Official Protocol Title:	A Phase III, Open-Label, Clinical Trial to Study the Safety and Immunogenicity of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Particle (VLP) Vaccine in 9- to 15-Year-Old Japanese Boys
NCT number:	NCT02576054
Document Date:	21-AUG-2015

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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase III, Open-Label, Clinical Trial to Study the Safety and Immunogenicity of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Particle (VLP) Vaccine in 9- to 15-Year-Old Japanese Boys

EudraCT NUMBER: Not Applicable

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1.0 TRIAL SUMMARY

Abbreviated Title	Safety and Immunogenicity trial of V501 in Japanese boys
Trial Phase	Phase III
Clinical Indication	Prevention of condyloma acuminata and anal cancers and related precancers caused by Human Papillomavirus (HPV) 6, 11, 16 and 18
Trial Type	Interventional
Type of control	No control
Route of administration	Intramuscular injection
Trial Blinding	Unblinded Open-label
Vaccination Groups	V501
Number of trial subjects	Approximately 100 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 34 months (Study Period for Clinical Trial Notification (CTN): From Sep 2015 to Jan 2019) from the time the first subject signs the informed consent until the last subject completes the last study-related phone call or visit, discontinues from the trial or is lost to follow-up (i.e., the subject is unable to be contacted by the investigator).
Duration of Participation	Each subject will participate in the trial for approximately 30 months from the time the subject's legally acceptable representative signs the Informed Consent Form (ICF) through the final contact. Each subject will receive 3 doses of the study vaccine intramuscularly at Day 1, Month 2 and Month 6. After the completion of vaccination, each subject will be followed for 24 months.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a nonrandomized, multi-site, open-label trial of V501 [quadrivalent HPV (Type 6, 11, 16 and 18) L1 Virus-Like Particle (VLP) vaccine] in healthy Japanese boy subjects to be conducted in conformance with Good Clinical Practices. This study will consist of two periods. Period I of the study is to evaluate the immunogenicity and tolerability of V501 up to the point of Month 7. Period II of the study is to evaluate the long-term immunogenicity and safety from Month7 to Month30. Two analyses are planned. The first analysis will be conducted when all subjects have completed their Month 7 visit or have been discontinued before that time. The second analysis will be conducted at the end of study.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

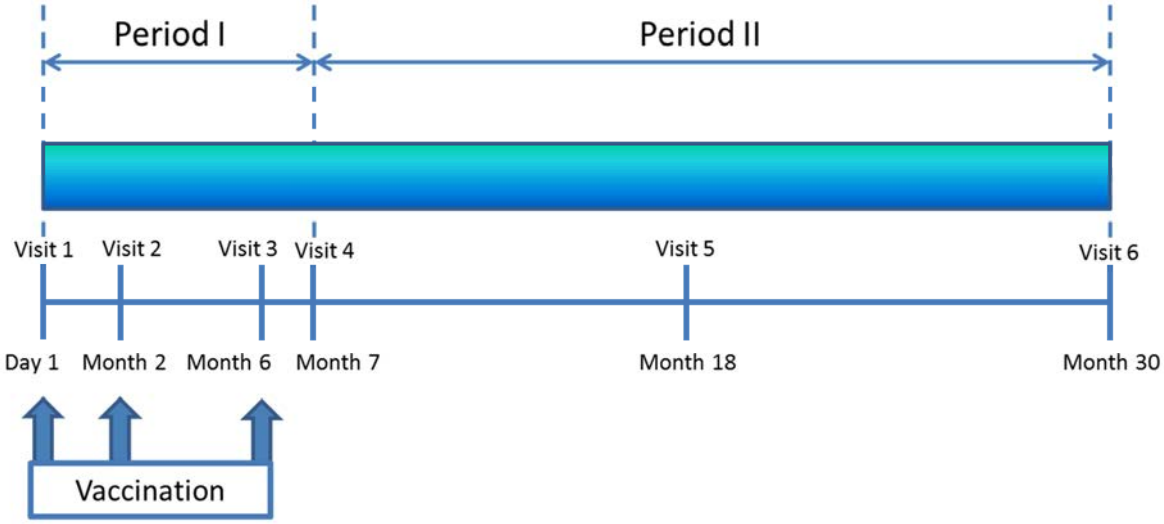

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To demonstrate that administration of V501 induces high seroconversion rates for the vaccine HPV types (6, 11, 16 and 18) at 4 weeks post dose 3 in 9- to 15-year-old Japanese boys.

> **Hypothesis**: Seroconversion rates for the vaccine HPV types (6, 11, 16 and 18) at 4weeks post dose 3 will be high (The success criterion for the primary analysis requires that point estimates for seroconversion rates be greater than 90% for all 4 HPV types).

(2) **Objective:** To demonstrate that a 3-dose regimen of V501 to 9- to 15-year-old Japanese boys is well tolerated.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To demonstrate that administration of V501 induces non-inferior geometric mean titers (GMTs) for serum anti-HPV 6, 11, 16 and 18 at 4 weeks post dose 3 in Japanese boys aged 9- to 15-year-old compared with those in Japanese men aged 16- to 26-year-old in Phase III study (Protocol 122) for V501 at 4 weeks post dose 3.

Hypothesis: V501 generates anti-HPV 6, 11, 16 and 18 GMTs 4 weeks post dose 3 in Japanese boys aged 9- to 15-year-old that are non-inferior to those in Japanese men aged 16- to 26-year-old. (The statistical criterion for success requires that the lower bound of two-sided 95% confidence interval of GMT ratio between boys enrolled in V501-200 and men enrolled in the Phase III study V501-122 be greater than 0.5 for each HPV type.)

(2) Objective: To describe the persistence of the serum antibody titers for the vaccine HPV types 24 months following the third dose of V501.

(3) Objective: To estimate the immune response for the vaccine HPV types (6, 11, 16 and 18) at 4 weeks post dose 3 using GMTs.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on V501.

4.1.1 Pharmaceutical and Therapeutic Background

V501 is quadrivalent HPV (Types 6, 11, 16 and 18) vaccine having been developed based on VLPs, which are produced by self-assembly of recombinant HPV L1 capsid proteins.

4.1.1.1 Disease Burden and Epidemiology of Human Papillomaviruses

HPV infection causes benign and malignant dysplastic disease, localized primarily in the anogenital area, and also in the aerodigestive tract, in both men and women [1, 2, 3]. Disease burden of HPV in men includes:

Anogenital Warts. Anogenital warts are generally benign, exophytic, hyperkeratotic lesions on the penile shaft (most common site of lesions), scrotum, perineum, and anus in men. In general, the lesions do not cause any physical discomfort [4]. Some patients experience itching, burning, bleeding, moisture, irritation or soreness, especially with lesions in the perianal region. Patients are often distressed by unsightly lesions. Treatment consists of chemical or physical ablation and is often unsuccessful. Recurrence rates are high [5]. While Japan's Infectious Disease Surveillance system [6] publishes the counts of genital warts cases that are reported into the surveillance system, it does not report actual incidence rates. However, the surveillance system does show a nominally higher number of warts cases in males compared to females. This is consistent with most worldwide data, showing slightly higher rate of genital warts in males than in females.

Anal Cancer and Penile Cancer. Most anal cancers, and ~50% of penile cancers are caused by HPV. Rates of anal cancer are increasing [7, 8].

The cumulative lifetime risk for HPV infection in sexually active women exceeds 50%. Available data suggest that HPV infection is also very prevalent in men [9, 10]. HPV infection is transmitted via contact with an infected individual or a contaminated object and occurs most often during sexual activity. Sixty percent (60%) of sexual partners of infected individuals develop lesions 4 weeks to 8 months after exposure [11]. HPV is often acquired immediately after sexual debut. The risk of HPV infection is strongly correlated with the number of lifetime sexual partners [12, 13]. Men and women in their late teens and early twenties are at the highest risk for HPV infection, as early sexual activity is accompanied with a higher likelihood of having new sexual partners, thus increasing the risk of exposure to the virus.

A few prospective studies have examined the incidence and duration of genital HPV infection in men. These studies indicate that HPV infection in men is self-limited and a risk factor for HPV genital disease. It appears that the majority of HPV infections in men clear within 12 months with a median time of clearance of ranging from 5.9 to 7.5 months [14, 15]. However, HPV 16 infections tend to last longer and clear at a median of 12.2 months [15]. HPV testing positive for HPV 6 or 11 is the strongest predictor of developing genital warts [16]. HPV 16 infection is a recognized risk factor for penile cancer [17].

Infection with HPV has been shown to be associated with cervical, vulvar, vaginal, anal, penile, oral and oropharyngeal cancers in women and/or men [1, 2]. Each of non-cervical HPV-related diseases is much less frequent than cervical cancer. But taken together, they represent a significant human health and economic burden in both men and women [9, 18]. Of particular concern, the incidence of anal cancer has been increasing over the past several decades [19]. The risk of anal cancer is increased in men and women with a high number of sexual partners, current smokers, and among men who are not exclusively heterosexual or women who have a history of receptive anal intercourse [20]. Anal cancer is preceded by high-grade anal intraepithelial neoplasia (AIN) [21, 22]. Over 80% of anal cancers and over 90% of high-grade AIN contain high-risk HPV [23]. The high proportion of HPV-positive tumors suggests that HPV infection is necessary for developing anal cancer.

4.1.1.2 Biology of Human Papillomaviruses

HPV consist of a family of small, nonenveloped icosahedral capsid viruses containing double-stranded DNA. 2 capsid proteins are encoded in the viral genome; L1, major capsid protein and L2, minor capsid protein. Mature viral particles are composed of 72 pentamers of L1 proteins arranged in icosahedral symmetry.

HPV types targeted by V501 belong to Species A7, A9, and A10. Species A7 and A9 contain most of the high-risk types. Species A10 contains low-risk HPV Types 6 and 11, which are responsible for over 90% of anogenital warts. The A7 Species includes HPV 18, 39, 45, 59, and 68. The A9 Species includes HPV 16, 31, 33, 35, 52, and 58. HPV 16 and 18 are responsible for most cases of anal cancer [23].

HPV infection and replication is entirely intraepithelial. By remaining exclusively intraepithelial, HPV largely avoids exposure to the host immune system and evades immune

recognition, which allows HPV infection to proceed [24, 25, 26]. Accordingly, immune responses to natural viral infection are poor. Nonetheless, most HPV infections are eventually cleared. It is thought that naturally acquired immune responses contribute to the clearance of infection, although the mechanisms are not well elucidated [27]. Those infections that are not cleared can result in dysplasia and cancer (especially the high-risk types).

4.1.1.3 Prophylactic HPV Vaccines

A 3-dose regimen of V501 is delivered intramuscularly and induces high levels of type restricted neutralizing antibodies and seroconversion in virtually 100% of the vaccinated subjects.

As of February 2015, V501 was approved and marketed under the names GARDASIL™/SILGARD™ in over 130 countries including Japan. In clinical trials in 16- to 26-year-old women, prophylactic efficacy against HPV 6, 11, 16 and 18 related lesions have already been shown [28]. Efficacy was maintained for at least 6 years after the first vaccination [29]. Moreover, in an overseas Phase III study (V501 Protocol 020), V501 was found to be over 89% and 85% efficacious in preventing the development of HPV 6- or 11-related condyloma acuminata and HPV 6-, 11-, 16- or 18-related persistent infection in 16- to 26- year-old men, respectively [30], and 77.5% efficacious in preventing HPV 6-, 11-, 16- or 18- related AIN in 16- to 26-year-old MSM [31]. Based on these data, V501 has also been approved for males for prevention of vaccine type HPV-related genital warts and anal cancer and/or precancers in over 70 countries. In US, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of GARDASIL™ in males 11 or 12 years of age in addition to the vaccination to females [32]. In Japan, the clinical trial in Japanese male aged 16 to 26 years old to evaluate efficacy and tolerability, V501-122, is on-going. Male indication of V501 has not been approved yet in Japan.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

HPV vaccination could contribute to reducing the burden of HPV diseases in males. V501 is highly efficacious to prevent vaccine type HPV-related genital warts and anal cancer and precancers in males overseas. Moreover, in contrast to cervical cancer in women, there is no widespread screening program for any HPV related cancers in men, making prophylactic vaccination the only realistic preventive measure for HPV diseases in men, in both developed and developing countries. An additional potential benefit of HPV vaccination in men is the generation of herd protection, which in turn could lead to a substantial reduction of HPV diseases in both males and females [9].

Previous public health experience has shown that gender-restricted vaccination programs are substantially less effective than universal vaccination. It is likely that the most effective means to reduce the burden of HPV disease using a safe and effective prophylactic vaccine is to vaccinate both males and females.

This trial is designed to bridge V501 efficacy findings in young adult men in overseas clinical trial, V501-020 and on-going Japanese clinical trial, V501-122, to Japanese boys, via the comparison of the immunogenicity against HPV type 6, 11, 16 and 18 between 9- to 15-year-old Japanese boys and 16- to 26-year-old Japanese men enrolled in V501-122.

4.2.2 Rationale for Dose Selection/Regimen

In Japan, V501 has been approved and marketed under the name of GARDASIL™ only for women 9 years of age or older. However, V501 has been approved for both females and males outside Japan and its effectiveness is well established. The formulation and regimen are identical between females and males. Therefore, the same regimen (3 doses at Day 1, Month 2 and Month 6) and the same formulation [HPV 6 L1 VLP 20 μg, HPV 11 L1 VLP 40 μg, HPV 16 L1 VLP 40 μg, HPV 18 L1 VLP 20 μg and Amorphous Aluminum Hydroxyl phosphate Sulfate (AAHS) 225 μg] as approved in many countries including Japan will be used in this trial.

4.2.3 Rationale for Endpoints

4.2.3.1 Immunogenicity Endpoints

Anti-HPV 6, 11, 16 or 18 will be analyzed as the indicator of immune responses to each vaccine components. Assessment of efficacy of V501 in 16- to 26-year-old men is ongoing under a different study (Protocol 122). Direct efficacy evaluation of prophylactic HPV vaccine in 9- to 15-year-old subjects is not feasible due to social and cultural constraints surrounding the notion of sexual activity among younger adolescents and the limited ability to perform anogenital examination in this age group.

Serum will be collected from all subjects for analysis of anti-HPV 6, 11, 16 and 18 by competitive Luminex Immunoassay (cLIA) at Day 1, Month 7, Month 18 and Month 30. Serum sample will be collected at Day 1 for identification of subjects who had an HPV infection prior to enrollment.

4.2.3.2 Safety Endpoints

Since majority of the adverse events (AEs) occurs within a few days after the vaccination, the subjects will be followed for 14 days following each vaccination. The Vaccination Report Card (VRC) will be utilized to collect subject's (1) oral temperature and local (i.e., injection site) AEs (including erythema, swelling and pain/tenderness) for 5 days starting the day of each vaccination, (2) systemic AEs and serious adverse events (SAEs) for 15 days (14 days following each vaccination), and (3) vaccine-related SAEs and deaths throughout the study.

4.2.3.3 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens collected for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from vaccination during participation, as clinical trials are designed to provide information about the safety and immunogenicity of an investigational vaccine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Healthy Male subjects between the ages of 9 and 15 years (inclusive) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be a healthy, Japanese male between the age of 9 years and 0 days and 15 years and 364 days on the day of the first study vaccination.

2. Have a legal representative who provides written informed consent for the trial on the subject's behalf. The legal representative may also provide consent for Future Biomedical Research on the subject's behalf. However, the subject may participate in the main trial without participating in Future Biomedical Research.

3. Have a legal representative who is able to read, understand, and complete the vaccine report card.

4. Agree to provide study personnel with a primary telephone number as well as an alternate telephone number/email address for follow-up purpose.

5. Show no temperature ≥37.5˚C (oral) within 24 hours prior to vaccinations. If the subject does not meet this criterion, the Day 1 visit will be rescheduled for a time when this criterion can be met.

6. Must not yet have had coitarche and does not plan on becoming sexually active during the Day 1 through Month 7.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is concurrently enrolled in clinical studies of investigational agents

2. Has history of known prior vaccination with an HPV vaccine or plans to receive the HPV vaccine outside of the study.

3. Has receipt of inactivated vaccines within 14 days prior to enrollment or receipt of live virus vaccines within 28 days prior to enrollment. If the subject meets this criterion, the Day 1 visit will be rescheduled for a time when this criterion is not met.

4. Has history of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension or shock) that required medical intervention.

5. Is allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).

6. Has received any immune globulin or blood derived products within the 6 months prior to the first injection, or plan to receive any through Month 7 of the study.

7. Has history of splenectomy or is currently immunocompromised or has been diagnosed as having a congenital or acquired immunodeficiency, HIV infection, lymphoma, leukemia, systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), inflammatory bowel disease, or other auto immune condition.

8. Is receiving, or has received in the year prior to enrollment the following immunosuppressive therapies: radiation therapy, cyclophosphamide, azathioprine, methotrexate, any chemotherapy, cyclosporin, leflunomide, TNF-α antagonists, monocolonal antibody therapies (including rituximab), intravenous gamma globulin, antilymphocyte sera, or other therapy known to interfere with the immune response. With regard to systemic corticosteroids, a subject will be excluded if he is currently receiving steroid therapy, has recently (defined as within 2 weeks of enrollment) received such therapy, or has received 2 or more courses of high dose corticosteroids

(orally or parenterally) lasting at least 1 week in duration in the year prior to enrollment. Subjects using inhaled, nasal, or topical corticosteroids are considered eligible for the study.

9. Has known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

10. Has history of recent (within the last 12 months) or ongoing alcohol or drug abuse. Alcohol and drug abusers are defined as those who drink or use drugs despite recurrent social, interpersonal, and legal problems as results of alcohol or drug use.

11. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might confound the results of the study, or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate.

12. Is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.

13. Has a history of genital warts or a positive test for HPV.

14. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Vaccination(s)

The vaccine to be used in this trial is outlined below in Table 1.

Table 1 Trial Vaccination

Vaccine.	Dose/Potency	Dose Frequency	Route of Administration	Vaccination Regimen	Use
V501	0.5 mL	3	Intramuscular injection	Day 1, Month 2 and Month 6	Investigational

Trial vaccination is given on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

V501 will be administered as a 0.5 mL intramuscular injection at Day 1, Month 2 and Month 6.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the vaccine administered.

5.3 Randomization or Vaccine Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

See the exclusion criteria for specific restrictions for prior and concomitant medications at Day 1.

To reduce their potential interference with the evaluation of the immunologic response and reactogenicity of the study vaccine, non-study inactivated vaccines must not be administered within the 14 days before or 14 days after any dose of study vaccine. Non-study live virus vaccines must not be administered within the 28 days prior to or 14 days after any dose of study vaccine. Non-study HPV vaccine must not be used at any time during the study. Immune globulin or blood-derived products must not be administered within 6 months prior to vaccination through Month 7. Systemic corticosteroids should not be administered within 2 weeks prior to vaccination through Month 7, if at all possible. Subjects may receive allergen desensitization therapy and tuberculin skin testing while participating in the study.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

No special restrictions will apply except for those noted under the inclusion/exclusion criteria.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Discontinuation from treatment is "permanent". Once a subject is discontinued, he/she shall not be allowed to restart treatment.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The subject participation portion of the overall trial ends when the last subject completes the last study-related phone call or visit, discontinues from the trial or is lost to follow-up (i.e., the subject is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall trial ends when the Sponsor receives the last serology assay result or subject data from the last study-related phone call or visit.

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Trial Period:	Period I				Period II	
Visit Number:	1	2	3	4	5	6
Scheduled Day/Month :	Day 1	Month 2	Month 6	Month 7	Month 18	Month 30
Visit Window [1]:		2 months after Day 1 ± 3 weeks	6 months after Day 1 ± 4 weeks	3 to 7 weeks after Month 6	18 months after Day 1 ± 4 weeks	30 months after Day 1 ± 4 weeks
Administrative Procedures						
Informed Consent/Assent [2]	X					
Informed Consent for Future Biomedical Research	X					
Inclusion/Exclusion Criteria	X					
Subject Identification Card	X					
Medical History	X					
Update Medical History (New condition not already recorded as medical history or adverse experiences)		X	X	X	X	X
Concomitant Medication and Non Study Vaccination Review [3]	X	X	X	X	X	X
Assign Screening and Randomization/Treatment number	X					
Clinical Procedures/Assessments						
Vital Signs (oral temperature, height, weight, sitting pulse, blood pressure, and respirations) [4]	X	X	X			
Provide Vaccination Report Card (VRC)	X	X	X			
Review and collect VRC data		X	X	X		
V501 Administration [5]	X	X	X			
Adverse Events Monitoring	X	X	X	X	X	X
Laboratory Procedures/Assessments						
Serum for Anti-HPV antibody testing (including retention serum) [6]	X			X	X	X
Blood (DNA) for Future Biomedical Research [7]	X					

1. To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days.
2. Written assent of the subject himself is to be obtained as far as possible.
3. See section 7.1.1.5 of the protocol for details for prerequisites for medications and non-study vaccines
4. If the subject has a fever (defined as an oral temperature of ≥37.5°C) within the 24-hour period prior to receiving a study vaccination, the subject should not receive study vaccine, and the vaccination visit should be rescheduled until after the fever has resolved. Vital sign should be measured prior to each vaccination. Height and weight are measured at Visit 1 only.
5. Observe subjects for 30 minutes after each vaccination for immediate untoward effects.
6. Serum for anti-HPV measurements must be collected before vaccination.
7. Informed consent for future biomedical research samples must be obtained to collect the DNA sample.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. At Visit 1 (Day 1), medical history for the year prior to Visit 1 will be collected. After Visit 1, any new medical history that has not been previously documented (either as adverse experiences or as medical history conditions) will be collected.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, and record prior medication taken by the subject before first dose of trial vaccination. Refer to the exclusion criteria for specific restrictions for prior medications and vaccines at Day 1.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

Use of medicines and non-study vaccines should be documented in the data collection system in the following manner:

- Medications (corticosteroids, immunosuppressives, immune globulins, and blood products) from 3 days prior to Day 1 through Month 7;
- Medications from 3 days prior to each study vaccination through 14 days after each study vaccination;
- Non-Replicating (Inactive) Vaccines for 14 days prior to each study vaccination through 14 days after each study vaccination; and
- Replicating (Live) Vaccines for 28 days prior to each study vaccination through 14 days after each study vaccination.
- Non-study HPV vaccine must not be used at any time during the study. However, for the specific case where a subject mistakenly receives any non-study HPV vaccines, the nonstudy HPV vaccine must be reported on the appropriate eCRF, regardless of when the non-study vaccine was received.

Please refer to the eCRF Entry Guidelines for further details.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Vaccination)

Administration of trial vaccination will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Vital Signs

Vital signs (oral temperature, sitting pulse, blood pressure and respirations) will be taken before each study vaccination. Height and weight are measured at Visit 1 only.

Height and weight at Visit 1, and pre-vaccination oral temperature will be documented in the data collection system and the other vital signs will be documented in the subject's chart. If the subject has fever (defined as an oral temperature of ≥37.5˚C) within the 24-hour period prior to receiving a study vaccination, the subject should not receive study vaccine, and the vaccination visit should be rescheduled.

7.1.2.2 Vaccination Report Card (VRC)

Each subject will receive a VRC at the study vaccination visit. On the VRC, the parent/guardian of the subject will be asked to record his oral temperature in the evening after each study vaccination and daily for 4 days after each study vaccination for the purpose of identifying febrile events. Also, beginning after each study vaccination and for a total of 15 days including the day of vaccination, the parent/guardian of the subject will be asked to record injection-site and systemic adverse experiences, concomitant medications, and concomitant vaccinations on the VRC. The information on VRC should be generated only by the parent/guardian of the subject and must be signed and dated by the subject's parent or guardian to confirm the accuracy of the recorded information. The subject's parent or guardian will be asked to bring the VRC to the study site at the next scheduled visit.

When the VRC is returned, the VRC should be reviewed for completeness by study site personnel. If clarification is needed, the study site personnel will discuss the VRC with the subject's parent/guardian. Original information on the VRC should never be altered by study personnel, although comments can be written in the designated area for study site personnel on the front of the VRC. Corrections to the VRC can only be made by the subject's parent/guardian. Any corrections to the VRC should be made by using an ink pen to add the omitted data and/or to draw a single line through the error and add the correct information. The subject's parent/guardian should initial/date all VRC corrections.

All VRC information will be recorded in the Electronic Data Capture (EDC) system. The physician investigator/sub-investigator will determine causality of systemic and injection-site adverse experiences recorded on the VRC using the reporting guidelines given in the protocol and will classify each event as a serious adverse experience (SAE) or non-serious adverse experience (NSAE). If an oral temperature indicates a fever (defined as an oral temperature of ≥37.5°C), the adverse experience of "fever" must be documented in the eCRFs. At the time of VRC review at the next scheduled visit, subjects will be questioned regarding any new medical conditions that occurred beyond Postdose Day 15. The physician investigator/sub-investigator will determine if the medical condition is to be reported as an SAE using the reporting guidelines provided in Section 7.2.2.1.

7.1.2.3 Study Vaccine Administration

7.1.2.3.1 Preparation for Administration

The study vaccine must be used as supplied (no dilution before administration). Prior to administration, mix the contents of the vial thoroughly by rolling the vial between the palms of both hands for 30 seconds. Withdraw a 0.5-mL dose from the vial, which contains approximately 0.75 mL of study vaccine. The study vaccine should be a whitish, semitranslucent suspension when thoroughly mixed. If the appearance is otherwise, do not administer, and contact the SPONSOR immediately.

7.1.2.3.2 Study Vaccine Administration

At each vaccination visit, subjects will receive V501 as a 0.5-mL intramuscular injection. The deltoid muscle of the nondominant arm is the preferred site of vaccination. Study vaccinations should not be administered into the buttocks area. Injections should not be given within 2 cm of a tattoo, scar, or skin deformity.

Study vaccine should be administered using a 1.0-mL syringe. Injections should be administered at a 90° angle into the muscle tissue using a needle long enough to ensure intramuscular deposition of vaccine.

All subjects will be observed for at least 30 minutes after each study vaccination for any untoward effects, including allergic reactions. This observation period will be documented in the subject's chart.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn over the course of the trial, including approximate blood volumes drawn by visit by sample type per subject can be found in Section 12.4.

7.1.3.1 Serum for Anti-HPV Measurements

The 4-valent HPV cLIA is the primary assay used for the primary and secondary objectives of the trial. Additional testing may be conducted using other HPV immunological assays (Total IgG Luminex Immunoassay, Pseudovirion-based Neutralization Assay) for supportive exploratory analyses.

For each visit that requires a serum specimen for anti-HPV measurements, a 10-mL (nonheprinized, non-serum separator, red-top tube provide by the SOPONSOR-designated Central Laboratory) blood specimen will be collected and should be separated to avoid hemolysis. A minimum of 3.0 mL of serum should be aliquoted to a vial provided by the SPONSOR-designated Central Laboratory. An additional 1.5 mL of serum ("Retention Serum") should be aliquoted to a vial provided by the SPONSOR-designated Central

Laboratory and labeled with the "Retention Serum" label provided by the SPONSOR designated Central Laboratory.

"Serum" vials will be stored at -20˚C (or lower) until shipped on dry ice. The Retention serum should be shipped separately from the Serum sample.

7.1.3.2 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- Blood (DNA) for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the next trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events .

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Refrigerator
- Centrifuge

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Prerequisites for Study Vaccination Visit

See the inclusion/exclusion criteria for specific restrictions at Visit 1 (Day 1). For visits with study vaccination (Visit 1, 2 and 3), study personnel should verify by questioning the subject and/or by examination that:

- The subject has not had a fever (define as an oral temperature of ≥37.5˚C) within 24-hour period prior to any study vaccination visit.
- The subject has not received any systemic (oral or parenteral) corticosteroids in the 2 weeks prior to any study vaccination visit.
- The subject has not received a non-study inactive vaccine within 14 days prior to any study vaccination visit or a non-study live vaccine within 28 days prior to any study vaccination visit.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of allocation/randomization through 14 days (42 days for live attenuated vaccines) following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days (42 days for live attenuated vaccines) thereafter, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than 1 dose (> 0.75 mL) of any individual study vaccine in any 24 hour period will be considered an overdose for this protocol..

If an adverse event(s) is associated with (“results from”) the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event, using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic

reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Immediate Reporting of Adverse Events to the Sponsor

7.2.2.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 2 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days (42 days for live attenuated vaccines) following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days (42 days for live attenuated vaccines) thereafter, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event brought to the attention of an investigator who is a qualified physician at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is either:

1. A death that occurs prior to the subject completing the trial, but outside the time period specified in the previous paragraph.

or

2. A serious adverse event that is considered by an investigator who is a qualified physician to be vaccine related.

All subjects with serious adverse events must be followed up for outcome.

7.2.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 2. The investigator's assessment of causality is required for each adverse event. Refer to Table 2 for instructions in evaluating adverse events.

Table 2 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities) **Injection site redness or swelling from the day of vaccination through Day 5 post-vaccination will be evaluated by maximum size.**
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose that:	
	†**Results in death; or**	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements; **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse event? The determination of the likelihood that the test vaccine caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the test vaccine and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g., diary), seroconversion or identification of vaccine virus in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine? Is the time of onset of the AE compatible with a vaccine-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject reexposed to the test vaccine in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose vaccine trial.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:		**Use the following criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**
Yes, there is a reasonable possibility of vaccine relationship.		There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to the administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause.
No, there is not a reasonable possibility of vaccine relationship		Subject did not receive the test vaccine OR temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)

7.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

The immunogenicity and safety analysis of Day 1 through Month 7 will be performed after the data through Month 7 have been declared final and complete. The analysis of Month 18 through Month 30 immunogenicity and safety data will take place at the end of the study. The results of this study will be summarized in 2 separate reports. The first report is the CSR including the immunogenicity and safety results based on the data through Month 7. The second one is an update to the CSR, including persistence of immune response and safety results through the end of the study.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A phase III, open-label, clinical trial to study the safety and immunogenicity of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Particle (VLP) vaccine in 9- to 15-year-old boy
Treatment Assignment	Subjects meeting inclusion/exclusion criteria will be allocated to V501.
Analysis Populations	Immunogenicity: Per-Protocol Immunogenicity (PPI) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Primary immunogenicity endpoint will be seroconversion rate for the vaccine HPV types (6, 11, 16 and 18) at 4 weeks post dose 3.
Key Secondary Endpoints	Key secondary endpoint includes cLIA geometric mean titers (GMTs) for the vaccine HPV type (6, 11, 16 and 18) at 4 weeks post dose 3.
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary hypothesis with respect to anti-HPV 6, 11, 16 and 18 seroconversion percentages by 4 weeks post dose 3 will be evaluated by computing point estimates and constructing 95% confidence interval. (The success criterion for the primary analysis requires that point estimates for seroconversion rate be greater than 90% for all 4 vaccine HPV types.) The secondary hypothesis will be evaluated by comparing anti-HPV 6, 11, 16 and 18 GMTs at 4 weeks post dose 3 in 9- to 15-year-old boys from this study with those in 16- to 26-year old young men (all young men who were vaccinated by V501 and met the per-protocol immunogenicity criteria of PN122 will be included) by constructing a 95% confidence interval for the ratio of GMTs.

Statistical Methods for Key Safety Analyses	The adverse experiences of interest in this study include injection site adverse experiences/vaccine-related adverse experiences prompted for on the VRC occurring Day 1 through Day 5 following any vaccination, systemic adverse experiences/vaccine-related adverse experiences reported Day 1 through Day 15, elevated temperatures from Day 1 to Day 5 following any vaccination. Summary tables will be provided.
Interim Analyses	The immunogenicity and safety analysis of Day 1 through Month 7 will be performed after the data through Month 7 have been declared final and complete. The analysis of Month 18 through Month 30 immunogenicity and safety data will take place at the end of the study.
Multiplicity	For the primary hypothesis, no multiplicity adjustment is required since success requires the observed seroconversion rates for all 4 vaccine HPV types to be greater than 90%. Similarly, for the secondary hypothesis for comparing GMTs between 9- to 15-year-old boys and 16- to 26-year old young men, success is required on all 4 vaccine HPV types. Therefore, no multiplicity adjustment will be made to account for the multiple HPV types. The secondary hypothesis will only be tested if the primary hypothesis is demonstrated successfully.
Sample Size and Power	This study will enroll 100 subjects to receive V501, and will allow estimation of seroconversion percentage with a 95% confidence interval with a half-width of approximately 5 percentage points to assess the primary objective. Given the true seroconversion percentage of 95%, there is 92% probability that the point estimates are greater than 90% for all 4 vaccine HPV types. This is based on the assumption of an approximately 5% dropout and/or protocol violation rate. For the secondary hypothesis, a sample size of 95 boys from this study and 400 young men from PN122 has more than 99% probability that the lower bounds of 95%CI exceed 0.5 for all 4 HPV types given the underlying true GMT ratio is 1.0. This is based on the following assumptions for young men from PN122 in addition to that for boys described above: no general protocol violation of 95%; exclusion rate due to Day 1 seropositive or PCR positive between Day 1 and Month 7 to HPV 6, 11, 16, and 18 is approximately 15%; 90% of randomized subjects completed vaccination phase.

8.2 RESPONSIBILITY FOR ANALYSES/IN-HOUSE BLINDING

The statistical analysis of the data obtained from this study will be the responsibility of the designee/Clinical Biostatistics department of the SPONSOR. This trial is being conducted as a non-randomized, open-label study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

8.3 HYPOTHESES/ESTIMATION

Objectives and hypotheses of the study are stated in Section 3.1.

8.4 ANALAYSIS ENDPOINTS

Immunogenicity and safety endpoints that will be evaluated for within- and/or between-age group differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Immunogenicity Endpoints

The primary immunogenicity endpoints are seroconversion percentages to HPV 6, 11, 16 and 18 by 4 weeks post dose 3. Seroconversion is defined as changing serostatus from seronegative to seropositive. A subject with a competitive Luminex Immunoassay (cLIA) titer at or above the serostatus cutoff for a given HPV type is considered seropositive for that HPV type. The key secondary immunogenicity endpoints include cLIA geometric mean titers (GMTs) to HPV 6, 11, 16 and 18 at 4 weeks post dose 3. Other secondary endpoints include both cLIA GMTs and seroconversion percentages for each vaccine HPV type at Months 18 and 30 to assess persistence of immune responses.

8.4.2 Safety Endpoints

Safety assessment will focus on the injection site adverse experiences/vaccine-related adverse experiences and elevated temperatures on Days 1 to 5 post-vaccination, and systemic adverse experiences/vaccine-related systemic adverse experiences on Days 1 to 15 post-vaccination, reported on the Vaccination Report Card (VRC). Serious adverse experiences reported Days 1 to 15 post-vaccination, vaccine-related serious adverse experiences reported any time during the study and new medical condition occurring any time during the study will also be summarized.

8.5 ANALYSIS POPULATION

8.5.1 Immunogenicity Analysis Populations

Per Protocol Immunogenicity (PPI) Population

The Per Protocol Immunogenicity (PPI) population will serve as the primary population for the analysis of immune response to each of the 4 HPV types (6, 11, 16 and 18). To be included in this population, subjects must:

(1) Have received all 3 vaccinations with the correct dose of the correct clinical material, and each vaccination visit must occur within acceptable day ranges (See Table 3 for acceptable day ranges for vaccination visits).

(2) Have provided Month 7 serology result within 21 to 49 days post dose 3.

(3) Be seronegative to the appropriate HPV type at Day 1 (See Table 4 for acceptable day ranges for serum samples at Day 1).

(4) Have no other protocol violations that could interfere with the evaluation of subject's immune response to the study vaccine.

To be included in the PPI population for HPV 6 or 11, subjects must be seronegative to both HPV 6 and 11 at Day 1. To be included in the PPI population for any other vaccine HPV type, subjects need to be seronegative at Day 1 only for the HPV type being analyzed. The final determination on protocol violations, which will be used for determining the Per-Protocol Immunogenicity population, will be made prior to the database lock and will be documented in a separate memo.

Table 3 Acceptable Day Ranges for Vaccination Visits

Dose of 4-Valent HPV L1 VLP Vaccine Scheduled for Injection	Protocol Specified Visit Window	Day Range for Inclusion in Statistical Analysis (Relative to Day 1[†])
Dose 1	Day 1[†]	0
Dose 2	Month 2 ± 3 weeks	36 to 84
Dose 3	Month 6 ± 4 weeks	148 to 218
[†] Day 1 refers to the date when dose 1 of 4-valent HPV L1 VLP vaccine is injected.		

Table 4 Acceptable Day Ranges for Collection of Serum Samples

Study Visit	Sample Type	Target Collection Day (Relative to Day 1[†])	Day Range for Inclusion in Statistical Analysis (Relative to Day 1)[†]
Day 1	Serum	0	–14 to 0
Month 7	Serum	30 days post dose 3	21 to 49 post dose 3
Month 18	Serum	548	366 to 730
Month 30	Serum	913	731 to 1004
[†] Day 1 refers to the date when dose 1 of 4-valent HPV L1 VLP vaccine is injected. For Month 7, indicated target collection/day range is relative to date of injection of dose 3 of 4-valent HPV L1 VLP vaccine.			

All Type-Specific Naïve Subjects with Serology (ANSS) Population

A supportive immunogenicity analysis will be carried out on the all type-specific naïve subjects with serology population. To be included in this population, subjects must:

(1) Have received all 3 vaccinations

(2) Have provided post dose 3 serology data

(3) Be seronegative to the appropriate HPV type at Day 1

To be included in the ANSS population for HPV 6 or 11, subjects must be seronegative to both HPV 6 and 11 at Day 1. To be included in the ANSS population for any other vaccine HPV type, subjects need to be seronegative at Day 1 only for the HPV type being analyzed. Unlike the PPI population, this population will include general protocol

violators. In addition, no ranges on the timing of the vaccination will be applied. Acceptable day ranges for serum samples at Day 1 will be the same as in the PPI population. Acceptable day range for serum samples at Month 7 will be broader than in the PPI population, extending from Day 1 post dose 3 to Day 105 post dose 3.

8.5.2 Safety Analysis Populations

All subjects who received at least 1 study vaccination and have follow-up data will be included in the analysis of safety.

8.6 STATISTICAL MEDHODS

Statistical testing and inference for safety analyses are described in 8.6.2. Immunogenicity results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Nominal p-values may be computed for other immunogenicity analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

8.6.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the primary and secondary objectives.

Estimation of seroconversion percentage

The primary immunogenicity hypothesis with respect to anti-HPV 6, 11, 16 and 18 seroconversion percentages by 4 weeks post dose 3 will be evaluated by computing point estimates and constructing 95% confidence interval. Calculation of the confidence interval is based on the exact binomial method proposed by Clopper and Pearson (1934). Success of this study requires that the point estimates of seroconversion percentage on all the 4 HPV types exceed 90%.

Estimation of GMTs

Anti-HPV 6, 11, 16 and 18 GMT at 4 weeks post dose 3 will be evaluated by computing point estimates and constructing 95% confidence interval. The values will be log-transformed before analysis. As such, the confidence intervals for the means will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means titer and confidence intervals about the geometric means titer on the original scale.

Comparison of immune response (9-15 years old boys vs. 16-26 years old young men)

The secondary hypothesis that the immune response in 9- to 15-year-old boys is non-inferior to that in 16- to 26-year-old young men (all men who were vaccinated by V501 and met the per-protocol immunogenicity criteria of PN122) will be addressed by 95% confidence intervals based on one-sided tests (one corresponding to each HPV type) conducted at the α=0.025 level (1-sided). For each HPV type, the hypotheses to be tested are:

$$H_0: GMT_1/GMT_2 \leq 0.5$$

$$H_1: GMT_1/GMT_2 > 0.5$$

where GMT_1 represents the GMTs at Month 7 in the 9- to 15-year-old boys and GMT_2 represents the GMTs at Month 7 in the 16- to 26-year old young men. The test above will be performed using an analysis of variance model with a response of log-transformed individual titers and a fixed effect for age group. The statistical criterion requires that the lower bound of two-sided 95% confidence interval of GMT ratio (9- to 15-year-old boys divided by 16- to 26-year-old young men) be greater than 0.5 for all 4 HPV types. For exploratory purposes, 95% confidence interval for the difference (9- to 15-year-old boys minus 16- to 26-year-old young men) in seroconversion percentages by 4 weeks post dose 3 for each of the vaccine HPV types will be constructed. The calculation will be based on the method proposed by Miettinen and Nurminen (1985).

Persistence of immune responses

Anti-HPV 6, 11, 16 and 18 GMTs and seroconversion percentages at Months 18 and 30 will be summarized in the PPI population to assess the persistence of immune responses. Longitudinal plots of the GMTs from Day 1 through Month 30 will also be provided for graphical display.

Table 5 summarizes the immunogenicity analyses.

Table 5 Analysis Strategy for Immunogenicity Variables

Endpoints	Variable	Primary /secondary /supportive	Margin	PPI	ANSS	Point estimate and 95% CI
Immune Response at 4 weeks post dose 3						
Seroconversion percentage to HPV 6, 11, 16 and 18 by 4 weeks post dose 3 (each type will be analyzed separately)	Seroconversion percentage by 4 weeks post dose 3	Primary	N/A	●	●	●
Anti-HPV 6, 11, 16 and 18 Titer at 4 weeks post dose 3 (each type will be analyzed separately)	GMT at 4 weeks post dose 3	Secondary	N/A	●	●	●
Comparison of immune response between 9- to 15- year-old boys and 16- to 26-year-old young men						
Anti-HPV 6, 11, 16 and 18 Titer at 4 weeks post dose 3 (each type will be compared separately)	Ratio of GMT at 4 weeks post dose 3 (9- to 15- year-old boys divided by 16- to 26- year-old men)	Secondary	2- fold (0.5)	●		●
Seroconversion percentage to HPV 6, 11, 16 and 18 by 4 weeks post dose 3 (each type will be summarized separately)	Difference in seroconversion percentage by 4 weeks post dose 3 (9- to 15- year-old boys minus 16- to 26-year-old men)	Supportive	Not determined	●		●
Persistent Immune response						
Anti-HPV 6, 11, 16 and 18 Titer at each time point (each type will be compared separately)	GMT at each time point	Secondary	N/A	●		●
Seroconversion percentage to HPV 6, 11, 16 and 18 by each time point (each type will be summarized separately)	Seroconversion percentage by each time point	Supportive	N/A	●		●
PPI=Per protocol immunogenicity; ANSS= all type-specific naïve subjects with serology.						

The strategy to address multiplicity issues with regard to multiple immunogenicity endpoints, and/or multiple time points is described in Section 8.8, Multiplicity.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs).

The analysis of safety results usually follow a tiered approach in the studies conducted by the SPONSOR. However, this study has only 1 treatment group. Thus, the following summaries will be provided as described in Table 6.

– Incidence is defined as (number of subjects with the indicated endpoint divided by the total number of subjects with follow-up over the relevant period)*100%.

– For the measured adverse experiences of redness and swelling, 0 to 1 inch will be categorized as mild intensity, >1 inch to 2 inches will be categorized as moderate intensity, and >2 inches will be categorized as severe intensity

The specific events of interest in this study will be injection-site adverse experiences prompted for on the VRC, such as pain/tenderness, swelling and redness occurring Day 1 through Day 5 following any vaccination, and elevated temperature (≥37.5°C), from Day 1 to Day 5 following any vaccination.

Table 6 Analysis Strategy for Safety Parameters

Adverse Experience Endpoint	Follow-Up Period		
	After Any Vaccination Visit		
	Day 1 to Day 5[†]	Day 1 To Day 15[†]	Any Time During Study
Clinical AEs/vaccine-related AEs			
Any AE/vaccine-related AE		●	
Deaths			●
Injection site AEs/vaccine-related AEs			
AEs/vaccine-related AEs of pain/tenderness, swelling, and redness	●		
Other injection site AEs/vaccine-related AEs	●		
Severe injection site AEs[§]/vaccine-related AEs	●		
Number (%) of subjects by maximum intensity rating, over all injection site AEs[§]/vaccine-related AEs	●		
Number (%) of subjects by maximum intensity rating, within each of the categories of injection site AEs[§]/vaccine-related AEs	●		
Systemic AEs/vaccine-related AEs			
Systemic AEs/vaccine-related AEs		●	
Number (%) of subjects by maximum intensity rating, over all systemic AEs/vaccine-related AEs		●	
Temperatures			
Elevated temperatures[#]	●		
Maximum temperatures[††]	●		
AEs of Special Interest			
Serious AEs		●	
Serious vaccine-related AEs			●
New medical conditions[‡‡]			●

[†] The day of vaccination is counted as Day 1. Day 1 to Day 5 refers to the period within 4 days of a vaccination. Day 1 to Day 15 refers to the period within 14 days of a vaccination.
[§] For the measured adverse experiences of redness and swelling 0 to 1 inch will be categorized as mild, >1 inch to 2 inches will be categorized as moderate and >2 inches will be categorized as severe.
[#] Defined as maximum (over the follow-up period) temperature ≥37.5°C.
[††] Distribution of maximum temperatures over the relevant follow-up period.
[‡‡] Including new medical conditions considered potentially of an autoimmune nature.
AEs = Adverse experiences;

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics and demographic variables

Baseline characteristics and demographic variables will be summarized by the use of tables and/or graphs. The number and percentage of patients screened, enrolled, vaccinated and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics and prior and concomitant therapies (relevant pre-injection day ranges for summarization will be 3 days for medications, 14 days for non-live virus vaccines and 28 days for live virus vaccines) will be summarized either by descriptive statistics or categorical tables.

Baseline HPV Status

A serum sample will be collected from all subjects at the Day 1 visit for the purpose of assessing baseline HPV serostatus to the 4-valent HPV L1 VLP vaccine HPV types (HPV 6, 11, 16 and 18). A subject will be considered seropositive to a given HPV type at Day 1 if the subject's anti-HPV titer is ≥ the corresponding serostatus cutoff for that HPV type or seronegative to a given HPV type at Day 1 if the subject's anti-HPV titer is < the corresponding serostatus cutoff for that HPV type. For each HPV type, the proportions of subjects who are seronegative or seropositive will be summarized.

8.7 INTERIM ANALYSES

The immunogenicity and safety analysis of Day 1 through Month 7 will be performed after the data through Month 7 have been declared final and complete. The analysis of Month 18 through Month 30 immunogenicity and safety data will take place at the end of the study.

8.8 MULTIPLICITY

For the primary hypothesis, no multiplicity adjustment is necessary since success requires the observed seroconversion rates for all 4 vaccine HPV types to be greater than 90%. Similarly, for the secondary hypothesis for comparing GMTs in 9- to 15-year-old boys with those in 16- to 26-year old Japanese men, success is required on all 4 vaccine HPV types. Therefore, no multiplicity adjustment will be necessary to account for the multiple HPV types. The secondary hypothesis will only be tested if the primary hypothesis is demonstrated successfully.

8.9 SAMPLE SIZE AND POWER CALCULATION

8.9.1 Sample Size for Estimating Immune Response

Seroconversion percentage by Month 7

This study will enroll 100 subjects to receive V501, and will allow estimation of seroconversion percentage among subjects receiving V501 with a 95% confidence interval with a half-width of approximately 5 percentage points. This is based on the following assumptions: 1) an approximately 5% dropout and/or protocol violation rate, 2) an underlying response rate of 95% in the study population. Previously conducted studies of V501 indicate the seroconversion percentage is approximately 100%. For reference, seroconversion percentages (95% confidence intervals) were 97.5% (91.3, 99.7), 98.8% (93.2, 100), 98.8% (93.4, 100) and 98.8% (93.4, 100) for HPV 6, 11, 16 and 18, respectively, in Japanese girls (PN028). The calculation is based on the exact binomial method proposed by Clopper and Pearson (1934) with 95 subjects in the population expected to be included in the analysis, and is carried out using SAS ver. 9.2. Table 7 summarizes estimates of probability that the point estimates of seroconversion percentage on 4 HPV types exceed 90%.

Table 7 Probability for Primary Immunogenicity Objective

True seroconversion percentage	Probability that the point estimate exceeds 90% for a specific HPV type	Probability that the point estimates exceed 90% for all 4 HPV types
95%	0.98	0.92
99%	> 0.99	> 0.99
The criterion requires that the point estimates of seroconversion percentage exceed 90%.		

GMT at Month 7

This study will allow estimation of GMT among subjects receiving V501 with a 95% confidence interval with a half-width of 0.24 (ln mMU/mL) on the natural log scale (equivalently 1.27 fold on the original scale). The precision is based on the following assumptions: 1) an approximately 5% dropout and/or protocol violation rate, and 2) a SD of the natural-log-transformed titers of 1.2.

8.9.2 Sample Size for comparing immune response between 9- to 15-year-old boys and 16- to 26-year-old Young men

Table 8 summarizes the probability calculations for various true GMT ratios. The probability shown in the table is for meeting the secondary immunogenicity hypothesis in all 4 HPV types for 9- to 15-year-old boys vs. 16- to 26- year-old young men (all young men who were vaccinated by V501 and met the per-protocol immunogenicity criteria of PN122). The probability is based on the following assumptions: 1) an approximately 5% dropout and/or protocol violation rate in 9- to 15-year-old boys, 2) an approximately 40% of subjects are excluded from 550 young men vaccinated by V501 from PN122, 3) a margin of 2-fold, and 4) a standard deviation of 1.2 on the log scale (ln(mMU/mL)). The calculation is based on the t-test at alpha=0.025 (one-sided) with 95 boys and 400 young men expected to be included in the analysis and is carried out using SAS ver. 9.2. As shown in Table 8, this study will have more than 99% probability that the lower bounds of 95% confidence interval exceed 0.5 for all 4 HPV types given the underlying true GMT ratio is 1.0.

Table 8 Power for Secondary Immunogenicity Objective (9- to 15-Year-Old Boys vs. 16- to 26-Year-Old Young men)

True GMT Ratio	Probability that 95%CI lies above 0.5 for a specific HPV type	Probability that 95%CI lies above 0.5 For all 4 HPV types
1.0	>0.99	>0.99
1.5	> 0.99	> 0.99
The statistical criterion requires that the lower bound of two-sided 95% confidence interval of GMT ratio (boys vs. young men) being greater than 0.5.		

8.9.3 Sample Size and Power for Safety Analyses

The probability of observing at least one specific adverse experience in this study depends on the number of subjects vaccinated and the underlying percentage of subjects with a specific adverse experience in the study population. If the underlying incidence of a specific adverse experience is 1%, there is a 63% chance of observing at least one specific adverse experience among 100 subjects. If no adverse experiences are observed among the 100 subjects, this study will provide 80% confidence that the underlying percentage of subjects with an adverse experience is <1.6%.

8.10 SUBGROUP ANALYSES AND EFFECT OF BASELINE FACTORS

Point estimates along with 95% confidence intervals for Month 7 anti- HPV Types 6, 11, 16 and 18 GMTs will be provided for 9-12 and 13-15 year old age strata.

8.11 COMPLIANCE (MEDICATION ADHERENCE)

Compliance is defined in this study as receipt of all scheduled study vaccinations. To summarize compliance, the numbers of subjects who receive each vaccination will be tabulated. Compliance with the planned vaccination schedule (Day 1, Month 2, Month 6) will be described by histograms of actual intervals between vaccinations relative to the expected interval.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 9

Table 9 Product Descriptions

Product Name & Potency	Dosage Form
V501 (Quadrivalent HPV Vaccine) 20/40/40/20 µg/0.5 mL HPV types 6/11/16/18	1 dose (0.5 mL) Sterile suspension for intramuscular injection

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label single-dose vials at Day 1 (Visit 1), Month 2 (Visit 2) and Month 6 (Visit 3). No kitting is required.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Vaccine (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site

is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although

publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.2 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of patient consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main

trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated

with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

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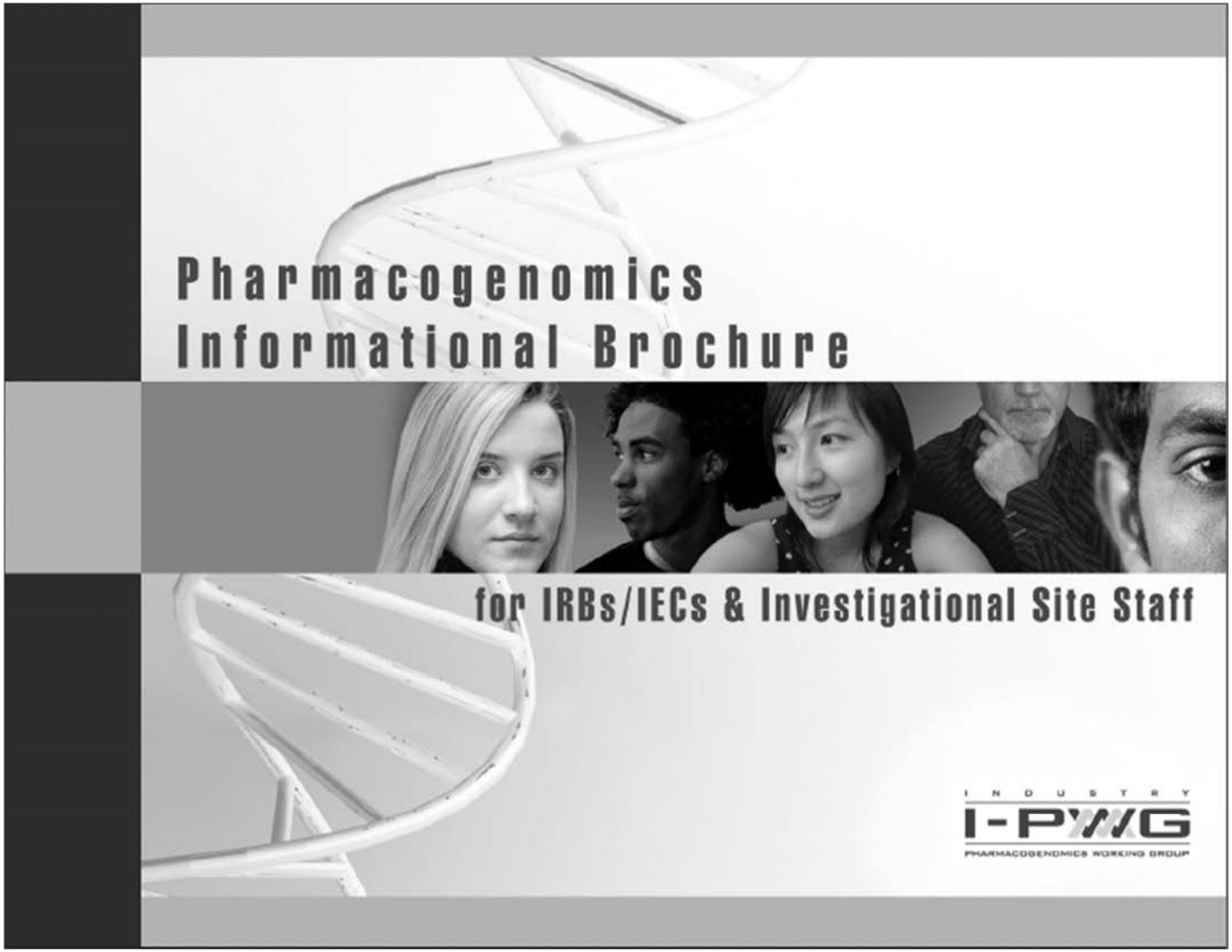
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



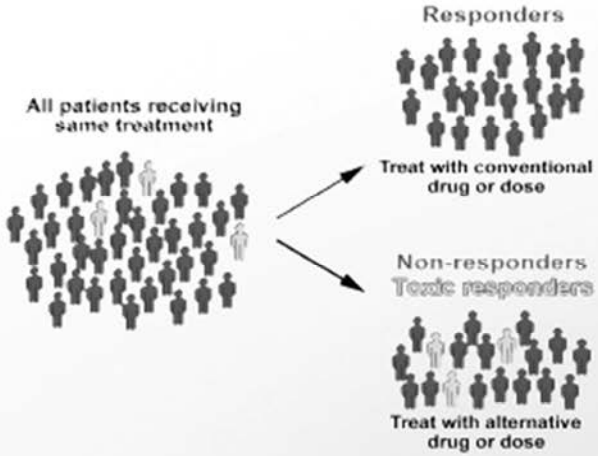
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

2

Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:
www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

3

Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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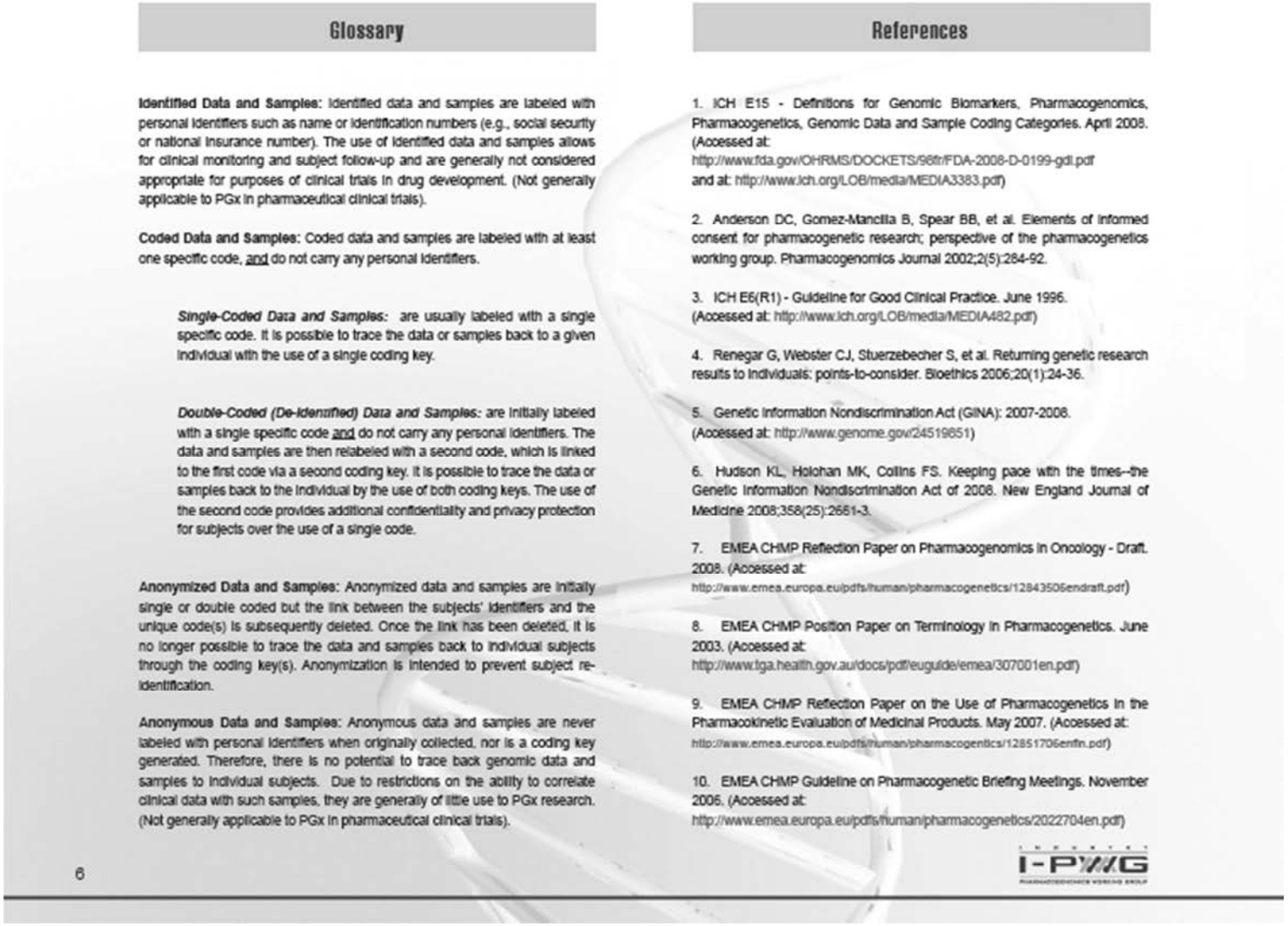

Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

6

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9. EMEA CHMP Reflection Paper on the Use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products. May 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/12851706enfin.pdf)

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12.4 Approximate Blood Volumes Drawn by Trial Visit and by Sample Types

Trial Visit/Cycle/etc:	Visits 1 Day 1	Visit 4-6 Month 7-30
Blood Parameter	**Approximate Blood Volume (mL)**	
Serum for Anti-HPV antibody	10 mL	10 mL
Blood (DNA) for Future Biomedical Research	8.5 mL	NA
Expected Total (mL)	18.5 mL	10 mL

12.5 Clinical Study Conduct System

Clinical study conduct system is shown in Attachment 1 and 2.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	