STATISTICAL ANALYSIS PLAN
for
PATH Protocol CVIA 087

Study 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

ClinicalTrials.gov ID: NCT04508309

Version 3.0

Date: 03NOV2023

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, Version 1.6
Development Phase:	Phase 3
Products/Route:	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)
Indication Studied:	Human Papillomavirus (HPV) prevention
Sponsor:	PATH Vaccine Solutions (PVS) 455 Massachusetts Ave., NW, Suite 1000, Washington, DC 20001
Date of this Plan:	03NOV2023
Version Number:	3.0

This study will be performed in compliance with Good Clinical Practice.

CVIA 087 STATISTICAL ANALYSIS PLAN REVISION HISTORY

Version Number	Version Date	Summary of Changes
1.0	17MAR2021	Finalized Document
2.0	04AUG2022	Change in PATH Statistician. Clarification of the Interim analysis plan. Minor typo/error fixes and clarifications throughout document.
3.0	03NOV2023	Additional analyses to include seropositivity rates and kinetic depiction through a figure (**Figure 18**). Also, a new listing for vital signs is included (Listing 16) and 2 new tables were added similar to existing tables (**Table 89 and 97**) that summarize unsolicited SAEs and non-serious AEs separately, combining AEs and SAEs. Both tables will be used for posting on ClinicalTrials.gov

SIGNATURE PAGE

PROTOCOL NUMBER: CVIA 087: v1.6

STATISTICAL ANALYSIS PLAN: v3.0

PATH Statistician

Signed:

PATH Medical Officer

Signed:

Emmes Statistician

Signed:

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Events
C	Celsius
CI	Confidence Interval
cm	Centimeter
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CVIA	Center for Vaccine Innovation and Access
DAIDS	Division of Acquired Immunodeficiency Syndrome
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
ICH	International Conference on Harmonisation
ID	Identification
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug
kg	Kilogram
L	Liter
LLOQ	Lower Limit of Quantitation
LMIC	Low- and Middle-Income Countries
Mcg or µg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram

List of Abbreviations (*continued*)

Abbreviation	Explanation
mL	milliliter
mm	millimeter
mmHg	millimeter of mercury
MMR	Measles, Mumps, and Rubella
PBNA	Pseudovirion-based Neutralization Assay
PI	Principal Investigator
PP	Per-Protocol
PSRT	Protocol Safety Review Team
PT	Preferred Term
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULOQ	Upper Limit of Quantitation
WHO	World Health Organization

List of Abbreviations (*continued*)

1. PREFACE

This Statistical Analysis Plan (SAP) for "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" (PATH protocol CVIA 087) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, figures, and listings planned for the interim and final analyses (see Appendix A, Appendix B, and Appendix C). Regarding the interim analysis, final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provide sufficient detail to meet the requirements identified by ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains a review of the study design, general statistical considerations, comprehensive statistical analysis methods for safety and immunogenicity outcomes, and a list of proposed tables and figures. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

List of Abbreviations (*continued*)

2. INTRODUCTION

The main purpose of this study is to demonstrate 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 immunologic objectives include evaluation of 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, assessment of 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), evaluation of 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 and evaluation of non-inferiority of Cecolin® administered on 0-6 months to Gardasil® given on a 0-6 month schedule at 24 months post-first dose. Secondary safety evaluations include assessment of solicited adverse events within 7 days after each dose, unsolicited adverse events within one month after each dose and serious adverse events (SAEs) occurring at any time during study participation.

The 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, via intramuscular (IM) injection. For each arm, blood will be collected for immunologic testing at baseline and one month following the 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 of Gardasil followed by Cecolin and collect data on effects of interchangeability. All safety data will be summarized and reviewed by a Protocol Safety Review Team (PSRT) and Data and Safety Monitoring Board (DSMB).

This Statistical Analysis Plan describes the statistical methodology and summaries required to assess the demographics, safety, reactogenicity and immunogenicity of the bivalent HPV vaccine, Cecolin®, in alternate 2-dose regimens, and the comparator HPV vaccine, Gardasil®, in 9-14-year-old girls.

List of Abbreviations (*continued*)

3. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints from the protocol are described below, with added detail.

3.1. Study Objectives

3.1.1. Primary Objective

The co-primary objectives of the study are to 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. Bonferroni correction will be used to adjust the type I error rate for the multiple comparisons. The analyses will use anti-HPV 16 and 18 IgG antibody GMCs, measured by ELISA.

3.1.2. Secondary Objectives

The secondary (exploratory) objectives are to:

- 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.

3.1.3. Exploratory Objectives

The exploratory objectives are as follows:

- 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

List of Abbreviations (*continued*)

3.2. Study Endpoints

3.2.1. 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. The GMC ratios (Cecolin arm/Gardasil 0, 6) and corresponding two-sided 98.3% CI for each comparison will be computed.

3.2.2. Secondary Endpoints

3.2.2.1. Secondary Immunogenicity 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.

The corresponding two-sided 95% CI for each metric will be computed.

3.2.2.2. 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

3.2.3. Exploratory Endpoints

Exploratory endpoints include:

- 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

3.3. Study Definitions and Derived Variables

Definitions and Derivations Used in This Study:

List of Abbreviations (*continued*)

- A baseline value will be defined as the last value obtained prior to the first vaccination of study product.
- Age will be calculated from the date of first vaccination and will be presented in whole years.
- Fever: temperature ≥ 38.0°C or 100.4°F.
- For immunology, reciprocal endpoint titers less than the lower limit of quantitation (LLOQ) of the assay will be assigned a value of half the starting dilution, and those greater than the upper limit of quantitation (ULOQ) will be assigned a value equal to the ULOQ for computational purposes, except when using analysis methods that incorporate censoring.
- Seroconversion will be defined as a 4-fold rise in anti-HPV 16 and 18 IgG antibody (as measured by ELISA) compared to the baseline titer.
- Seropositive will be defined as a titer value for the ELISA assay of > 8 EU/mL for HPV-16 and >7EU/mL for HPV-18. For the PBNA assay, any IC_{50} titers that are ≥ 21 (HPV-16) or ≥ 16 (HPV-18) will be considered as positive titers.

List of Abbreviations (*continued*)

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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).

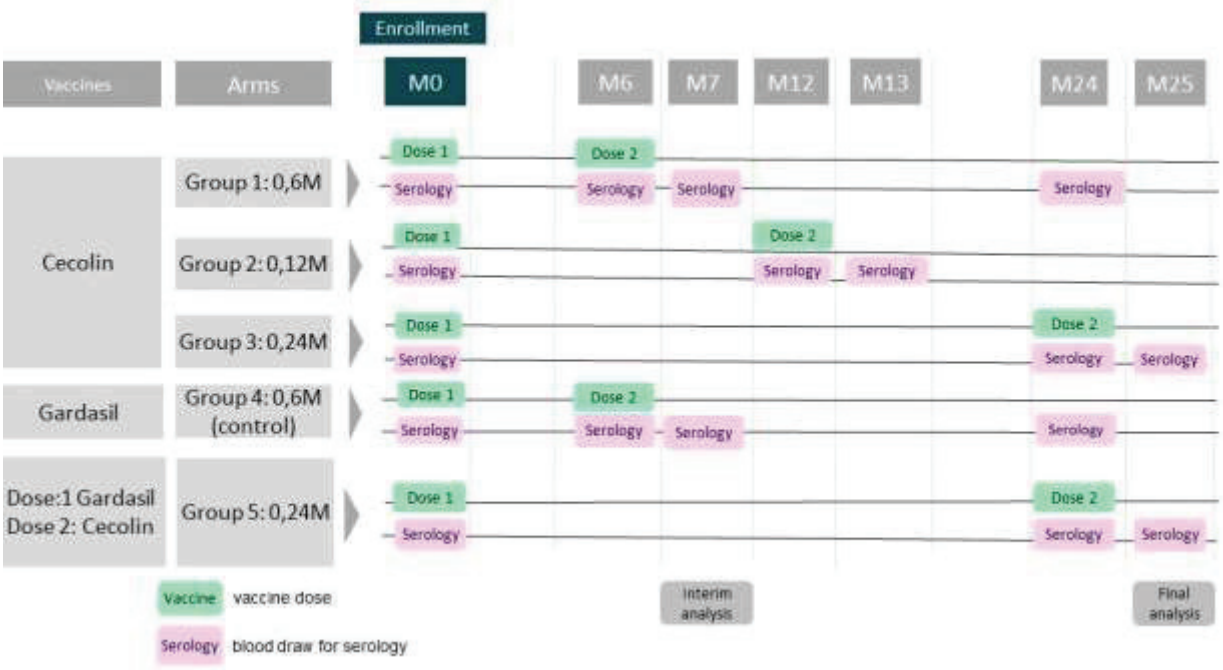
Subjects will be randomized 1:1:1:1:1 to one of the following groups to receive Cecolin® and/or Gardasil®. Each group will consist of 205 subjects.

- Group 1: Cecolin® at 0 and 6 months,
- Group 2: Cecolin® at 0 and 12 months,
- Group 3: Cecolin® at 0 and 24 months,
- Group 4: Gardasil® at 0 and 6 months (control), or
- Group 5: Gardasil® at 0 months and Cecolin® at 24 months.

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.

The clinical protocol time and events schedule is shown in Table 1, Appendix A and a copy of the study schematic is shown below.

Figure A.1 Study Schematic



List of Abbreviations (*continued*)

4.2. Discussion of Study Design

CVIA 087 is 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). Gardasil® is chosen as the comparator vaccine, as this vaccine is the most widely used in LMICs. This study was designed to evaluate non-inferiority data and collect additional safety data. 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.

4.3. Selection of Study Population

4.3.1. 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.

4.3.2. Inclusion Criteria for Enrollment

Subjects must meet all of the following criteria to be included in the study:

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

4.3.3. Exclusion Criteria for Enrollment

Subjects meeting any of the following criteria will be excluded from the study.

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

List of Abbreviations (*continued*)

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.

4.3.4. Criteria for Removal of a Subject from Therapy or Study Assessments

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. 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 disease or medical treatment that occur during the trial and might influence the study results or ability to continue to comply with trial procedures

A participant who cannot be located after 3 contacts and has missed 2 consecutive visits may be considered lost to follow-up. Any participant who fails to attend the final study visit will also be classified as lost to follow-up.

List of Abbreviations (*continued*)

4.4. Treatments

4.4.1. Treatments Administered

Study Vaccine

Cecolin® administered intramuscularly as 0.5 mL suspension in a single-dose vial.

Comparator/Control Vaccine

Gardasil® administered intramuscularly as 0.5 mL suspension in a single-dose vial.

4.4.2. Method of Assigning Subjects to Treatment Groups (Randomization)

Randomization is defined as the process of assigning a subject 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. Randomization will be stratified by site to balance the total subjects in each group from each site. Furthermore, since neutralization assays are labor intensive, technically more complex than Enzyme-Linked Immunosorbent Assay (ELISA) and not currently amenable to high throughput, approximately 20% of subjects from each group will be randomly selected to also participate in the Pseudovirion-based neutralization assay (PBNA) analysis.

Any enrolled subject who is randomized but withdraws for any reason prior to vaccination will be replaced. Subjects who are withdrawn for any reason after vaccination will not be replaced.

4.4.3. Blinding

This is an open-label study.

4.4.4. Prior and Concomitant Therapy

Routine vaccinations, which are listed in the exclusion criteria should not be given 4 weeks prior and after each dose of study vaccination. Receipt of an investigational or licensed HPV vaccine is also an exclusion criterion. 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.

4.4.5. Treatment Compliance

All subjects should receive two vaccinations according to the schedule of the group they are randomized to and the second vaccination should be administered within ±28 days of the scheduled visit time. 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. At each vaccination visit, the date and time of administration will be recorded on a CRF as well as whether the vaccination was administered fully and per protocol.

4.4.6. 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. All deviations from the protocol will be recorded on the Protocol Deviation eCRF. There are two types of protocol deviations in this study:

1. A protocol deviation is subject-specific.

List of Abbreviations (*continued*)

2. A Non-Subject Specific protocol deviation is any deviation that is not related to one specific study subject but rather to an incorrect process, procedure, or an issue at the clinic/facility level (e.g., a deviation that applies to a regulatory issue, temperature excursion or an incorrect process affecting multiple subjects at one time).

4.5. Immunogenicity and Safety Variables

The following section describes the collection of immunogenicity and safety variables. For a detailed schedule of activities, refer to Table 1. For a list of the primary and secondary immunogenicity and safety variables, refer to Section 3.2 and Section 9.

4.5.1. Immunogenicity Variables

To evaluate immunogenicity of Cecolin® and Gardasil®, anti-HPV 16 and 18 IgG antibody measured by enzyme-linked immunosorbent assay (ELISA) and anti-HPV 16 and 18 serum neutralizing antibodies measured by pseudovirion-based neutralization assay (PBNA) will be used. For each treatment group, blood will be collected for immunologic testing for the primary endpoint at one month following second dose. Additional blood collections will occur at baseline, immediately prior to the administration of the 6-month, 12-month or 24-month dose, and 24 months after the first dose in Groups 1 and 4 for noninferiority comparison.

4.5.2. Adverse Events

An adverse event (AE) 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.

4.5.2.1. Solicited Adverse Events

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. For this trial, solicited AEs will be assessed by study staff 30 minutes after each vaccination and 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:

Local Reactions:

- Pain, erythema/redness, swelling, induration, pruritus, abscess.

General/Systemic Reactions:

- Fever, headache, vomiting, nausea, fatigue, chills, muscle pain, cough, diarrhea, dizziness, allergic dermatitis, rash, syncope and anorexia.

4.5.2.2. Unsolicited Adverse Event

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. Unsolicited Adverse Events are non-serious adverse events

List of Abbreviations (*continued*)

occurring from the time of each study injection through approximately 30 days after each vaccination. Solicited adverse events with onset after the solicitation period and through Day 30 post-vaccination will be captured as unsolicited AEs.

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

Information to be collected on AEs includes event description, time of onset, assessment of severity, relationship to study product (assessed only by the PI), and time of resolution/ stabilization of the event.

4.5.2.3. Suspected Adverse Reactions (FDA), Adverse Drug Reactions (ICH), Unexpected Adverse Drug Reaction and Unexpected Suspected Adverse Reaction

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 (ADR). 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 reactions 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).

4.5.2.4. Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

SAEs are collected from the time of first vaccination through the end of the study for each.

List of Abbreviations (*continued*)

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

4.5.3. 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 (**https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf**). This 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.

4.5.3.1. Causality of Adverse Event

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

List of Abbreviations (*continued*)

5. SAMPLE SIZE CONSIDERATIONS

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; see Section 6.3 for definitions of the immunogenicity analysis populations.

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 ($0.952 \approx 0.90$).

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 log10 scale, adjustment for center, 10% baseline seropositive (see Section 3.3), 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.

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 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 shown in Table 2.

List of Abbreviations (*continued*)

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All analyses will be grouped by vaccination arm. In general, all data will be listed, sorted by treatment group, site and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment group (including a column for all participants) and will be annotated with the total population size relevant to that table, including any missing observations.

Except where otherwise indicated, 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 will be presented.

6.2. Timing of Analyses

Safety data of each study arm will be prepared and reviewed by the Protocol Safety Review Team (PSRT) and the Data and Safety Monitoring Board (DSMB). For details, refer to Section 6.6.2 and Section 6.6.3.

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, for groups 1 and 4, the analysis of the primary and secondary immunogenicity endpoints and the analysis of the secondary safety endpoints for these two groups. Only the sponsor will receive the report generated by Emmes, and will receive a selection of tables and listings (See section 6.6.1).

A final analysis of all data collected will be performed after all data queries have been resolved and the data base locked.

6.3. Analysis Populations

6.3.1. Enrolled Population

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

6.3.2. 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.

6.3.3. 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 for the relevant time point, 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.

List of Abbreviations (*continued*)

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.

6.4. Covariates and Subgroups

All safety analyses will be presented by group, site, and overall. All immunogenicity analyses will include adjustment for site. A sensitivity analyses of all immunogenicity data with an adjustment for baseline concentration or titer on the log scale will be conducted if 10% or more subjects are seropositive at baseline. Additionally, if 10% or more subjects are seropositive at baseline descriptive summaries of immune response among baseline seropositive and seronegative subjects will be generated.

6.5. Missing Data and Outliers

All attempts will be made to collect all data per protocol. Missing safety data will not be imputed and only observed data collected from participants and available in the appropriate study population will be used for analysis.

The analysis of immunogenicity will be performed primarily on the PP set. Missing immunogenicity data will not be imputed.

6.6. Interim Analysis and Data Monitoring

6.6.1. 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 (i.e., vaccination groups 1 and 4), an interim analysis will be initiated. The interim analysis will include the analysis of the primary and secondary immunogenicity endpoints for groups 1 and 4 and the analysis of all available secondary safety endpoints for these two groups. A DRM will assess protocol deviations for groups 1 and 4 up to month 7. Only the sponsor will receive the report generated by Emmes, and will receive the following tables, figures, and listings:

- Tables 3-16, 18-23, 26-29, 31-38, 46-51, 55-63, 65-67, 74-77, 79-81 83-106, Figures 9-12, and Listings 8, 10, 11, 15, 20, 21.

6.6.2. Protocol Safety Review Team (PSRT)

The PSRT will be comprised of site Principal Investigators, PATH Medical Officer and CRO medical monitor who will routinely monitor safety throughout the duration of the trial.

A separate document will detail the mock table shells, listings and figures to be reviewed by the PSRT.

6.6.3. Data and Safety Monitoring Board (DSMB)

The PATH DSMB will convene prior to study initiation and then at least every six months prior to and following the interim analysis 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

List of Abbreviations (*continued*)

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.

A separate document will detail the mock table shells, listings and figures to be included in DSMB reports.

6.7. Multiple Center Studies

There are 2 sites in this study. All safety and immunogenicity results will be presented by site and overall. Statistical analyses of immunogenicity results will include adjustment for trial site.

6.8. Multiple Comparisons/Multiplicity

The primary objective includes three non-inferiority comparisons of Cecolin® at 0 and 6 months, 0 and 12 months, and 0 and 24 months with Gardasil® at 0 and 6 months. To control the type I error rate 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.

No other adjustments for type I error rate will be made.

List of Abbreviations (*continued*)

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Table 3 will present a summary of the reasons that subjects were screened but not enrolled. The composition of analysis populations, by study group and visit (for immunogenicity), will be presented separately for the Total Vaccination and Per Protocol Populations (Table 4**,** Table 7, and Table 10). Summaries will also be generated by site. The disposition of subjects and receipt of study vaccinations will be tabulated by study group for all subjects. Summary of subject disposition will include number of subjects screened, randomized, receiving study product, completing the study, and with immunogenicity results available (Table 13). A CONSORT diagram of the study will also be prepared (Figure 1**,** Appendix B). A summary of visit attendance will be prepared, along with vaccine administration and blood collection (Table 16).

A listing of subjects who discontinued vaccinations or terminated from study follow-up and the reason will be included in Listing 1, Appendix C. Further, a listing of visit completion status by subject will be prepared (Listing 2).

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the deviation category, deviation type, and study group for all subjects (Table 17). All subject-specific protocol deviations and non-subject-specific protocol deviations will be included as data listings (Listing 3 and Listing 4). Protocol deviations will not necessarily always lead to exclusion from the Immunology analysis population.

7.3. Demographic and Other Baseline Characteristics

A summary table of continuous measures (age, height, weight) and categorical measures (race) will be presented overall, by treatment group and by site (Table 18, Table 19 and Table 20). Descriptive statistics 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. This table will also be repeated for the per-protocol population, overall and by site (Table 21, Table 22, and Table 23). Demographic listing will also be prepared (Listing 5).

7.3.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 20.1 or higher. Summaries of subjects' pre-existing medical conditions will be prepared (Table 24), and individual subject listings will be prepared for all pre-existing medical conditions (Listing 6).

7.3.2. Prior and Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. The concomitant medications used during the 7 days post vaccination after any dose, after dose 1 and after dose 2 will be summarized by ATC level 1 and level 4 within level 1, and by study group for the total vaccinated population (Table 25). Additional by subject listings of prior and concomitant medications (administered within the 30 days after vaccination) (Listing 19) and administered after any SAE occurring during the study period (Listing 20) will be prepared. Listings will

List of Abbreviations (*continued*)

be generated of all vaccinations administered prior to the first dose (Vaccination History: Listing 7) and for all non-study vaccines administered during the study (Listing 8).

7.4. Measurements of Treatment Compliance

A summary of the number of doses of study product administered to subjects will be prepared as part of the subject disposition table (Table 13). Vaccine administration details will be listed (Table 16, Listing 9).

List of Abbreviations (*continued*)

8. IMMUNOGENICITY EVALUATION

The primary immunogenicity assessments will be assessed using the per protocol population. Supplementary analyses will be conducted in the total vaccinated population. 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 will be supplemented by reverse cumulative distribution (RCD) curves with each group for a given visit displayed on the same plot, with different panels for different visits. Assay values <LLOQ will be replaced by LLOQ/2 and values achieving the ULOQ will use the ULOQ as the observed data point in each analysis, except in analyses incorporating left and/or right censoring, in which case all values <LLOQ or >ULOQ will be censored at LLOQ and ULOQ, respectively.

GMC/T, GMC/T ratio, and corresponding confidence limits of the log-scale coefficients will be calculated using SAS PROC GLM with the LSMEANS statement of the log-scale coefficients which will be back-transformed in order to compute the estimate and corresponding confidence limits on the original scale. All models will use the log-transformed concentrations as the dependent variable, treatment group as the explanatory variable, and trial center as a covariate. All GMC/T ratios will be computed using the Cecolin containing arm as the numerator.

The GMC/T ratio and corresponding two-sided 98.3% CI for each comparison will be computed separately for each comparison to Gardasil® 0,6. Sensitivity analyses will be performed 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 if 10% or more observations are censored.

A listing of all immunogenicity results is provided in Listing 10 and Listing 11.

8.1. Primary Immunogenicity Analysis

The primary objective of this study is to 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. Non-inferiority will be achieved if the lower bound of the 98.3% CI for the GMC ratio is > 0.5.

Anti-HPV 16 and 18 IgG antibody GMC and corresponding 95% CIs, measured by ELISA at baseline and one month after the second dose for the two-dose Cecolin® and Gardasil® arms will be summarized. These results will be supplemented with a 95% CI for the median (Table 26). GMC summaries will be repeated for each trial center (Table 27 and Table 28).

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 at one month after the second dose (Table 29). The GMC ratios and CIs will also be presented in a figure along with the non-inferiority margin (Figure 2).

Graphs displaying the GMC will be created, displaying all visit numbers and treatment groups, including overlaid data points as well as error bars denoting the 95% CI, using the appropriate log scale for the y-axis (Figure 3 and Figure 4).

The analyses will be repeated as sensitivity analyses based on the total vaccinated cohort utilizing SAS PROC LIFEREG (Table 40 and Table 41).

List of Abbreviations (*continued*)

8.2. Secondary Immunogenicity Analyses

The secondary objective is to further evaluate immunogenicity of Cecolin® and Gardasil® based on HPV IgG antibody levels and to evaluate immunogenicity based on PBNA.

The primary summary of the anti-HPV 16 and 18 IgG antibody GMC and corresponding 95% CIs, measured by ELISA will be further extended to all time points and to the mixed dose arm (Table 26). GMC summaries and seropositivity rates will be repeated for each trial center (Table 27 and Table 28).

The GMC ratio and corresponding two-sided 95% CI for the 0,6 Gardasil® arm compared to the 0,24 mixed dose arm at one month post-second dose (Visit 6) will be calculated to assess immunogenicity of the mixed dose arm. Additionally, the GMC ratio and corresponding two-sided 95% CI for the 0,6 Gardasil® arm compared to the 0,6 Cecolin® arm at twenty-four months post-dose one (Visit 7) will be calculated to assess persistence (Table 30).

Seroconversion in anti-HPV 16 and 18 IgG antibody, defined as a 4-fold rise from baseline, will be summarized by frequency and percentage of participants per treatment group at one month after the second dose. The difference in the percentages will be computed between the Cecolin® and mixed arms compared to the Gardasil® arm one month after the second dose with a corresponding 95% CI computed via the Miettinen and Nurminen score method (Table 31). Seroconversion summaries will be repeated for each trial center (Table 32 and Table 33).

Anti-HPV 16 and 18 serum neutralizing antibody GMTs measured by PBNA and corresponding 95% CIs, will be summarized by time point and treatment group. These results will be supplemented with a 95% CI for the median (Table 35). GMT summaries will be repeated for each trial center (Table 36 and Table 37).

Graphs displaying the GMT will be created, displaying all visits and treatment groups, including overlaid data points as well as error bars denoting the 95% CI, using the appropriate log scale for the y-axis (Figure 5 and Figure 6).

Seroconversion in anti-HPV 16 and 18 measured by PBNA will be analyzed the same as anti-HPV 16 and 18 IgG antibody (Table 38).

Correlation between neutralizing antibody titers measured by PBNA and IgG antibody concentrations measured by ELISA will be summarized on the continuous scale for anti-HPV 16 and 18 and the following three categories Cecolin only, Gardasil only, and the mixed arm with colors identify timepoints (Figure 7 and Figure 8). The Spearman correlation between ELISA and PBNA results will be computed by type and for Cecolin only, Gardasil only, and the mixed arm. Summaries will be provided by three categories Cecolin only, Gardasil only, and the mixed arm and HPV type (Table 39).

Analysis of immunological assays will be supplemented by reverse cumulative distribution (RCD) curves for each treatment group for a given visit displayed on the same plot, and different panels for different visit (Figure 9 through Figure 12). Log concentration/titer will be on the x-axis and cumulative percent will be on the y-axis.

The analyses for GMC/T and GMC/T ratio will be repeated as a sensitivity analyses based on the total vaccinated cohort utilizing SAS PROC LIFEREG (Table 42 through Table 45).

8.3. Exploratory Immunogenicity Analyses

Immunologic bridging analyses are outside the scope of this SAP.

List of Abbreviations (*continued*)

Exploratory analyses covered in this SAP include summaries of GMTs, GMCs, seroconversion rates and seropositivity rates at the time of the second dose (sample collected prior to the dose) and one month after the second dose. Analyses will be performed for both ELISA and PBNA. Summaries will be repeated within each of the trial centers. Spaghetti plots of the antibody and titer results will be provided by study day and treatment group (Figure 13 through Figure 16). In addition, summaries of the GMC ratio one month after the second dose between the Cecolin® schedules will be generated, where the 0, 12 group and 0, 24 group will be compared (individually) to the 0, 6 group (Table 34).

GMCs/GMTs, seroconversion and seropositive rates after a single dose of Cecolin® or Gardasil® will be summarized at multiple timepoints. Arms will contribute the following timepoints

- Arm 1 (0, 6 Cecolin®): 6-month single dose for Cecolin®
- Arm 2 (0, 12 Cecolin®): 12-month single dose for Cecolin®
- Arm 3 (0, 24 Cecolin®): 24-month single dose for Cecolin®
- Arm 4 (0,6 Gardasil®): 6-month single dose for Gardasil®
- Arm 5 (0- Gardasil® and 24- Cecolin®): 24-month single dose for Gardasil®

These summaries will be contained in Table 26, Table 31, and Table 38. Additionally, single dose comparisons at 6- months (Arms 1 and 4) and 24- months (Arms 3 and 5) will be explored via the GMC ratios (Table 34).

In addition, in each arm, for both ELISA and PBNA HPV16 and HPV18, Antibody Kinetics model-estimate GMC/GMT from mixed models for repeated measures (MMNR9) will fit to log transformation of the concentration (or titres). Each model will include subject as random effect, visit and country as fixed effects and will assume compound symmetry for the covariance structure. As all subjects in the Per-Protocol population are seronegative at baseline, visit 1 will not be included in the model and presented as below LLQ. Fitted GMC/GMT and 95% CI will be presented in Table 46, Table 47 and in Figure 17 to Figure 19. The percentage decay at 18 months post-dose 2 relative to 1 month post-dose 2 for groups 1 and 4, estimated from the model, will also be presented in Table 46 and Table 47.

List of Abbreviations (*continued*)

9. SAFETY EVALUATION

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.

9.1. Adverse Events

A secondary objective of this study is safety of Cecolin® vaccination. 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 ofeach vaccination.

9.1.1. Reactogenicity

- Reactogenicity will be assessed according to immediate (at least 30 minutes post-vaccination) and delayed reactogenicity (through Day 7), after any and each vaccination. Delayed and immediate solicited AEs will be summarized by category (local/systemic), by reaction and by post-vaccination time point, overall and by site (Table 48 through Table 59). Solicited AEs will also be summarized by severity within reaction and within category by post-vaccination time point and by site and by vaccine type (Table 60 through Table 69), and by severity and reaction according to post-vaccination day by post-vaccination time point and by site. The summaries will present each severity up to the maximum severity reported for each reaction/day combination (Table 70 through Table 75). Each subject will be counted only once under the maximum severity of each reaction and/or category, where relevant, in these summaries. 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 (Listing 12). Duration of reactogenicity events will be summarized by reaction and time period and by site (after any dose, after first dose and after second dose) (Table 76 through Table 81).
- Measured injection site features will be summarized by group and post-vaccination time point, including but not limited to erythema/redness, swelling, and induration (Table 82 through Table 85).

Individual listings of solicited AEs ongoing at 7 days after any dose will be generated (Listing 12).

9.1.2. 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, overall and by site, 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 (Table 86 through Table 89). All AEs, related AEs and AEs leading to study withdrawal will be summarized by severity, where a subject only contributes once under

List of Abbreviations (*continued*)

the maximum severity event recorded (Table 90 through Table 97). Summary tables will also be prepared for each of these categories, by post vaccination time point, 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 (non-serious AEs will be summarized in Table 98 through Table 100 and Table 102 through Table 107; SAEs will be summarized in Table 108 through Table 110). An additional non-serious AE summary table will include preferred terms occurring in ≥5% of subjects (across group, regardless of seriousness, severity, or relationship), sorted in descending order of incidence (Table 101). 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 (Listing 13). Listing of Grade 2 or Grade 3 non-serious AEs will also be included (Listing 14).

9.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

Deaths, SAEs and other significant AEs will be presented (Listing 15), including Subject ID, Site, Age (years), MedDRA Preferred Term, Event Description, Prior Dose Received, Onset/End Date and Day Post-Dose, Duration, Relationship to Study Product, Alternate Etiology if Not Related, Action Taken with Study Treatment, Medications taken for the event, Study discontinuation, Outcome and any Additional Comments.

9.3. Pregnancies

Pregnancies will be summarized by treatment group and country (Table 112) and a listing of pregnancies and outcomes will be presented (Listing 21).

9.4. Vital Signs and Physical Evaluations

Vital sign measurements including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), oral temperature (°C), heart rate (beats/minute) and respiration rate (breaths/min) are to be assessed at all visits except visits 2 and 5. A listing of vital signs will be prepared (Listing 16) including pre- and post-vaccination results as well change from baseline.

A complete physical examination will occur at screening, on day 730 in groups 1 and 4, and prior to dose 2 in groups 2, 3 and 5. Targeted physical examinations may occur at visits 1, 3, 4 and 6 if indicated. Abnormal physical exam findings will be summarized by body system, treatment group and visit (Table 111). Separate listings of pre-vaccination and 30 days post-vaccination physical exam values, indicating any abnormalities, will be presented (

Visit Number: Time Point	Actual Study Day	Assessment Time	Assessment (Change From Baseline) [a]				
			Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse (beats/min)	Respiration Rate (breaths/min)
<Study center>, <Subject ID>, <Treatment Group 1 or 4>							
00: Screening	-xx	xx:xx	xx.x	xxx	xxx	xxx	xxx

List of Abbreviations (*continued*)

Visit Number: Time Point	Actual Study Day	Assessment Time	Assessment (Change From Baseline) [a]				
			Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse (beats/min)	Respiration Rate (breaths/min)
01: Pre-Dose 1	1	xx:xx	xx.x	xxx	xxx	xxx	xxx
01: Post-Dose 1	1	xx:xx	xx.x	xxx	xxx	xxx	xxx
03: Day 30	xxx	xx:xx	xx.x (± xx.x)	xxx (± xx)	xxx (± xx)	xxx (± xx)	xxx (± xx)
04: Day 180, Pre-Dose 2							
04: Day 180, Post-Dose 2							
04S: Unscheduled							
05: Day 187							
06: Day 210							
07: Day 730							
<Study center>, <Subject ID>, <Treatment Group 2>							
00: Screening	-xx	xx:xx	xx.x	xxx	xxx	xxx	xxx
01: Pre-Dose 1	1	xx:xx	xx.x	xxx	xxx	xxx	xxx
01: Post-Dose 1	1	xx:xx	xx.x	xxx	xxx	xxx	xxx
01: Dose 1	1	xx:xx	xx.x	xxx	xxx	xxx	xxx
03: Day 30	xxx	xx:xx	xx.x (± xx.x)	xxx (± xx)	xxx (± xx)	xxx (± xx)	xxx (± xx)
04: Day 365, Pre-Dose 2							
04: Day 365, Post-Dose 2							
06: Day 395							
<Study center>, <Subject ID>, <Treatment Group 3 or 5>							
00: Screening	-xx	xx:xx	xx.x	xxx	xxx	xxx	xxx
01: Pre-Dose 1	1	xx:xx	xx.x	xxx	xxx	xxx	xxx
01: Post-Dose 1	1	xx:xx	xx.x	xxx	xxx	xxx	xxx
01: Dose 1	1	xx:xx	xx.x	xxx	xxx	xxx	xxx
03: Day 30	xxx	xx:xx	xx.x (± xx.x)	xxx (± xx)	xxx (± xx)	xxx (± xx)	xxx (± xx)
04: Day 730, Pre-Dose 2							
04: Day 730, Post-Dose 2							
06: Day 760							

Baseline is the last observed value prior to administration of dose 1

[a] Results correspond to the assessment value and, for post-dose 1 assessments, the change from baseline.

Programming note: Include all unscheduled visits.

Listing 17 and Listing 18).

10. REPORTING CONVENTIONS

P-values will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001" and p-values greater than 0.999 will be reported as ">0.999". The median (except for ties), minimum and maximum will be reported on the same scale as the original data. The mean, standard deviation and CIs will be reported to one additional decimal place. Proportions and percentages will be reported to one decimal and corresponding 95% CIs will be to two decimals. 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.

11. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings.

12. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

An additional exploratory analysis has been added (not included in version 1.6 of the protocol) where the antibody kinetics model will be implemented.

A listing of all pre- and post-vaccination vital signs, including change from baseline, will be included but no summary tables will be presented, as they are not considered to be medically relevant in a stage 3 study.

Extra versions of Tables 84 and 87 will be generated that will include all SAEs and all unsolicited AEs rather than only those within one month (30 days) of each dose. These 2 tables (Tables 89 and 97) will be submitted to ClinicalTrials.Gov.

13. REFERENCES

Not applicable.