Local reactogenicity
    - Pain
    - Swelling
    - Erythema (redness)
    - Induration
    - Pruritus
    - Abscess
- Systemic reactogenicity
    - Fever (oral or axillary temperature ≥ 38.0°C),
    - Headache
    - Vomiting
    - Nausea
    - Fatigue
    - Chills
    - Muscle Pain
    - Cough

- Diarrhea
- Dizziness
- Allergic dermatitis
- Rash
- Syncope
- Anorexia

6.9 Measures related to COVID-19

During the course of the study, any guidelines and their updates issued by local authorities related to public health crisis, such as COVID-19, will need to be complied with.

Please see Appendix III for such guidelines in Ghana.

7 LABORATORY EVALUATIONS /REQUIREMENTS

7.1 Sample collection, distribution, and storage

Serum specimens collected for assessment of immunogenicity will be separated into aliquots per study-specific process and timelines outlined in the Study Laboratory Manual and stored at ≤-20° C before being shipped to Frederick National Laboratory for Cancer Research. Samples will be stored in monitored, controlled-temperature freezers, with backup power supply to assure proper sample storage. Back-up specimens will be retained in storage at each site through the end of the study and verification of study results.

At the discretion of PATH, quality assurance audits may be conducted to ascertain adequate processing of immunogenicity specimens. Following testing, residual specimens will be stored at -80° C until long term storage at a designated biobank facility (TBD).

7.2 Immunological laboratory assays

The immunological assays to be performed include:

- Anti-HPV Type 16 and 18 IgG by ELISA
- Anti-HPV Type 16 and 18 Pseudovirion-based neutralization assay (PBNA)

The details of the assay will be in the study Laboratory Manual. Since neutralization assays are labor intensive, technically more complex, and not currently amenable to high throughput, IgG by ELISA is chosen as primary endpoint determinant to demonstrate a response to the vaccine. There is good correlation established between PBNA and ELISA[15]. Samples will be selected via stratified

random sampling using the Advantage eClinical system to achieve a representative sample (20% of subjects) by study arm and site for PBNA assessment.

Samples sent to the laboratory will include a sample ID which links samples to subjects. The laboratory personnel in charge of performing the immunological testing for all immunogenicity endpoints will not be provided with the randomization list containing the treatment allocation.

7.3 Assays qualification, standardization, validation

All assays employed to determine study endpoints must be properly validated; research assays should be standardized and run with adequate controls.

7.4 Future use of stored samples

Additional samples may be shipped for storage at other laboratories or repositories. Samples will be retained in accordance with regulatory guidance for retention of essential study documents, provided that the integrity of the stored sample permits testing. Subject or subject's parent/LAR will be informed about and asked whether they agree to the long-term storage of the subject's specimens for use in future research as part of the informed consent process. Any new research on the stored samples will require approval by appropriate ethics committees, including the ethics committees of the countries where the study is conducted. At study closure, PATH may store the consented samples that are not stored on site at a designated biobank facility (TBD) for at least 5 years.

7.5 Biohazard containment

As transmission of blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood samples, as well as shipping and handling of all specimens for this study as recommended by the United States Centers for Disease Control and Prevention. All biological specimens will be transported using packaging mandated by United States Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

All protocol specimens will be shipped using packing that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for United Nation 2814 Category A Infectious Substances.

8 SAFETY ASSESSMENT AND REPORTING

8.1 Definitions

8.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a participant after administration of the investigational vaccine and that does not necessarily have a causal relationship with the investigational vaccine. An AE can therefore be any unfavorable and unintended sign (including

abnormal laboratory findings), symptoms, physical examinations, or disease temporally associated with the use of the investigational vaccine, whether or not related to the investigational vaccine. This definition includes exacerbations of pre-existing conditions. Stable pre-existing conditions which do not change in nature or severity during the study are not considered AEs; however, these should be reported as part of the medical history.

Solicited AEs are pre-specific local and systemic adverse events that are common or known to be associated with vaccination that are actively monitored as indicators of vaccine reactogenicity. Investigators will not be required to assess causality of solicited adverse events if the onset is during the solicitation periods.

For this trial, solicited AEs will be assessed by study staff 30 minutes after each vaccination then daily for 7 days by the participants (data to be collected for Days 1 through 7). Participants will be provided a memory aid to record the presence or absence of solicited AEs, severity of the solicited AEs and use of concomitant medication.

The following specific solicited adverse events will be monitored for this trial:

Possible Solicited Adverse Events	
Local/Injection Site	General/Systemic
Pain Erythema/redness Swelling Induration Pruritus Abscess	Fever (oral or axillary temperature ≥ 38.0°C) Headache Vomiting Nausea Fatigue Chills Muscle pain Cough Diarrhea Dizziness Allergic dermatitis Rash Syncope Anorexia

Unsolicited AEs are any AEs reported spontaneously by the participant, identified during interview at study visits, observed by the study personnel during study visits or those identified during review of medical records or source documents. Solicited adverse events with onset after the solicitation period and through Day 30 post-vaccination will be captured as unsolicited AEs (see below).

In the absence of a diagnosis, abnormal physical examination findings assessed by the investigator to be clinically significant will be recorded as an unsolicited AE.

8.1.2 Adverse drug reaction (ICH) / Suspected Adverse Reaction (FDA)

Adverse drug reaction is any AE in which the causal relationship to the investigational vaccine is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Having a reasonable suspected causal relationship to the investigational vaccine qualify as adverse drug reaction. The concept of "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug (vaccine) caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse reaction is any adverse event caused by the drug. Adverse event is a subset of suspected adverse reaction where there is reason to conclude that the drug caused the event. (FDA)

Unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the information in the Investigator's brochure. (ICH)

Unexpected suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. (FDA)

8.1.3 Serious Adverse Event (SAE)

Serious adverse event is any adverse event that results in any of the following outcomes:

1. Death
2. Is life-threatening (life-threatening means that the study participant was, in the opinion of the site PI or Sponsor, at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital abnormality or birth defect
6. Important medical event that may not result in one of the above outcomes but may jeopardize the health of the study participant or (and) require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious adverse event

Suspected unexpected serious adverse reaction (SUSAR) is any suspected adverse reaction that is both unexpected and serious.

8.2 Reporting Period and Parameter

Safety events are reported from the time of the first study injection through completion of the study. Specifically, solicited AEs to assess local and systemic reactogenicities will be collected at 30 minutes and then daily for 7 days after each vaccination. If a solicited AE started during the 7 days post vaccination and continues beyond the 7 days, it will continue to be reported as a solicited AE until resolution. Unsolicited AEs will be collected from Day 1 to the 30-day post vaccination visit after each vaccination. SAEs will be assessed from Day 1 through the end of the study for

each group. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.3 Severity of Adverse Events

The severity of all AEs will be assessed by the investigator and participant (as applicable) based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1, July 2017, of the US National Institute of Health in appendix II. The severity grading criteria provided in Appendix II grade AEs from Mild (grade 1) to Life Threatening (grade 4). All AEs leading to death are Grade 5 events. AEs are graded with the worst severity grade during the illness/symptoms.

8.4 Causality of Adverse Event

The study investigator/s will determine the causal relationship between the study vaccine and the AE. The causality assessment is made on the basis of the available information at the time of reporting and can be subsequently changed according to follow-up information. Determining of causality is based on clinical judgment and should take into considerations the following factors:

- Is there a temporal (time-based) relationship between the event and administration of the investigational product?
- Is there a plausible biological mechanism for the investigational product to cause the AE?
- Is there a possible alternative etiology for the AE such as concurrent illness, concomitant medications?
- Are there previous reports of similar AEs associated with the investigational product or other vaccines in the same class?

For this study, the investigator/s must classify the causality of the AE according to the categories defined below:

Related: There is a reasonable possibility that the product caused the event. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the study product and the AE.

Not Related: There is not a reasonable possibility that the administration of the study product caused the event.

8.5 Follow-up of Adverse Event

All reported AEs should be followed until resolution or stabilization, or until the participant's participation in the study ends. Participants who have an ongoing study product-related SAE at study completion or at discontinuation from the study will be followed by the PI or his designee until the event is resolved or determined to be irreversible, chronic, or stable by the PI.

The outcome of adverse event will be assessed as at the time of last observation as per the following categories:

- Recovered/resolved,

- Recovering/resolving,
- Not recovered/not resolved,
- Recovered/resolved with sequelae,
- Fatal,
- Unknown

8.6 General Guidance on Recording Adverse Event

To improve the quality and precision of acquired AE data, the PI should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs on the AE eCRF. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs, symptoms, and laboratory values (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).
- AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A "primary" AE, if clearly identifiable, generally represents the most accurate clinical term to record. If a primary serious AE (SAE) is recorded, events occurring secondary to the primary event should be described in the narrative description of the case.

For example:
Orthostatic hypotension → Fainting and fall to floor → Head trauma → Neck pain

The primary AE is orthostatic hypotension.

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the SAE form.
- For hospitalizations for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.
- Pregnancies that occur in study participants are not considered AEs and will be recorded on a separate Pregnancy eCRF. Pregnancy outcomes that include stillbirth and any congenital anomalies must be reported as SAEs.

8.7 Reporting of SAE

The details and modalities of safety reporting will be provided in the safety management plan (SMP) for the study. A brief description follows in the sections below.

8.7.1 Investigator Reporting to Sponsor

On behalf of the Sponsor, PATH will designate a contract research organization (CRO) with authority to coordinate SAE reporting activities. All SAEs that occur during the study, whether considered to be associated with the study vaccine or not, must be reported to the CRO within 24 hours of the site becoming aware of the event by one of the mechanisms provided (e.g., electronic

data capture [EDC] system, email, fax, or telephone). Contact details and instructions for submitting SAEs will be provided in a handout located in the Investigator Site File. If the SAE is fatal or life-threatening, the CRO medical monitor shall be informed immediately by telephone.

The investigator should not wait for additional information to fully document the event before notifying the CRO or the local regulatory agency. When additional information becomes available, a follow-up submission(s) will be submitted. The initial SAE form should be completed with all information known at the time and should include minimal elements for initial assessment:

- Name and contact of the investigator submitting the SAE report
- Participant ID number
- Date participant received study vaccine
- Description of the SAE and date of event onset
- Investigator's preliminary assessment of severity and causality

When applicable, hospital case records and autopsy reports (including verbal autopsy) should be obtained (without name or personal identifiers).

The investigator will be responsible for notifying the IEC/IRB and the regulatory agency. Reporting procedures for all SAEs will be followed as per applicable country-specific regulatory guidelines. The SMP will contain all the details of regulatory reporting. Copies of each report and documentation of IEC/IRB and regulatory notification/submission and receipt will be kept in the study files.

8.7.2 Notification and Review of SAEs

The CRO medical monitor will be responsible for initial review of SAE forms submitted by investigators to check for completeness and accuracy. After preliminary review, the CRO medical monitor will send the SAE report to the PATH medical officer for review. If there are any queries or requests for clarification, the CRO medical monitor will contact the investigator to obtain additional information and clarification, as needed.

PATH MEDICAL OFFICER:	Anne Schuind, M.D. PATH Center for Vaccine Innovation and Access (CVIA) [redacted]

Medical Officers from PATH serving as technical consultants will provide technical guidance regarding SAE management including classification and reporting.

The Data Monitoring Center is responsible for notifying PATH and also convening a safety review within 24 hours by the DSMBs if the investigator reported the SAE as fatal or life-threatening or

suspected to be related to study vaccine. The CRO medical monitor will review all unanticipated events involving risk to participants or others, SAEs and all participant deaths associated with the protocol and will provide a written report. At a minimum, the CRO medical monitor must comment on the outcomes of the event or problem and, in case of an SAE or death, comment on the relationship to participation in the study. The CRO medical monitor must also indicate whether he/she concurs with the details of the report provided by the site PI.

Details of the reporting requirements are to be found in the Safety Management Plan.

8.7.3 Sponsor Reporting to Regulatory Agency

PATH may authorize the CRO to execute its responsibility for safety reporting to the appropriate regulatory authorities within specified time period of notification.

CRO or the investigator (depending on the country) will be ultimately responsible for reporting to the local regulatory authorities of*:

- Suspected unexpected serious adverse reaction within 15 days of Sponsor's awareness
- Fatal or life-threatening suspected adverse reaction within 7 days of Sponsor's awareness
- All fatal and life-threatening, unexpected adverse drug reactions should be reported within 7 calendar days after first knowledge by the applicant. The initial notification must be followed by as complete a report as possible, within an additional 8 calendar days.
- Serious, unexpected adverse drug reactions that are not fatal or life-threatening must be reported as soon as possible, and not later than 15 calendar days after first knowledge by the regulatory applicant.
- The local regulatory authorities must be notified, within 15 calendar days after first knowledge by the applicant, when there is a suggestion of a change in the nature, severity or frequency of expected adverse drug reactions or when new risk factors are identified. The basis on which these assessments are made should be included.
- Any information, that may in any way influence the benefit-risk assessment of a medicine or that would be sufficient to consider changes in the administration of the medicine or in the overall conduct of a clinical trial, must be reported to local regulatory authorities. The applicant must submit this information to the local regulatory authorities within three calendar days of first knowledge by the regulatory applicant.

*Note: timelines are maximum allowable for reporting. Local regulatory authority timelines will be met if reporting criteria are shorter. There may be additional specific local requirement, not listed here, will be addressed at the time of safety report submission.

8.8 Protocol Deviations

A protocol deviation is defined as an isolated occurrence involving a procedure that did not follow the study protocol, or study specific procedures. Deviations will be reported to IECs/IRBs according to committee-specific and local regulatory requirements for reporting timelines and procedures.

The timeline for reporting protocol deviations to the IRB is determined by the categorization of the deviation: (1) emergent/significant or (2) non-emergent/minor. Unanticipated problems should

be reported in the appropriate timeframe according to the seriousness of the event as a SAE, a significant deviation, or a minor deviation.

Emergent/significant deviations, also known as 'major deviations', are departures from protocol that have a significant impact on the completeness, accuracy and/or reliability of the study data or that may significantly affect a subject's right, safety or well-being. Such deviation reports may be initiated without prior Sponsor approval, only in cases where the change(s) is /are necessary to eliminate an immediate apparent hazard.

Non-emergent/minor deviations are routine departures that typically involve a participant's failure to comply with the protocol. Examples: missing scheduled visits; failing to complete required questionnaire.

8.8.1 Reporting Timelines for Deviations:

Emergent/significant deviations (major deviations) will be reported promptly (within 48 hours) to the IRB, the Regulatory Body (as applicable) and the study sponsor, upon becoming aware of the event, by telephone or email. The site will also keep a current and ongoing log of all major protocol deviations.

Minor deviations will be reported to the sponsor and the IRB, the Regulatory Body (as applicable) in a summary report with the continuing review report and with the study closeout report.

A cumulative deviation report will be submitted to the IRB with each protocol continuing review report or with the final report, whichever comes first.

9 SAFETY OVERSIGHT

Extensive safety monitoring will be provided for this protocol. The site PIs and/or designated site staff will be responsible for continuous close safety monitoring of all study participants and for alerting PATH if unexpected concerns arise or study pause criteria are met.

9.1 Routine Reviews by Protocol Safety Review Team

The Protocol Safety Review Team (PSRT), comprised of site principal investigators, PATH Medical Officer and CRO medical monitor, will routinely monitor safety throughout the duration of the trial. The PSRT will be chaired by the PATH Medical Officer and may seek additional independent expert medical opinion as dictated by needs. The CRO statistician with assistance of the data management staff will prepare safety reports for review by the PSRT. These reports will provide at a minimum the following information: 1) accrual and participant status data with regard to completion of study vaccinations and study visits; and 2) summaries of solicited and unsolicited adverse events. The PSRT safety review will be conducted by teleconference (or electronically when appropriate) occurring approximately biweekly during vaccinations for each study site and as needed thereafter for the remainder of the study. In addition to safety review, the PSRT may elect to discuss trial conduct issues that impact study integrity and participant safety. These may include but not limited to data quality, critical monitoring findings, study product, research specimens, etc. The CRO will also notify the PSRT of ad hoc safety reviews whenever it is aware of SUSAR or adverse events that meet pre-specified study pause criteria as per section 9.3.

9.2 Data and Safety Monitoring Board (DSMB) Reviews

9.2.1 PATH DSMB

The PATH DSMB will convene prior to study initiation and then subsequent to the interim analysis at least every six months to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the study as designed.

In addition to routinely scheduled calls, if the PSRT has serious safety concerns or study pause criteria are met, the PATH DSMB will convene by teleconference to jointly review the data. The PATH DSMB reviews will be summarized with recommendations to the study Sponsor as to whether there are safety concerns and whether the study should continue without change, be modified, or be terminated.

If at any time, a decision is made to permanently discontinue administration of study product in all participants, the site investigators of record will notify the local NRAs and the responsible Institutional Ethics Committees/ Institutional Review Boards (IEC/IRB) expeditiously. A PATH DSMB Charter will be developed for the study.

9.2.2 icddr,b DSMB

The icddr,b has its own regulations and standards for safety oversight, which are independent from the PATH DSMB. The Ethical Review Committee (ERC) of icddr,b will arrange for the formation of a local DSMB for this study. The icddr,b DSMB is an independent safety oversight body from the PATH DSMB. The membership of the local DSMB consists of at least 2 members from the ERC, as well as 1-2 members from icddr,b who are not the study investigators (~4-5 members); there may also be 1-2 external members (experts) invited to participate in the local DSMB review—thus there are typically 5-6 individuals participating in the local DSMB for a particular study. The study PI, together with the key investigators, is expected to formally present the study safety data directly to the icddr,b DSMB at specified time points during the conduct of the study. The safety data will be generated from web-reports that are updated daily in the electronic data system.

The first anticipated time for a icddr,b DSMB review will be prior to initiation of the study and will be followed by meetings for presentation of safety results as soon as it becomes available in regular intervals. Following each icddr,b DSMB meeting, a recommendation will be provided to proceed with the study. Ad hoc local icddr,b DSMB meetings will be convened whenever there are any unexpected safety events. Following completion of the study, a final DSMB meeting is held to update the committee on the results.

The icddr,b Principal Investigator will share records of all such DSMB meetings with the Sponsor and CRO for filing in the study files.

9.3 Study Pause Rule

The following study pause rules will automatically halt any further study vaccinations; however, participants already enrolled will continue to be followed for safety during the pause. These pause rules refer to suspected adverse reactions and will be triggered automatically if any of the events described below are met in a study group during the conduct of the study:

- One or more participants experience an SAE assessed as related to vaccine
- 20% or more participants with the same severe (grade 3) solicited AE within 7 days following vaccination that cannot reasonably be attributed to a cause other than study vaccine
- 20% or more participants experience the same study vaccine-related grade 3 or higher AE

9.4 Study Pause Procedure

The PSRT will be notified immediately by the CRO if they ascertain that a pause rule has been met. If a site investigator or the PSRT first become aware that a pause rule has been met, they will inform the CRO immediately. The CRO will cease randomization and notify the site PI that a pause rule has been met and that no further enrollment should occur, and no study vaccines are to be administered until specific notification is provided that study vaccinations can resume.

As soon as it is confirmed that a study pause rule has been met, the PATH DSMB will be notified and will expeditiously (within 48 hours, if possible) convene by teleconference to review all available, relevant information. The PATH DSMB reviews will be summarized with recommendations to the study Sponsor as to whether there are safety concerns and whether the study should continue without change, be modified, or be stopped.

If, at any time, a decision is made to permanently discontinue administration of study vaccine in all participants, expeditious notification will be provided by the PI to the IEC/IRB and regulatory agency within 48 hours.

If the Sponsor re-starts the study after PATH DSMB review and recommendation, enrollment and study vaccination may resume. The PI will report the study pause and decision to resume to the IEC/IRB and regulatory agency.

10 DATA HANDLING and RECORDKEEPING

The site Principal Investigators are responsible for assuring that the data collected is complete, legible, attributable, accurate, and recorded in a timely manner. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI.

Whenever possible, methods for data collection could include methods that limit direct contact with research participants and could include the use of online surveys or telephone interviews. The use of alternate methods of data collection such as online survey and telephone interviews will designed to be scientifically valid and address ethical issues related to privacy and data protection.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the CRF or electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site PI or designee.

A CRO designated by the Sponsor is responsible for data management activities, including quality review, analysis, and reporting of the study data according to SOPs.

10.1 Definitions

10.1.1 Source Data

All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies. (ICH E6 section 1.51),

10.1.2 Source Documents

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of adverse events, 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, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. (ICH E6 section 1.52)

In addition, CRFs if used as source document will be pre-specified in the Study Manual of Procedures.

10.2 Data Capture Methods (Case Report Form Development and Completion)

The clinical data in source documents will be entered directly into a 21 CFR Part 11-compliant Electronic Data Capture (EDC) system by trained and qualified study staff. The electronic Case Report Form (eCRF) for the EDC system will be developed by the CRO data management with input from site PI's, study staff and approval of the Sponsor. 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 for each participant will be entered directly to the eCRF from the source documents.

It is the site PIs' responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the participant's eCRF and any supporting documentation. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Source documentation supporting the eCRF data should document the dates and details of study procedures, AEs and participant status. The site PIs/institutions will maintain all information in the eCRFs and all source documents that support the data collected from each participant in a secure area and treated as confidential material.

10.3 Data Management

The CRO responsible for data management will develop a Data Management Plan for approval by the Sponsor before implementation. The Plan will describe roles of stakeholders and specific procedures to ensure appropriate handling of data at all steps of the data management process to assure valid and high-quality database at the end of the study, ready for analysis.

10.4 Retention of Study Record

The site PIs are responsible for retaining study records for a period of 3 years following the date that a local marketing application is approved for the product or, if no application is to be filed or, if a file application is not approved, until 5 years after the investigation is discontinued and the NRA is notified. The Sponsor will be responsible for providing the site with date of vaccine local approval or IND/regulatory withdrawal. No records will be destroyed without the written consent of PATH. PATH will inform the Investigators in writing of the need for record retention and will notify the Investigators in writing when the trial related records are no longer needed.

These records are also to be maintained in compliance with local ERC and local authority medical records retention requirements, whichever is longest. Storage of all trial-related documents will be such that confidentiality will be strictly maintained to the extent provided by local law.

11 STATISTICAL CONSIDERATIONS

11.1 Overview and General Design

This is a multi-center, randomized, active-controlled, open-label study which will enroll total of 1025 girls aged 9 to 14 years in two countries; Bangladesh and Ghana. Subjects will be block randomized 1:1:1:1:1 and stratified by site to receive Cecolin® at 0 and 6 months, 0 and 12 months, or 0 and 24 months, Gardasil® at 0 and 6 months, or Gardasil® at 0 months and Cecolin® at 24 months (see Figure 1). The primary objective is to demonstrate non-inferiority of the three Cecolin® arms to Gardasil® arm. Key secondary objectives are related to safety and tolerability, seroconversion, and immunogenicity of all five arms.

A formal statistical analysis plan (SAP) will be developed and finalized prior to interim analysis. The SAP will include additional statistical analysis detail (e.g., more detail of analysis populations, summary of statistical strategies).

11.2 Randomization Procedures

Randomization is defined as the process of assigning a participant to a study arm. Recruited and enrolled subjects will be block randomized in a 1:1:1:1:1 ratio into their assigned treatment group via a system developed and managed by the PATH designated CRO. Participants will be enrolled into the study and randomized using the Interactive Web Response System component of the Advantage eClinical database system. The system will assign subjects to study arms based on the randomization plan. Randomization will be stratified by site to achieve approximately half of the total subjects in each group from each site. Full details of the randomization procedures will be detailed in a randomization plan developed by the PATH designated CRO.

11.3 Sample Size

Immunogenicity:
It is anticipated that no more than 10% of subjects will be seropositive at baseline and that no less than 85% of subjects will be evaluable for the immunogenicity assessments.

The primary objective includes three non-inferiority comparisons of Cecolin® at 0 and 6 months, 0 and 12 months, or 0 and 24 months compared to Gardasil® at 0 and 6 months. To control the

type I error for the three co-primary non-inferiority hypotheses a Bonferroni correction resulting in a one-sided alpha of 0.0083 and corresponding to 98.3% confidence intervals (CI) will be used. To account for the simultaneous assessment of serotypes 16 and 18, 95% power is required for each comparison to achieve 90% power overall for the primary objective ($0.95^2 \approx 0.90$).

Non-inferiority will be demonstrated if the lower bound of the 98.3% CI of the geometric mean concentration (GMC) ratio is greater than 0.5 for both HPV 16 and HPV 18. Assuming an IgG standard deviation of 0.65 of the $\log_{10}$ scale, adjustment for center, 10% baseline seropositive, and 15% dropout 205 subjects per arm will result in 90% power overall for the primary non-inferiority comparisons. The non-inferiority margin of 0.5 was selected in accordance with the WHO Technical Report Series #962. [15]

A sample size of 205 in the mixed schedule Gardasil® at 0 months and Cecolin® at 24 months provides 96% power for similar non-inferiority comparisons to Gardasil® at 0 and 6 months for both serotypes at the one-sided alpha 0.025 level. Similarly, the 24-month comparison of the 0,6 Gardasil® and 0,6 Cecolin® groups has greater than 90% power for non-inferiority comparisons for both serotypes at the one-sided alpha 0.025 level.

Analyses of the PBNA data will be descriptive in nature. However, the 20% sub-sample of subjects, resulting in approximately 20 subjects per arm per site or 200 overall for relevant timepoints, will provide a lower bound above 0.6 for the 95% CI for a Spearman's rank correlation of 0.7 or higher.

Safety:
There is greater than 90% power to observe a severe or serious AE at a rate of ≥0.4% among the 615 subjects that will receive Cecolin® in month 0 and a rate of ≥0.6% among the 410 receiving at least one dose of Gardasil®. Within any arm there is a greater than 90% probability of observing at least one severe or serious AE with a ≥1.2%. The upper bounds of the 95% CIs implied if no AEs are observed are show in Table 2.

Table 2: Detectable rates of AEs and 95% CI upper bounds if no events are observed.

Sample size	>90% probability to observe at least one if severe or serious AE rate is	Upper bound of 95% confidence interval if no events are observed
615	0.4%	0.6%
410	0.6%	0.9%
205	1.2%	1.8%

11.4 Definitions of Populations to be Analyzed

11.4.1 Enrolled Population

All screened participants who provide informed consent and are randomized regardless of the participant's treatment status in the trial.

11.4.2 Total Vaccinated Population

All participants in the enrolled population who were randomized and received at least one dose of study vaccination. All safety analyses will be performed using this population. Treatment groups for safety analysis will be assigned according to the actual treatment received at Day 1.

11.4.3 Per Protocol population

All participants in the total vaccinated population with no major protocol deviations that are determined to potentially interfere with the immunogenicity assessment of the study vaccine, were seronegative for the relevant HPV type at baseline, and have a valid serology result for the relevant time point. This population will serve as the primary analysis population for the immunogenicity endpoints. The population will be adapted by time point to include all eligible subjects' data up to the time of the disqualifying protocol deviation.

The criteria for exclusion of participants from the Per Protocol Population will be based on the review of protocol deviations at a Data Review Meeting (DRM) attended by the sponsor, investigator, and CRO representatives.

11.5 Analytical Methodology

All analyses will be performed by the PATH designated CRO, under the supervision and responsibility of the sponsor. All statistical methods shall be detailed in a Statistical Analysis Plan (SAP) that will be finalized prior to the interim analysis.

SAS version 9.4 or greater will be used for analysis. Except where otherwise indicated in this document or the SAP, summary statistics will be composed of the mean, standard deviation, 1st, 2nd, and 3rd quartile, and the minimum and maximum for continuous variables. For categorical variables, the count and proportion (using one digit beyond the decimal point) will be presented. All study data will be presented in listings. In general, summary tables will be presented by group, including a column for the total across all participants.

For all immunological assays with predefined limits of quantitation, percentiles, and bootstrap-based confidence intervals (CIs) which achieve the LLOQ or ULOQ will be replaced with "<LLOQ" or ">ULOQ", as appropriate. Analysis of immunological assays may be supplemented by reverse cumulative distribution (RCD) curves with each group for a given time point displayed on the same plot, and different panels (preferred) or figures for different time points.

Baseline characteristics, including age, height and weight will be summarized for both the total vaccinated and per protocol populations. Baseline characteristic summaries will be supplemented with two-sided level $\alpha = 0.05$ statistical assessment of differences between groups, using Fisher's exact test for categorical variables, and the Kruskal-Wallis test for continuous variables. For the total vaccinated population, medical history will be listed and summarized by category. Prior and concomitant medications will be coded according to WHO Drug version 2018, listed, and summarized by Anatomic Therapeutic Chemical classification level 1 and level 4 within level 1, where each subject only contributes once per drug category. Summaries of participant disposition will be prepared for all subjects, including the number and percent screened, enrolled, and within each study population, as well as a CONSORT diagram describing study participation and dropout. The reasons not enrolled will be summarized, along with the withdrawal rate and the reasons for

withdrawal, as well as listed. A summary and listing of visit attendance will be prepared, in addition to a summary and listing of vaccine administration, and a sample collection/availability for each sample type.

11.5.1 Analysis of primary objective/s

11.5.1.1 Immunogenicity

The primary immunogenicity assessments will take place within the per protocol population. Supplementary analyses will be conducted in the total vaccinated cohort. GMC/T, GMC/T ratio, and corresponding confidence limits, will be calculated using SAS LSMEANS of the log-scale coefficients which will be back-transformed in order to compute the estimate and corresponding confidence limits for the relevant quantity. The GMT ratio and corresponding two-sided 98.3% CI for each comparison will be computed separately for each comparison to Gardasil® 0,6. All analyses will include adjustment for trial center. Sensitivity analyses may be considered for application in the total vaccinated cohort utilizing SAS PROC LIFEREG, incorporating censoring where appropriate at LLOQ and ULOQ, and a Normal error distribution on the log scale, and adjustment for baseline concertation or titer on the log scale.

11.5.1.1.1 Anti-HPV 16 and 18 IgG

Anti-HPV 16 and 18 IgG antibody GMCs, measured by ELISA at baseline and one month after the second dose on Month 7 (for the 0, 6-month arms), Month 13 (for the 0, 12-month arm) or Month 25 (for the 0, 24-month arm) for the two-dose Cecolin® and Gardasil® arms will be summarize using assay-specific LLOQ/ULOQ as appropriate by arm and by trial center.

Serotype-specific GMCs will be summarized by arm as a continuous variable and corresponding 95% CIs will be provided. These results will be supplemented with a CI for the median, computed via the percentile bootstrap method, using n=10,000 replicates.

The GMC ratios and corresponding two-sided 98.3% CI for each comparison of a Cecolin® arm to the Gardasil® 0-6 arm will be computed. If the lower bound of the 98.3% CI is >0.5, non-inferiority will have been demonstrated.

11.5.2 Analysis of secondary objective/s

11.5.2.1 Immunogenicity

The analysis of secondary objectives will utilize the same study populations and analytic methods. However, 95% confidence intervals will be used for secondary objectives unless otherwise stated.

11.5.2.1.1 Anti-HPV 16 and 18 IgG

Anti-HPV 16 and 18 IgG antibody GMCs, measured by ELISA at baseline and one month after the second dose on Month 7 (for the 0, 6-month arms), Month 13 (for the 0, 12-month arm) or Month 25 (for the 0, 24-month arm) for the two-dose Cecolin® and Gardasil® arms as well as the mixed regimen arm, will be summarize using assay-specific LLOQ/ULOQ as appropriate by arm and by trial center.

For each time point, serotype-specific GMCs will be summarized by arm as a continuous variable and corresponding 95% CIs will be provided. These results will be supplemented with a CI for the median, computed via the percentile bootstrap method, using n=10,000 replicates.

The GMC ratio and corresponding two-sided 95% CI for the comparison of a Cecolin® arms and mixed dose arm to the Gardasil® 0,6 arm will be computed.

Similarly, the GMC ratio and corresponding two-sided 95% CI for the 0,6 Cecolin® arm and 0,6 Gardasil ® arm and 24-months after the first dose will be computed.

Seroconversion rate, defined as a 4-fold rise in anti-HPV 16 and 18 IgG antibody as measured by ELISA at baseline and one month following the last dose will be summarized as a categorical variable. The type-specific difference in response proportion between the Cecolin® and mixed arms compared to the Gardasil® arm 1 month after the second dose will be computed with a corresponding 95% CI computed via the Miettinen and Nurminen score method.

11.5.2.1.2 Anti-HPV 16 and 18 serum neutralizing antibody titers

Anti-HPV 16 and 18 serum neutralizing antibody GMTs measured by PBNA on a representative subset (20%) of samples at all time points will be summarized using assay-specific LLOQ/ULOQ as appropriate by arm and by trial center.

For each time point, serotype-specific GMTs will be summarized by arm as a continuous variable and corresponding 95% CIs will be provided. These results will be supplemented with a CI for the median, computed via the percentile bootstrap method, using n=10,000 replicates.

Correlation between neutralizing antibody titers measured by PBNA and IgG antibody concentrations measured by ELISA will be summarized on the continuous scale and seroconversion agreement will be summarized.

11.5.2.2 Safety

All safety assessments will take place in the total vaccinated population, according to the treatment received and will be summarized overall and by study site. All subject-level percentages (solicited/unsolicited AEs etc.) will be supplemented with two-sided 95% CIs computed via the Clopper-Pearson method. Summaries will include all events occurring on or after the date of each vaccination. Individual summaries (denominators for percentages) will be limited to the number of subjects within the appropriate analysis population with data available for analysis for the given endpoint.

11.5.2.2.1 Unsolicited Adverse Events

All unsolicited AEs, including serious and/or severe AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later. A summary table will be prepared for unsolicited AEs presenting incidence of any AE, any related AE, any serious AE, any severe AE, any AE of grade ≥2, any related AE of grade ≥2, and any AE leading to study withdrawal where a subject only contributes once. Additional tabulations among these categories will be presented by severity, where relevant, where a subject only contributes once under the maximum severity event recorded. Summary tables will also be prepared for each of these

categories presenting summaries across System Organ Class (SOC), and across PT within SOC, where again each subject only contributes once per SOC/PT combination, and once per SOC. An additional table will include preferred terms occurring in ≥2 subjects (across group, regardless of seriousness, severity, or relationship), sorted in descending order of incidence. Each of these tables will use the form "n (%) m", where n is the number of subjects with an event, (%) is the percent of subjects experiencing that event, using the number in the total vaccinated population for the specific group as the denominator, and m is the number of events of that type within that group, regardless of the number of subjects from which they originate. Listings will be prepared including each of the categories of unsolicited AEs listed above including the verbatim term, the SOC, PT, type, the date and study day of onset and resolution, as well as the seriousness, severity, causality assessment, actions taken, and the outcome.

11.5.2.2.2 Reactogenicity

Reactogenicity will be assessed according to immediate (at least 30 minutes post-vaccination) and delayed reactogenicity (within 8 days post-vaccination), as well as combined after each vaccination. Solicited AEs will be summarized overall, by category (local/systemic), by reaction, and by severity within reaction and within category, and by severity and reaction according to post-vaccination day, where each subject is counted once under the maximum severity of each reaction and/or category, where relevant. Analyses involving severity will include those graded ≥2. Summaries of solicited AEs observed across the solicitation period will be accompanied by a two-sided Fisher exact test p-value for a difference among groups, for both local and systemic events (overall and by reaction), as well as across these events (overall). Reactogenicity events ongoing at 7 days post-vaccination will be listed. Duration of reactogenicity events will be summarized by reaction.

Measured injection site features will be summarized by group and post-vaccination time point, including but not limited to pain, erythema/redness, swelling/induration, abscess and pruritis.

11.5.2.2.3 Vital Signs

Vital signs, including change from pre-vaccination baseline for post-vaccination visits/time points, will be summarized by parameter and time point. A listing of all vital signs will be produced, which includes the study day, value, units, and change from baseline.

11.5.2.2.4 Physical Exam

Baseline (full) physical examination results will be listed, as well as summarized as categorical descriptive statistics, where each subject is only counted once per category. Post-baseline physical examination abnormalities will be summarized by category, and a separate listing will be provided.

11.5.3 Analysis of exploratory objective/s

The durability of a single dose of HPV vaccine compared to the two-dose regimen will be explored via utilization of kinetic modeling.

Additional exploratory analyses will include comparisons of GMTs, GMCs, and seroconversion rates following a single dose at 6, 12, and 24 months of Cecolin® compared to a single dose of Gardasil® at 6 months. Similarly, a single dose of Gardasil® and Cecolin® will be compared at 24 months by comparing the 0, 24 Cecolin® and 0,24 Gardasil® and Cecolin® arms prior to the second

vaccination. Finally, the single and two-dose regimens of Cecolin® and Gardasil® in this trial will be compared with rates observed at corresponding time points in recent or ongoing trials of Gardasil® and Cervarix®.

11.6 Handling of Dropouts and Missing Data

Missing immunogenicity data will not be imputed and will be analyzed as if they were missing at random. Over the study period, the frequency and percentage of subjects who discontinue from the study will be provided by treatment group. All subjects who discontinue post-randomization will be further described regarding their time to and their reasons for discontinuation. For subjects who discontinue from the study, their data collected before discontinuation will be analyzed under the analysis populations as applicable.

11.7 Interim Analysis

Upon collection, shipment, and laboratory analysis of the Month 7 serology sample from the subjects in the 0,6 Cecolin and Gardasil arms, an interim analysis will be initiated. The interim analysis will include the analysis of the primary and secondary immunogenicity endpoints and the analysis of the secondary safety endpoints. Only the sponsor will receive the report, and will receive tables only, without listings. Additional detail will be provided in the SAP.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Guidance on internal and external processes to assure effective protocol implementation, quality of the research conducted and compliance with sponsor and applicable regulatory requirements

12.1 General Considerations

The study will be conducted in full compliance with the protocol and ICH GCP to provide public assurance that the rights, safety, and well-being of trial participants are protected, and that the clinical trial data are credible. To ensure quality and standardization, the site will develop Standard Operating Procedures (SOPs) for key protocol procedures and conduct the study guided by the study Manual of Procedures or other written guidelines. The sites will also develop routine operational checks to verify that critical protocol requirements and procedures are executed correctly and completely at the time the work is being performed. Prior to the initiation of the study, the Sponsor and / or the CRO delegated by the Sponsor will conduct training on the protocol, including applicable SOPs, for all study staff.

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

12.2 External Monitoring

PATH, the sponsor of this study is responsible for ensuring that the study is conducted in accordance with ICH GCP and regulatory requirements. For this purpose, monitors under contract from the Sponsor will provide external monitoring for this study. A site initiation visit will be conducted prior to beginning the study, and monitoring will be conducted at initiation, during, and at closeout of the study. During the study, monitors will visit the clinical site at intervals to verify compliance to the protocol; completeness, accuracy, and consistency of the data and study product

accountability; adherence to ICH GCP and applicable regulations. As needed and when appropriate, the monitors will also provide clarifications, additional training to help the site resolve issues identified during the monitoring visit. As appropriate and informed by risk assessment, remote centralized monitoring activities may be considered in place of or to supplement onsite monitoring. These may include analysis of data quality (e.g. missing or inconsistent data, outlier data), identify data trend not easily detected by onsite monitoring and performance metrics (e.g., screening or withdrawal rates, eligibility deviations, timeliness and accuracy of data submission).

The extent and frequencies of the monitoring visits will be described in a separate Study Monitoring Plan developed prior to study initiation. The investigator will be notified in advance of the scheduled monitoring visit. The monitor should have access to all trial related sites, participant medical records, study product accountability and other study-related records needed to conduct monitoring activities. The Sponsor will share the findings of the monitoring visit, including any corrective actions, with the site investigator. The site PI and the monitor must agree to cooperate to ensure that any problems detected in the course of these monitoring visits are resolved in a predefined timeframe.

12.3 Independent Auditing

The Sponsor or its designee may audit the study to ensure that study procedures and data collected comply with the protocol and applicable SOPs at the clinical site and that data are correct and complete. The site PIs will permit auditors (employees of the Sponsor or employee of a company designated by the Sponsor) to verify source data validation of the regularly monitored clinical study. The auditors will compare the entries in the eCRFs with the source data and evaluate the study site for its adherence to the clinical study protocol and GCP guidelines and applicable regulatory requirements.

12.4 Regulatory Agency Auditing

The site PIs must be aware that regulatory authorities, including IEC/IRB may wish to inspect the site to verify the validity and integrity of the study data, and protection of human research participants. The site PIs will notify the Sponsor within 24 hours following contact by a regulatory authority. The site PIs must make the relevant records available for inspection and will be available to respond to reasonable requests and audit queries made by authorized representatives of regulatory agencies. The site PIs will provide the Sponsor with copies of all correspondence that may affect the review of the current study or his qualification as an investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance in responding to regulatory audits or correspondence.

13 ETHICAL CONSIDERATIONS (AND INFORMED CONSENT/ASSENT)

This study will be conducted in accordance with the ethical principles set forth in the World Medical Association Declaration of Helsinki / The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subject and in conformity with ICH GCP and local regulatory requirements.

13.1 Ethical Review

WIRB-Copernicus Group Institutional Review Board (WCG IRB) and designated local ethics committees will review the study (see cover page which outlines specific ethical reviewers). The site PI will be responsible for assuring that this protocol and the associated informed consent forms (ICFs), assent forms and study-related documents are reviewed and approved by the applicable local IEC/IRB prior to implementation of the protocol and PATH will be responsible for assuring review of applicable documents by WCG IRB. A copy of the protocol, proposed ICF, assent form, other written participant information, and any proposed advertising material will be submitted to WCG IRB and the site's IEC/IRB for written approval. Any amendments to the protocol, ICFs, assent forms, or other study-related documents must be approved in writing in advance of implementation by all IECs/IRBs and the study Sponsor, PATH, prior to implementation, except when the changes are required to eliminate immediate hazards to study participants. The investigator must submit and obtain, as necessary, approval from the IEC/IRB for all subsequent protocol amendments and changes to the ICF/assent form. The investigator will notify the IEC/IRB of SAEs and of protocol deviations according to the protocol requirements, as well as local regulatory authority and IEC/IRB requirements. The study will be conducted in full compliance with the protocol.

13.2 Informed Consent/Assent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Before any study-related activities and in agreement with applicable regulatory requirements, the PI or designee, must ensure that the parent/adolescent participant is fully informed about the aims, procedures, potential risks, and potential benefits of the study. The parent will be given the written, local IEC/IRB approved ICF (and adolescent participant the approved assent form), allowed ample time to read the form, encouraged to ask questions about the study, have the questions answered and then be given time to decide if s/he would like to participate in the study. It will be emphasized that participation is voluntary, and that the parent/participant has the right to decline to participate or subsequently withdraw from the study at any time without prejudice.

During the assent process, adolescent participants will have the opportunity to decide if they want to take part, and to decline if they are not interested. An assent form will be prepared, and the procedure is very similar to that of obtaining consent with an adult. A more complete oral description of the research using layman's terminology will be given to the child.

The PI, or designee, must obtain the parent's voluntary, signed, and dated ICF (and adolescent's signed assent form) before any study-related procedures are performed. Study staff must document the informed consent/assent process. The original, signed ICF and assent form must be kept in the site study file. A copy of the ICF and assent from will be given to parents/adolescent participants for their records.

13.3 Participant Confidentiality

The investigators, sponsor and all staff from organizations involved with the implementation of the trial must ensure that the subject's confidentiality is maintained. Personal identifiers will not be included in any study report. All study records will be kept confidential to the extent provided

by national and local laws. Medical records containing identifying information may be made available for review when the study is monitored by the sponsor or an authorized regulatory agency. Direct access may include examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

When appropriate and to the extent possible, study procedures will be conducted to protect participant privacy and confidentiality.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link Participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for monitoring or for legal proceedings.

13.4 Reimbursement

Pending local IEC approval, participants/parents of participants will be reimbursed for travel to study visits. The study ICF will state the plan for reimbursement. Participants/parents of study participants will not be charged for study injections, research clinic visits, research-related examinations, or research-related laboratory tests.

13.5 Risk and Benefits

No benefits can be guaranteed to participants for their participation in this research study.

Since Gardasil is an approved vaccine in both countries where the study will be conducted, and it will be given per the approved product label, the participants may benefit from receiving Gardasil.

Participants who receive Cecolin may potentially benefit from receiving a recommended vaccine which is based on the immunobridging study done amongst adolescents of the same age in China despite Cecolin not being locally licensed or routinely available.

Participation in this study will hopefully contribute to more widespread availability of a vaccine to address a global public health concern.

As noted in section 1.6, the usual side effects of Cecolin® is generally mild and include fever, allergic dermatitis, rash, syncope, abscess, anorexia, pruritus, pain, induration, swelling, erythema, discomfort at injection site, headache, fatigue, cough, muscle pain, nausea, diarrhea, dizziness, and vomiting.

Hypersensitivity reactions may occur following the administration of any vaccine, including licensed vaccines, which in rare circumstances may be life-threatening. Investigators are informed in the protocol and product insert of this possibility following study vaccine administration. All subjects shall be informed in the ICF and observed for a minimum of 30 minutes following study

vaccine administration. As with all immunizations, appropriate emergency medical treatment shall be made available at the site of vaccination in case of severe immediate reactions, such as anaphylaxis. Subjects with a known hypersensitivity to any component of the study vaccine will be excluded from the study.

Blood drawing and venipuncture associated risks may include minor bleeding or bruising at the venous access site, mild discomfort, upset stomach, dizziness, light-headedness, syncope, or very rarely infection. Blood samples will only be drawn by trained staff members using aseptic technique and medical assistance will be available in case of any complications. Subjects will be informed of risks in the ICF and will be in a seated or supine position during blood draws.

The potential risks of conducting the study under the recent COVID-19 pandemic conditions must be considered. It is important to follow national preventive directives on COVID-19 and try to minimize the risks to the participants via proper outreach and public education. The study team will ensure that the proposed research and methods for data collection can be conducted in a safe environment that adheres to national directives on social distancing measures, as needed.

13.6 Risk to Study Personnel

Risk to study personnel is principally the handling of needles that may be contaminated with blood or body fluids and the associated risk of acquiring a blood-borne pathogen (including hepatitis B and C viruses and human immunodeficiency virus (HIV) during phlebotomy. Adherence to standard operating procedures (SOP) for working with infectious agents and universal precautions will reduce the risk of exposure to many pathogens, including COVID-19. Further measures to protect staff and the environment are described in Section 7.5, Biohazard Containment.

13.7 Reporting of Communicable Disease

Local requirements and plans for study staff to comply with and applicable local requirements for reporting to health authorities of communicable disease identified in study participants will be followed.

13.8 Compensation for Research Related Injury

Sponsor is responsible to have untoward medical occurrences related to study participation, even if before investigational vaccine administration, reported in a timely manner.

The study sites will provide immediate emergency short-term medical care to study participants at no cost for any injury resulting from direct participation in this research. Participants will be insured against injury caused by the study according to legal requirements, which will provide compensation for research related injury (to include costs of long-term and future medical care needs), should it occur. The costs of the treatment will be paid with the clinical trials insurance policy.

For injuries not caused as a direct result of taking part in the study, the participant will be referred for further treatment, if necessary. The Local Hospital may charge a user fee which will be paid by the study funds. In emergency situations all efforts will be made to provide the participant with transport to the clinic and back home if necessary. The participant will be informed that this is not a waiver or release of their legal rights.

14 FINANCING AND INSURANCE

The trial is supported by a grant from Kreditanstalt für Wiederaufbau Bankengruppe and The Bill and Melinda Gates Foundation to PATH. [redacted]

PATH will provide locally admitted clinical trial insurance for the payment of any expenses related to the treatment of injuries directly attributable to participation in this study. The vaccine manufacturer will self-insure against product liability.

15 PUBLICATION POLICY

It is understood by the investigators that the information generated in this study will be used by the sponsor in connection with the development of the product and therefore may be disclosed to government regulatory agencies in various countries. The sponsor (and Innovax) also recognizes the importance of communicating study findings and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences, while protecting the integrity of the ongoing trial. Any publication, lecture, manuscripts of the findings of this study by any individual involved with the study will be governed by the procedure outlined in the Clinical Trial Agreement. Within any presentation or publication, confidentiality of individual subjects will be maintained, with identification by subject code number and initials, if applicable.

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APPENDIXES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

Study Visit	Screening	Day 1	Day 8	Day 30	Day 180	Day 187	Day 210	Day 730	Day 365	Day 372	Day 395	Day 730	Day 737	Day 760
Study Window	-28 to -1	N/A	+3	+7	±28	+3	+7	±28	±28	+3	+7	±28	+3	+7
(Study Groups) Visits	**(All) V0**	**(All) V1**	**(All) V2**	**(All) V3**	**(1&4) V4**	**(1&4) V5**	**(1&4) V6**	**(1&4) V7**	**(2) V4**	**(2) V5**	**(2) V6**	**(3&5) V4**	**(3&5) V5**	**(3&5) V6**
Informed Consent/Assent	√													
Demographics	√													
Medical History	√	√[A]	√[A]	√[A]	√[A]	√[A]	√[A]	√[A]	√[A]	√[A]	√[A]	√[A]	√[A]	√[A]
Prior and Concomitant Medications	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Physical Exam	√	√[B]		√[B]	√[B]		√[B]	√	√		√[B]	√		√[B]
Vital Signs	√	√		√	√		√	√	√		√	√		√
I/E Criteria	√	√[C]			√[C]				√[C]			√[C]		
Pregnancy Test	√	√C			√C				√C			√C		
Randomization		√[C]												
Vaccination		√			√				√			√		
Visual Inspection of Injection Site		√			√				√			√		
Distribution of Memory Aid [D]		√			√				√			√		
Collection of memory Aid				√			√				√			√
Immunogenicity Blood Collection [C]		**10 mL[E]**			**10 mL**		**10 mL**	**10 mL**	**10 mL**		**10 mL**	**10 mL**		**10 mL**
Adverse Event Reporting		Solicited local and systemic reactions			Solicited local and systemic reactions				Solicited local and systemic reactions			Solicited local and systemic reactions		
			Unsolicited Adverse Events						Unsolicited Adverse Events					
			Serious Adverse Events											

A. Updated medical history only
B. Targeted physical examination, as indicated
C. Before vaccination
D. Participants will be called or visited in their homes daily through 7 days post-vaccination to verify daily completion of the memory aid
E. Immunology sample could be collected at time of screening

APPENDIX II: SEVERITY GRADING TABLE

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE grading table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. This table is available at:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

APPENDIX III: GHANA SITE_SPECIFICS

Ghana specifics COVID-19 Guidelines

The following COVID-19 protocols instituted by the Ghana Health Service will be strictly observed by the Ghana study site.

To ensure the safety and wellbeing of study participants, parents/caregivers and the entire research staff of this study following the outbreak of the COVID-19 pandemic in Ghana, the following general control measures have been implemented. To further make sure these control measures are strictly followed, a Standard Operating Procedure (SOP) on COVID-19 control measures has been developed and all staff have been trained on the SOP.

- Provision of basic protective and preventive equipment (hand sanitizers, alcohol based disinfectants, access to soap and running water, paper towels / hand dryer, locally manufactured reusable mask in addition to surgical mask as well as proper waste disposal items) to study participants, parents/caregivers and staff for clinic and home visits
- Parents/caregivers as well as study participants will be taught how to wear, remove and care for the reusable facemasks for themselves.
- Employees who feel unwell will be encouraged to stay home and seek immediate medical attention. Parents/caregivers and or study participants as part of study procedures are advised to contact designated study clinicians or field workers, if unwell and will continue to follow this procedure.
- Refraining from communicating false or unverified information on social media platforms that create fear and panic.
- Strictly observing the prescribed social or physical distancing
- Washing of hands under running water for at least 20 seconds at a time, and or using hand sanitizers with at least 70% alcohol
- Avoiding touching the face – especially eyes, nose, and mouth with hands.
- Sneezing and or coughing into tissues, or the elbow region, and disposing of the tissue appropriately.
- Adhering to any other measure(s) and directives put in place by the Ministry of Health, the Ghana Health Service and authorized agencies
- Making sure that if any staff or study participant shows signs and symptoms suggestive of COVID-19 infection, the most current protocols set up by Ghana Health Service are followed appropriately. The suspected person would be referred to the appropriate hospital for screening. If the test is positive, then the person will be put in isolation and the Ghana Health Service prescribed protocol followed. COVID-19 cases will be recorded appropriately in the eCRF.

For Home Visits

Staff will be provided with hand sanitizers or alcohol based disinfectants and masks to use during the home visits. The parents/caregivers and or study participants will in addition be encouraged and reminded to wear masks.

For Scheduled Clinic visits

- A maximum of 30 participants, with/without their caregiver, will be allowed to attend a clinic session. When needed, 2 clinic sessions in a day will be held (morning and mid-day sessions) to ensure appropriate distancing measures and minimal contact time.
- All study participants, caregivers and study staff will be transported in and out of the study centre by study vehicles following the social distancing protocols.
- All persons (staff, caregivers and study participants) are to strictly wear their face/nose masks before boarding the vehicle, and are to wear the mask during and after the visit session - until the person reaches home. Parents/caregivers as well as study participants will be reminded to use their provided masks and will not be allowed to board the bus or come to the study centre without the mask. The same guidance apply for home visits.
- 70% alcohol based hand sanitizers will be provided in each vehicle. Each study participant and parent/caregiver, as well as staff, are to sanitize their hands with hand sanitizer dispensed by the driver before boarding the study vehicle.
- Infrared (Gun) thermometers will be used to check the temperature of all persons visiting the clinic before allowing entry
- Running water and soap as well as paper towels/ hand dryers will be provided at the entrance and inside the clinic visit centre for hand washing before entry and after every clinic visit.
- Parents/caregivers and study participants not within the study catchment area and so requiring use of public transport to attend the clinic, will be contacted by phone for safety assessments of their child. These caregivers and study participants will be exempted from travelling to undertake clinic visits and the missed visit will be documented as a COVID-19 related protocol deviation.

For Unscheduled Clinics Visits

At any time, caregivers and study participants who may be sick are encouraged to seek health care for their child at the study hospital for management. Those who have travelled outside the study area are encouraged to access health care at the nearest Health Facility and inform the study team for documentation and treatment reimbursement.

For additional Ghana study site specifics, refer to the document " **Site specific information relating to PATH HPV vaccine Phase III trial entitled:**

A Phase 3 Randomized, Active-Comparator Controlled, Open-Label Trial to Evaluate the Immunogenicity and Safety of Alternate Two-Dose Regimens of a Bivalent Human Papillomavirus (HPV) Vaccine (Cecolin®) Compared to a Licensed Quadrivalent HPV Vaccine (Gardasil®) in Healthy 9-14 Year-Old Girls in Low and Low-Middle Income Countries"